EDITOR'S NOTE

Dear Friends,

Greetings!

As we marvel at the beauty and fury of monsoon, I call upon you to pick up a cup of Darjeeling tea, the latest issue of *JIACM* and sit in a quiet corner near the window, to enjoy the best offerings of this season.

A variety of original articles are presented to pique your interest; the oft ignored Magnesium ion can trouble a lot if not attended to, the heart is definitely and seriously affected by Dengue (again very pertinent for the coming months), and how Artificial Intelligence can be harnessed to diagnose a very common type of headache – migraine.

The humble urine examination always keeps on crying for attention in our daily practice, so we decided to put it up centre stage, for all to read and assimilate in their management algorithms for patients – a profoundly useful review article.

Case series portray *common cases* which internists must be aware of and never miss, if confronted with one. Indian weather lends happily to food-borne botulism (again during these months) and how a lack of essential vitamins can cause devastating strokes and thromboses – makes for absorbing reads.

A multitude of interesting and *uncommon cases* are presented – from various presentations of anaemia, Addison's disease, and hypokalaemia to life-threatening and tongue-twisting eponymous ones like Haemophagocytic Lymphohistiocytosis and Tracheobronchopathia Osteochondroplastica ! Sickle cell disease at 62 years of age and Diabetes causing chorea – it's all here.

So, read on and as my mentor used to say, *"Even if you can remember one line from the article you have read, it is more than sufficient"*.

We have re-introduced the section on "*Images in Clinical Medicine*" beginning with a case of Symmetrical Peripheral Gangrene due to *Acinetobacter baumannii* Infective Endocarditis.

There is a brand new section on "*Videos in Clinical Medicine*" in the online e-journal available at the website, where we will post-interesting videos in Clinical Medicine. The inaugural video is of two patients of Diabetic Chorea (we have a case report too in this issue!) – you will get to read and see this unusual phenomenon.

I encourage you to visit the website *www.jiacm.in* and enjoy all the above offerings and relish the flavours in an electronic format, along with past issues.

Finally, and most importantly, I request you *to inform, invite and involve your students, colleagues and friends from India and abroad to read and contribute to JIACM*.

Let us be proud Physicians, honoured members of *IACM*, and accomplished authors published in *JIACM*.

I and my Editorial team are always available for comments, queries, suggestions, criticisms and congratulations !

Long live Clinical Medicine, long live *IACM* and long live *JIACM*.

Jai Hind

– Dr Sumeet Singla

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Journal, Indian Academy of Clinical Medicine

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

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for the

Indian Association of Clinical Medicine

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Tel.: 9810104431

E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Scopus, IndMED

Listed in UGC Approved List of Journals

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

Published by Dr. Sumeet Singla
for and on behalf of the Indian Association of Clinical Medicine
from 108 SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052
and printed by him at Sumit Advertising, 2 DLF (Part) Industrial Area, Moti Nagar, New Delhi - 110 015.

Indian Association of Clinical Medicine

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Post-Graduate Department of Medicine, Sarojini Naidu Medical College,
Mahatma Gandhi Road, Agra - 282 002 (U.P.)

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ORIGINAL ARTICLE

JIACM 2024; 25 (3): 87-99

Artificial Intelligence in the Diagnosis of Migraine (with or without Aura) in Adults: A Systematic Review

Avnika Jain, Ojasvini Bali*, Nupur Ritchie*, Sumeet Singla***

Abstract

Objective: To assess the performance of artificial intelligence (AI) systems in the diagnosis of migraine with aura and migraine without aura in adults.

Background: Migraine is a chronic neurovascular disorder that affects over 1 billion people across the world. Currently diagnosed based on clinical criteria given by the International Headache Society, its accurate diagnosis is challenging because of the existence of numerous mimics.

Methods: Literature search of PubMed, Scopus, and Embase was conducted on July 6, 2021. Original peer-reviewed articles in which AI was applied for diagnosis of migraine with or without aura in adults (>18 years) were included. The risk of bias was evaluated using Quality Assessment of Diagnostic Accuracy Studies-2.

Results: Thirty-four papers were included, spanning close to a hundred AI models being used for neurophysiological, clinical or radiological diagnosis of migraine. The most common were Support Vector Machine and Artificial Neural Network. The median accuracy in the studies included was highest for those employing radiological data (88.85%) and lowest for clinical attributes (81%). Risk of bias assessment yielded four studies (11.8%) with an overall low-risk of bias. Twenty-three out of 34 studies had 'high'-risk of bias in the patient selection domain, the most frequent cause being a case-control study design.

Conclusion: Evidence suggests that AI is potentially valuable in the diagnosis of migraine. Concerted efforts are necessary to ensure uniformity in reporting of data, ethical handling of datasets, and for progress from experimental status to deployment in actual clinical settings.

Key words: Migraine, artificial intelligence, migraine with Aura, migraine without Aura.

Key message: Artificial intelligence (AI) models are being developed for application in various fields of medicine. This is the first systematic review to highlight the use of AI in the diagnosis of migraine and thirty-four papers were included. This review has found that AI has the potential to classify migraine with a high degree of accuracy with objective use of clinical, EEG or radiological data. Future studies in this field should aim to include larger and more diverse datasets, report outcomes in a standard manner, and integrate AI into actual clinical settings.

Introduction

Migraine is a chronic neurovascular disorder that affects over 1 billion people across the world[1]. It is the third most frequent disorder worldwide with a 1-year prevalence of 15%[2,3] and is the second most disabling disease globally contributing to 45·1 million years lived with disability (YLDs)[4,5]. It accounts for nearly 5·6% of the global disease burden[6]. This burden is largely avoidable with effective and affordable treatments. However, a major challenge is its accurate and timely diagnosis.

Headache is the most common presenting neurological symptom in primary care[7]. Currently, the diagnosis of headache disorders is based on clinical history and is therefore susceptible to a high degree of information bias. To standardise the process, a classification system was developed by the International Headache Society (IHS), the most recent of which is the third edition of the International Classification of Headache Disorders (ICHD-3), launched in 2018[8]. The ICHD classifies headache disorders into primary headaches, secondary headaches, and neuropathies and facial pains. Migraine is a primary headache disorder which has two major types-migraine with aura and migraine without aura. In migraine with aura, transient focal neurological symptoms may precede or accompany the headache. Migraine without aura is more than twice as frequent as migraine with aura[9].

Due to the existence of numerous migraine 'mimics', migraine is frequently underreported and misdiagnosed (in ~50% of headache cases) as sinusitis, other headache

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disorders like tension headache and cervical pain syndrome, stroke, transient ischaemic attack, multiple sclerosis, among others[5,10,11]. In another study, 88% patients who met the ICHD criteria for migraine were wrongly diagnosed with sinusitis[12,13]. Kernick *et al* reported that a formal diagnosis was not made in nearly 70% of patients presenting with new onset headache[14].

Data-driven approaches using machine learning (ML) or deep learning (DL) are being tested in the medical field to avoid biases attributed to human factors. Artificial intelligence (AI) models accelerate the identification and interpretation of relevant medical data from multiple sources and areas of interest[15]. ML methods analyse a large number of 'training' cases to produce the correct output for the given input on test cases. According to the types of tasks that they intend to solve, basic ML algorithms fall roughly into two categories: supervised and unsupervised. 'Supervised' algorithms learn from pre-labelled datasets to classify a specific outcome (e.g., presence or absence of migraine in the context of the current study). Newer 'unsupervised' AI systems such as DL analyse unlabelled data finding complex co-relations in previously unrecognised patterns (e.g., use of principal component analysis for feature selection). Supervised models may achieve high accuracies since the data used for training has already been labelled. Performance of ML models can be evaluated using different outcome measures such as accuracy, area under the receiver operating characteristic curve (AUC), recall (sensitivity), precision (positive predictive value) and calibration (goodness of fit). While accuracy and AUC are the most frequently reported performance metrics, if considered in isolation they may not always reflect the true performance of the model[16].

As per our knowledge, this is the first systematic review aiming to assess the potential role of different AI-based approaches in the diagnosis of migraine with and without aura in adults.

Methodology

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) guidelines[17]. The study protocol was registered and published on the international Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42021267186).

Search Strategy

A search syntax was created using relevant keywords for migraine and artificial intelligence. The search was conducted on July 6, 2021 on three databases, i.e., PubMed, Scopus, and Embase. Filters were applied to include English language search results published in or after 2000. The search results were compiled using EndNote software. The titles and abstracts were then independently screened by three reviewers (AJ, OB, NR). Disagreements were resolved either through discussion or by consulting the fourth reviewer (SS). Full texts of the selected results were retrieved and matched against the inclusion criteria in the same manner.

Selection Process

We included studies in which an AI algorithm was applied for diagnosis/ classification of migraine with and/or without aura in adult patients (>18 years) in any hospital setting. We excluded case reports, case series, reviews and meta-analyses as well as studies mentioning neither the accuracy nor AUC of the chosen model. Rare subtypes of migraine (e.g., familial, vestibular, hemiplegic) were not included in this review.

The studies were assessed for eligibility by AJ, OB and NR independently with a final consensus reached through discussion or by consulting SS.

The references of the full texts chosen for the study were screened for articles matching the eligibility criteria.

Data Collection

The data was extracted independently by the three reviewers, on (1) study characteristics; and (2) performance metrics of the index test and was then tabulated and cross-checked by all the reviewers (Tables I, II, III).

Since 31 out of 34 papers reported accuracy of their ML models, this was chosen as the primary performance metric. Median accuracy was subsequently calculated using the highest accuracy reported in each paper.

Risk of Bias Assessment

The risk of bias was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria[18]. Bias was assessed by AJ, OB and NR independently using various signalling questions tailored for the review. Each of the four domains could be of low, unclear or high-risk of bias. If the answer to any one signalling question was 'no' or 'unclear', the risk of bias of that domain was considered high or unclear respectively. A high or unclear risk of bias of any one domain resulted in the risk of bias of that study being high or unclear respectively.

Table I: Summary of the studies included in this systematic review using neurophysiological data as input.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/ Validation/ Test set/ Validation Method	Accuracy/ AUC	Sensitivity/ Specificity
Input data: Neurophysiological Investigations									
1.	Akben *et al*[19]	2012	IHS	MLPNN (and RBF, LVQ, SOM for comparison)	30 (15 migraineurs + 15 HC)	EEG	80%/–/20%	93.3% (4 Hz)	93.3% / 93.3%
2.	Akben *et al*[20]	2016	IHS	SVM	60 (30 MwoA + 30 HC)	EEG	–/–/–	88.4% (T3)	90% /86.7%
3.	Alkan *et al*[21]	2011	IHS	K-means clustering	30 (15 migraineurs + 15 HC)	EEG	90%/–/10%	86.6%	–/–
4.	Bellotti *et al*[22]	2007	–	ANN	31 (16 MwoA + 15 HC)	Spontaneous EEG	–/–/–	AUC >0.95 (tau-TDG)	–/–
5.	Cao *et al*[25]	2018	ICHD-2	LDA kNN MLPNN NB SVM, linear kernel SVM, RBF kernel	80 (40 MwoA + 40 HC)	Inter-ictal and pre-ictal phase EEGs	27/13/-K-fold CV (k = 3)	63.0 ± 6% (LDA) 71.0 ± 5% (kNN) 67.0 ± 6% (MLPNN) 65.0 ± 5% (NB) 71.0 ± 4% (SVM, linear kernel) 76.0 ± 4% (SVM, RBF kernel)	–/–
6.	de Tommaso *et al*[23]	2003	IHS	ANN SVM	30 (15 MwoA + 15 HC)	SVEP-EEG	–/–/–	AUC 0.78 (ANN; F1) AUC 0.88 (ANN; α wav) AUC 0.92 (SVM; F1) AUC 0.86 (SVM; α wav)	–/–
7.	Frid *et al*[24]	2020	ICHD-3 beta	SVM with RBF	53 females with episodic migraine	EEG	–/–/–	84.62%/AUC 0.88	–/–
8.	Subasi *et al*[26]	2019	–	SVM kNN ANN RF DT (CART) DT (C4.5) Rotation forest DT (REPTree) DT (Random Tree) DT (ADTree) DT (LADTree) DT (NBTree)	30 (15 MwoA + 15 HC)	EEG	–/–/– 10-fold CV, LOOCV	(Window period = 3s Without flash/with flash 80.74%/84.07% (SVM) 77.78%/83.33% (kNN) 75.93%/82.22% (ANN) 75.19%/85.19% (RF) 67.04%/77.78% (CART) 64.81%/77.04% (C4.5) 77.41%/83.70% (Rotation Forest) 65.93%/74.81% (REPTree) 68.15%/76.30% (Random tree) 66.67%/73.33% (ADTree) 70.74%/77.41% (LADTree) 65.93%/75.93% (NBTree)	–/–
9.	Taufique *et al*[27]	2021	–	ANN	57 (Patient data taken from Zhu *et al*)	SSEP-EEG	–/–/– 5-fold CV	76% (ANN)	–/–
10.	Zhu *et al*[28]	2019	–	DT (XGB trees) RF SVM kNN MLPNN LDA LR	57 (29 MII, 13 MI, 15 HCs)	SSEP-EEG	–/–/– 10-fold CV	HC-MI - 88.0% (XGBTree) HC-MI - 84.4% (RF) HC-MII - 84.6% (SVM) HC-MI - 78.5% (kNN) HC-MII - 83.3% (MLPNN) MI-MII - 69.5% (LDA) HC-MI - 69.7% (LR)	89.3%/90.3% (XGBTree) 84.1%/84%(RF) 85.7%/85.8% (SVM) 78%/78.2%(kNN) 82.6%/85.2% (MLPNN) 69.3%/67.1% (LDA) 68.9%/70.6%(LR)

ANN: Artificial neural network; CART: Classification and regression tree; DT: Decision tree; HC: Healthy controls; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNN: k-nearest neighbors; LDA: Linear discriminant analysis; LOOCV: Leave one out cross validation; LVQ: Learning vector quantisation; LR: Logistic regression; MI: Migraine ictal; MII: Migraine inter-ictal; MLPNN: Multi-layer perceptron neural network; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; RBF: Radial basis function; RF: Random forest; SOM: Self-organising map; SSEP: Somatosensory evoked potential; SVEP: Steady state visual evoked potential; SVM: Support vector machine; XGB: Extreme gradient boosting.

Table 2: Summary of the studies included in this systematic review using clinical attributes as input data.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/ Validation/ Test set/ Validation Method	Accuracy/ AUC	Sensitivity/ Specificity
					Input data: Clinical Attributes				
11.	Çelik *et al*[30]	2015	ICHD-2	Immunos-1 Immunos-2 Immunos-99 AIRS1 AIRS2 AIRS2-Parallel CLONALG CSCA	850 people with "headache problems" Questionnaire, 40 attributes	–/–/–	94.4706% (Immunos-1)	0.947/1 (Immunos-1) 71.6471% (Immunos-2) 95.6471% (Immunos-99) 99.2941% (AIRS1) 98.8235% (AIRS2) 99.6471% (AIRS2-Parallel) 98.7059% (CLONALG) 99.1765% (CSCA)	1/0 (Immunos-2) 0.949/1 (Immunos-99) 0.995/1 (AIRS1) 0.995/0.992 (AIRS2) 0.998/1 (AIRS2-Parallel) 0.998/0.967 (CLONALG) 0.995/0.992 (CSCA)
12.	Çelik *et al*[29]	2017	ICHD-2	ACO	850 people with "headache problems" Questionnaire, 40 attributes	–/–/–	10-fold CV	98.2%	0.982/0.967
13.	Holsteen *et al*[31]	2020	ICHD-3	Multivariable LR LR	178 patients with episodic migraine	Diary entry	178/–/– 10-Fold CV	0.56 (95% CI, 0.54 - 0.58)	–/–
14.	Katsuki *et al*[32]	2020	ICHD-3 beta	NLP using ANN	848 patients with primary headache	Questionnaire	–/–/–	77.59%	–/–
15.	Khayamnia *et al*33	2019	–	Fuzzy C MLPNN SVM	190 patients with headache (133 with migraine)	Clinical attributes	90%/–/10% 10-Fold CV	92% (Fuzzy C) 92% (MLPNN) 100% (SVM)	0.94/0.81 (Fuzzy C) 0.96/0.81 (MLPNN) 1/0.99 (SVM)
16.	Kwon *et al*[35]	2020	ICHD-3, ICHD-3 beta	XGBoost	2,162 patients	Clinical attributes	864/–/600 10-Fold CV	81%	88%/95%
17.	Krawczyk *et al*[34]	2012	ICHD-2	NB DT (C4.5) SVM Bagging Boosting RF	579 with headache (169 with migraine)	Clinical attributes	–/–/–10-Fold CV	72.02 ± 4.21% (NB) 76.51 ± 3.04% (C4.5) 76.34 ± 1.76% (SVM) 78.24 ± 2.98% (Bagging) 76.68 ± 2.43% (Boosting) 79.97 ± 3.13% (RF)	–/–
18.	Sarsam *et al*[36]	2020	–	SVM (SMO) DT (J48) 1-rule classifier (OneR) kNN (IBk)	237,098,462 English tweets	Tweets	90%/–/– 10-fold CV	95.53% (SMO) 61.49% (J48) 55.27% (OneR) 50.93% (IBk)	–/–
19.	Sedghi *et al*[37]	2016	Neurologist	NB SVM LR	6,912 records (392 migraine)	Clinical attributes	66%/–/33% 10-fold CV	79.3% (NB) 78.4% (SVM) 77.4% (LR)	–/–
20.	Simiae et al[40]	2020	ICHD-3	LR	579 instances (103 MwoA, 66 MwA)	Selected attributes from the IHS criteria	–/–/–	77.4%	–/–
21.	Simiae *et al*[38]	2021	ICHD-2	Weighted Fuzzy C-means Clustering Algorithm	579 with primary headache	Clinical features	–/–/–	75%	86%/–
22	Wu *et al*[39]	2015	ICHD-3	Multiple Fuzzy C-means Clustering Fuzzy C Fuzzy C with genetic algorithm ACO	379 total (213 for migraine)	20 weighted clinical features	–/–/–	97.2% (multiple Fuzzy C) 63.6% (Fuzzy C) 59.8% (Fuzzy C with genetic algorithm) 89.2% (ACO)	–/–

ACO: Ant colony optimisation-based classification algorithm; AIRS: Artificial immune-recognition system; ANN: Artificial neural network; CLONALG: Clonal algorithm; CSCA: Clonal selection classification algorithm; DT: Decision tree; HC: Healthy controls; IBk: Instance-based learning with parameter k; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNN: k-nearest neighbours; LR: Logistic regression; MLPNN: Multi-layer perceptron neural network; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; NLP: Natural language processing; RF: Random forest; SMO: Sequential Minimal Optimisation; SVEP: Steady state visual evoked potential; SVM: Support vector machine; XGB: Extreme gradient boosting.

Table 3: Summary of the studies included in this systematic review using radiological imaging as input data.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/Validation/ Test set/ Validation Method	Accuracy/AUC	Sensitivity/ Specificity
					Input data: Radiological Imaging				
23.	Chen *et al*[42]	2021	IHS	SVM	42 (21 MwoA + 21 HC)	fMRI	–/–/–LOOCV	83.33%	90.48%/76.19%
24.	Chong *et al*[41]	2017	–	DQDA	108 (58 with migraine + 50 HC)	fMRI	–/–/–10-fold CV	86.1%	–/–
25.	Chong *et al*[52]	2021	ICHD-3	LR	34 with migraine (18 MwA, 16 MwoA) and 48 with PPTH	MRI (T1 weighted and DTI) + Clinical data	–/–/–LOOCV	97.06%	–/–
26.	Garcia-Chimeno *et al*[51]	2017	–	SVM Boosting (Adaboost) NB	52 (15 HC, 19 sporadic migraine, 18 chronic migraine and medication overuse)	MRI (diffusion tensor) and multiple questionnaire	–/–/– Stratified K fold method for SVM	All Feature selection method 90% / 78-98% (SVM; best with gradient tree boosting) 93% / 87-95% (AdaBoost; best with random forest) 67% / 60-98% (NB; best with gradient tree boosting)	–/–
27.	Jorge-Hernandez *et al*[49]	2014	–	ANN LDA SVM k means Cluster kNN AdaBoost	53 (15 HC, 20 sporadic migraine, 19 with migration due to medication overuse)	fMRI	20/15/19	92.86% (ANN) 50% (LDA) 79.92% (SVM) 57.14% (k means cluster) 57.14% (kNN) 64.29% (AdaBoost)	1/0.9(ANN) 0.45/0.38 (LDA) 0.36/0.38 (SVM) 0.47/0 (k means) 0.49/0.47 (kNN) 0.74/0.64(AdaBoost)
28.	Li *et al*[48]	2020	–	SVM kNN DT NB RF ANN	26 (14 migraineurs + 12 HC)	fMRI	58% /–/42%	92% (SVM) 100% (kNN) 88% (DT) 92% (NB) 83% (RF) 93% (ANN)	–/–
29.	Meng *et al*[50]	2018	–	CNN	40 (20 migraineurs + 20 HC)	MEG	30/–/104-Fold CV	81.25%	–/–
30.	Rocca *et al*[43]	2021	ICHD-2	CNN	268 imaging scans (56 for migraine)	MRI	56%/14%/30%	92.90%	–/97.10%
31	'Schwedt *et al*[47]	2015	ICHD - 2	DQDA DT	120 (66 migraineurs + 54 HCs)	sMRI	90%/–/10% 10-fold CV	Migraine vs HC – 68% (DQDA) EM vs HC - 67.2% (DQDA) CM vs HC - 86.3% (DQDA) CM vs EM - 84.2% (DQDA) Migraine vs HC - 64.7% (DT) EM vs HC - 66.5% (DT) CM vs HC - 74.6% (DT) CM vs EM - 83% (DT)	–/–
32.	Tu *et al*[44]	2020	ICHD-2	Linear SVM	Study 1: 116 (70 MwoA, 46 HC) Study 2: 38 (19 MwoA, 19 HC) Study 3: 76 (18 MwoA, 58 non-migraine pain and HC)	MRI	–/–/–LOOCV	91.4% (SVM; Study 1) 84.2% (SVM; Study 2) 73.1% (SVM; Study 3)	93%/89% (SVM; Study 1) 84.2%/84.2% (SVM; Study 2 77.8%/71.4% (SVM; Study 3)
33.	Yang *et al*[45]	2018	ICHD - 2	AlexNet CNN Inception module - based GoogleNet CNN SVM(for comparison)	64 (21 MwoA, 15 MwA, 28 HC)	fMRI	80% /–/20%4 -fold CV	98.63% (AlexNet CNN ; HC vs migraine using RFCS) 99.25% (GoogleNet CNN; HC vs migraine using RFCS) 83.67% (SVM)	–/–
34	Zhang *et al*[46]	2016	ICHD - 2	Multi-kernel SVM	49 (21 MwoA, 28 HC)	fMRI and sMRI	–/–/–LOOCV	83.67%	92.86%/71.43%

ANN: Artificial neural network; CM: Chronic Migraine; CNN: Convolutional neural network; DT: decision tree; DQDA: Diagonal quadratic discriminate analysis; EM: Episodic migraine; HC: Healthy controls; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNNP: k-nearest neighbours; LDA: Linear discriminant analysis; LOOCV: Leave one out cross validation; LR: Logistic regression; MEG: Magnetoencephalogram; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; PPTH: Persistent post-traumatic headache; RF: Random forest; RFCS: Regional functional correlation strength; SVM: Support vector machine.

Results

Study selection

After removal of duplicates and manual reference checking, 884 citations from PubMed, Scopus and Embase were screened based on title/abstract. 75 studies were sought for retrieval. Finally, 34 articles remained after full-text screening (as shown in the PRISMA diagram).

Study characteristics

AI models gather data from a multitude of sources and emulate logical decision making to achieve the desired output. In the current review, these models aid neurophysiological, clinical and radiological diagnosis of migraine. The most popular models used were Support Vector Machine (SVM), Artificial Neural Network (ANN) and Decision Tree (DT). Other algorithms used include K-Nearest Neighbour (KNN), Logistic Regression (LR), Fuzzy-C, Naive Bayes (NB) (Fig. 1). A general trend showing an increasing number of studies on the use of AI algorithms in the diagnosis of migraine over the past 2 decades was noted (Fig. 2).

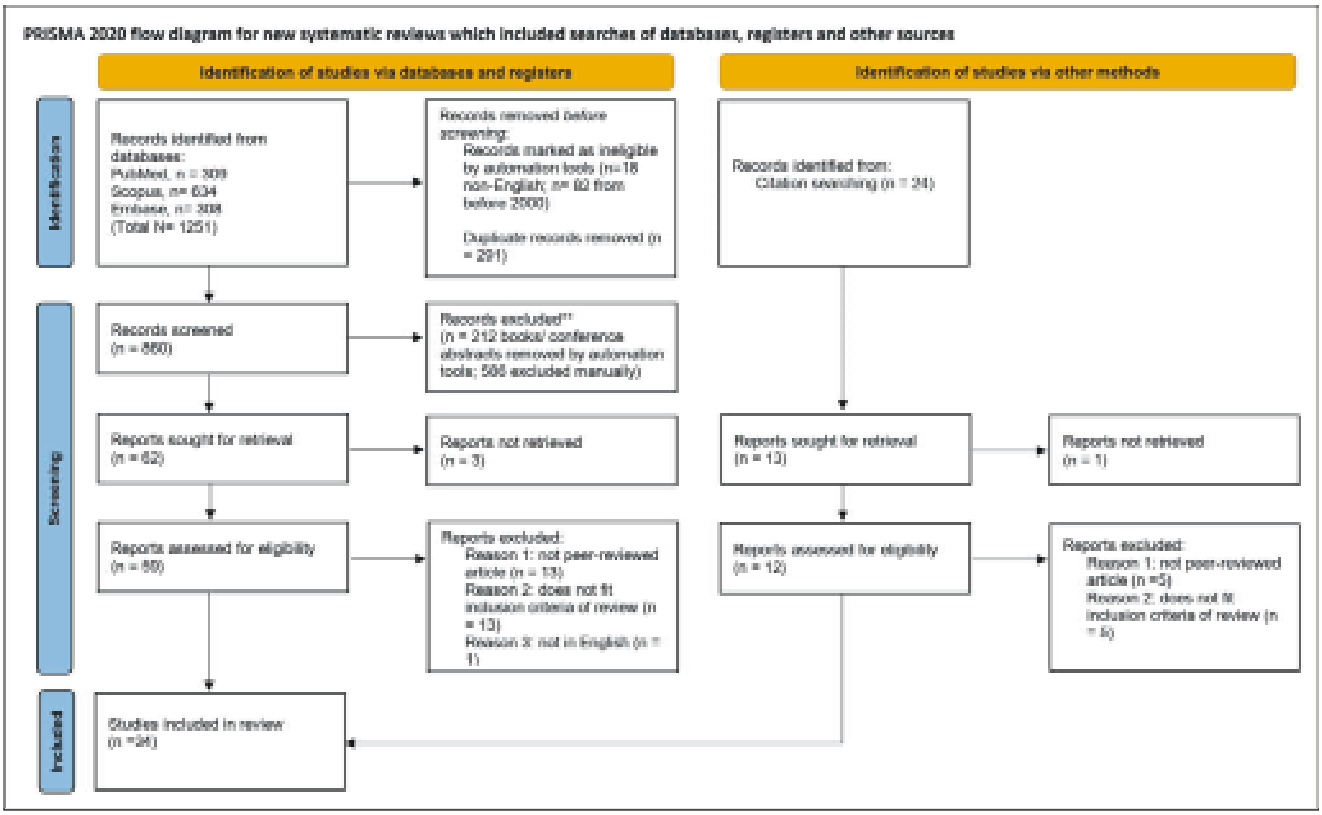
AI in Neurophysiological Diagnosis of Migraine

10 studies used AI models to diagnose migraine based on neurophysiological modalities. The median accuracy was found to be 85.9% (range 76.0 to 93.3%).

In their 2010 study, Akben *et al*[19] aimed to determine the most effective flash stimulation frequency and time duration to detect migraine using an Artificial (Multi-layer perceptron) Neural Network (MLPNN) classifier and radial basis function networks (RBF), learning vector quantisation and self-organizing map networks for comparison. Best accuracy obtained was 93.3% for MLPNN, at 4 Hz. Their 2016 study[20] assessed which EEG channels and brain lobes were the most decisive for diagnosis, using an SVM model. Power spectral densities (PSDs) obtained from flash stimulated and non-stimulated EEG signals were fed to the classifier. Best accuracy was 88.4% for T3 channel.

Alkan *et al* (2011)[21] used histogram differences of flash and non-stimulation EEGs to detect migraine using a K-means cluster algorithm, achieving an accuracy of 86.6%.

Bellotti *et al* (2007)[22] recorded spontaneous EEGs to classify migraineurs (without aura) and healthy controls. Using a supervised feed-forward two-layered neural network, they recorded an AUC of >0.95 (tau-TDG).



Flowchart 1: *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.*

From: Page MJ, McKenzie JE, Bossuyt PM et al. *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj.n71.*

de Tomasso *et al* (2003)[23] elicited steady-state visual evoked potentials (SVEPs) in the low frequency range (3-9 Hz) and studied the temporal variations in the F1 component obtaining a maximum AUC of 0.92 using SVM.

Frid *et al* (2020)[24] recorded 3-minute-long resting state EEGs in the interictal period to compare patients of migraine with and without aura. Using SVM with RBF kernel, they were able to obtain an average classification rate of 84.62%. The same model was found to achieve the highest accuracy (76 ± 0.04%) in a study by Cao *et al* (2018)[25] where they tested six AI models to compare the interictal and preictal phase brain electric activity using resting-state EEGs.

Subasi *et al* (2019)[26] assessed accuracy of 12 models in the diagnosis of migraine without aura using a 10 - 20 EEG system with 256 Hz sampling frequency. The highest accuracy obtained was 84.07% for SVM for a window period of 3 seconds with photic stimulation.

Taufique *et al* (2021)[27] used a hardware chip-based ANN classifier, with its utility in wearable settings, to facilitate early diagnosis of migraine. The somatosensory evoked potential (SSEP) data was pre-processed with features extracted – N20 latency, root-mean-square of late high frequency oscillations (HFO) and power spectral bands – and fed into the classifier. An accuracy of 76% was achieved.

Zhu *et al* (2019)[28] conducted a study to differentiate between migraineurs in the ictal and inter-ictal phases and healthy controls using various features of SSEP signals. A total of 8 ML algorithms were assessed, with the highest accuracy obtained for extreme gradient boosting (XGB) trees at 89.3% in the ictal phase.

AI in Clinical Diagnosis of Migraine

12 studies used AI models to diagnose migraine based on clinical attributes. The median accuracy was 81% (range 75 to 100%).

Celik *et al* diagnosed different types of primary headaches using an ant colony optimisation-based algorithm (2017 paper)[29] and multiple artificial immune system (AIS) algorithms (2015 paper)[30]; achieving best accuracy of 98.2% and 99.65% (AIRS2-Parallel) respectively (Table II).

Holsteen *et al* (2020)[31] developed an LR model to classify subjects with episodic headache into migraine day and

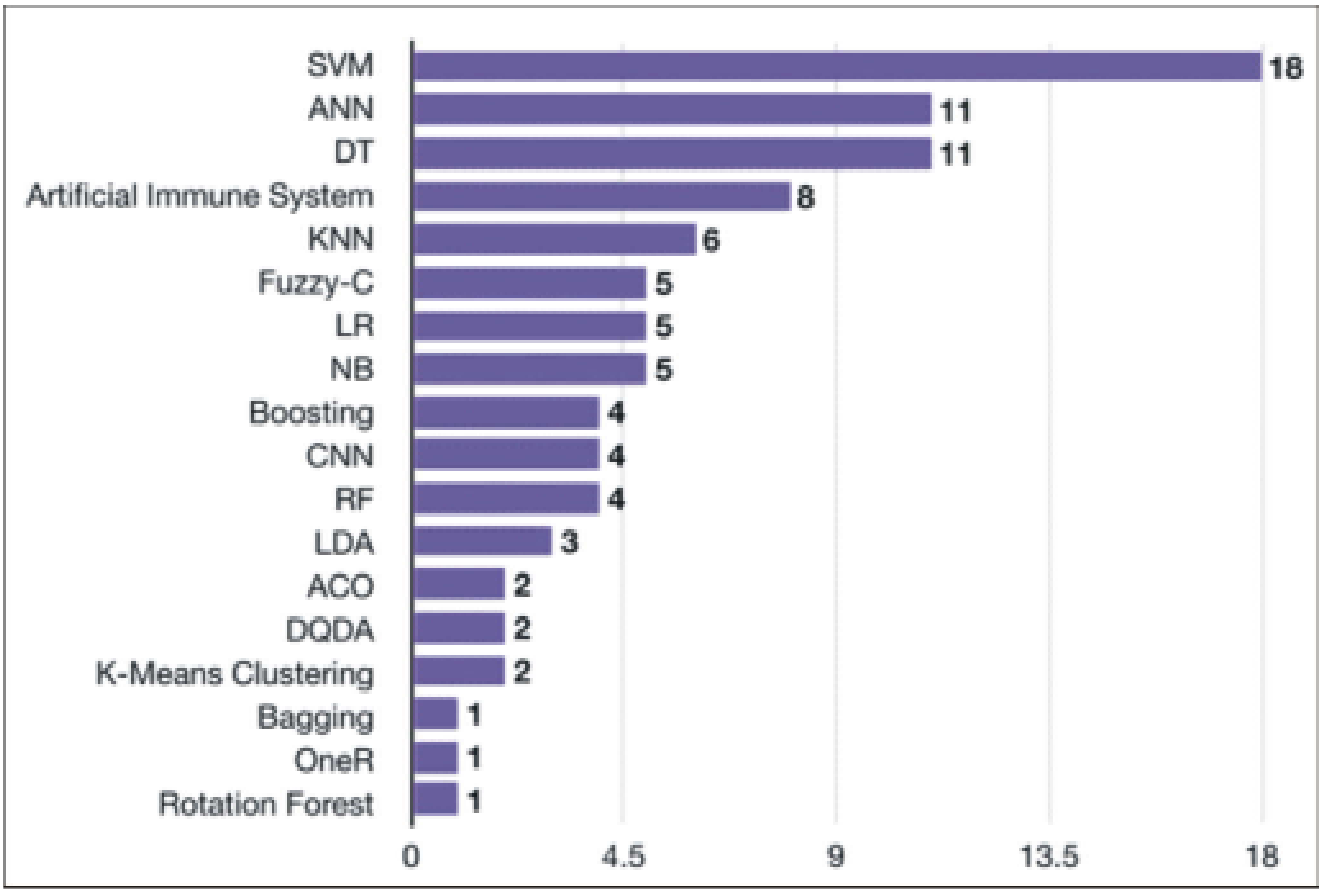


Fig. 1: *The various AI algorithms used in the diagnosis of migraine.*

healthy day categories based on prospective daily diary entries (including self-prediction and self-reported exposure to common trigger factors), using a custom mobile phone application. The model could predict migraine risk only slightly better than chance with an AUC of 0.56 (95% CI: 0.54, 0.58) (Table II).

Katsuki *et al* (2020)[32] developed an ANN model for automated diagnosis of primary headache using demographic characteristics and unstructured sentences (in Japanese) in the questionnaire which were analysed using natural language processing (NLP). The overall AUC, mean precision, mean recall, and mean F value of the model were 0.7759, 0.8537, 0.6086, and 0.6353, respectively (Table II).

Khayamnia *et al* (2019)[33] developed a fuzzy expert-based system using the Learning-From-Examples algorithm and Mamdani model for the diagnosis of common headache types including migraine. Diagnostic parameters like presence or absence of symptoms like aura, vomiting, diplopia, etc., were used as input variables. They also evaluated the performance of MLPNN and multiclass SVM. For classification of migraine, SVM was the most accurate (accuracy = 100%). Overall accuracy of SVM was 90% (vs 88% for MLPNN) (Table II).

In studies by Krawczyk *et al* (2012)[34] and Kwon *et al* (2020)[35], automated diagnosis of headache disorders was done based on clinico-demographic data collected using questionnaires. Krawczyk *et al* tested six machine learning algorithms (Table II). Highest accuracy of 79.97 ± 3.13% was achieved by the random forest model. Kwon developed a four layered binary XGBoost13 based stacked model. This model was compared with other classifiers (Table II). XGBoost13 using the least absolute shrinkage and selection operator (LASSO) method for feature selection was the most accurate (80.71%; sensitivity 52.73%, specificity 45.61%).

Sarsam *et al* (2020)[36] collected and labelled a total of 238,506,796 English tweets according to their geo-spatial location information. The data was clustered into 'sad' and 'neutral' using K-means clustering. The association rules mining approach (using Apriori algorithm) was applied to extract the features of migraine associated with certain climatic factors in each of the two emotions. Finally, four classification algorithms (Table II) were applied to detect migraine, with Sequential Minimal Optimisation (SMO) attaining the highest accuracy of 95.53%.

Sedghi *et al* (2016)[37] distinguished migraine patients from stroke or other mimics using structured and unstructured clinical data-sources. A sampling method was utilised to create two balanced datasets from the original imbalanced data and the data then analysed by NLP, text-mining and data mining methods. The performance of different classifiers was assessed (Table II) – with the highest average accuracy obtained for NB (79.3%).

Simiae *et al* (2021)[38], using the clinico-demographic data collected in an earlier study[34], estimated the optimal number of clusters using the Calinski-Harabasz index, assigned weights to the chosen attributes using the Analytical

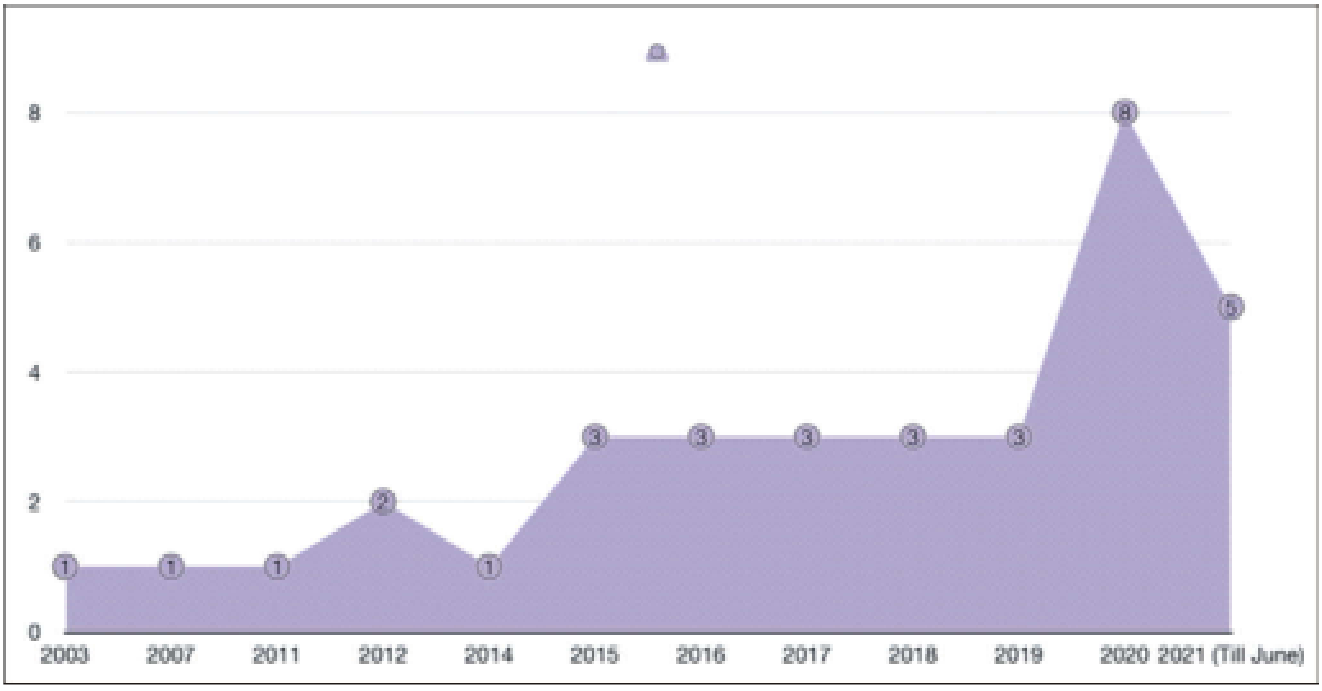


Fig. 2: *Number of studies conducted in the last two decades.*

Hierarchical Process and classified the various primary headache disorders using the Fuzzy C-Means Clustering algorithm; obtaining an overall accuracy of 75% (Table II).

Wu *et al* (2015)[39] also used weighted clinical features to

Fig. 3: *Methodological quality summary table and graph. (a) Risk of bias (left) and applicability concerns (right) summary: review authors' judgements about each domain for each included study. (b) Proportion of studies with LOW, UNCLEAR and HIGH risk of bias and applicability concerns as assessed by QUADAS-2 tool.*

diagnose primary headache disorders using the Multiple Fuzzy C-Means Clustering algorithm. Its accuracy was compared with other conventional models, and was the highest at 97.2% (in the diagnosis of migraine) (Table II).

In another study by Simiae *et al* (2020)[40] a hybrid fuzzy clustering approach created by combining the fuzzy partition method and maximum likelihood estimation clustering algorithm was used to diagnose primary headache disorders using selected clinico-demographic attributes. An accuracy of 77.4% was achieved (Table II).

AI in Radiological Diagnosis of Migraine

10 studies used AI models to diagnose migraine based on imaging modalities. The median accuracy was 88.85% (range 81.25 to 100%) (Table III).

Chong *et al* (2017)[41] obtained resting state functional connectivity (RSFC) data in the "eyes closed" state for the 108 individuals in their study. A total of 33 known pain-processing brain areas were selected. Pre-processing using principal component analysis (PCA) and subsequent classification using diagonal quadratic discriminate analysis (DQDA) found that six regions (bilateral amygdala, right middle temporal, posterior insula, middle cingulate, and left ventromedial prefrontal brain regions) had the highest contribution in discrimination between migraineurs and healthy controls. Their best accuracy was 86.1% (Table III).

Chen *et al* (2021)[42] performed dynamic amplitude of low-frequency fluctuations (dALFF) analyses on 42 subjects. In the migraineurs, significantly decreased dALFF was observed in certain brain regions (the bilateral anterior insula, bilateral lateral orbitofrontal cortex, bilateral medial prefrontal cortex, bilateral anterior cingulate cortex, and left middle frontal cortex). SVM was used for classification, giving an accuracy of 83.33% (Table III).

Rocca *et al* (2021)[43] collected a total of 268 T2 and T1 weighted brain MRI scans from patients of multiple sclerosis, migraine and other mimics of the former. The final trained model was compared with two expert neuroradiologists. An accuracy of 92.9% was attained using Convolutional Neural Network (CNN) (Table III).

Tu *et al* (2020)[44] conducted a multi-level study using linear SVM for identifying an fMRI marker for differentiating between migraineurs and healthy controls (HCs), assessing its generalisability, validating it by differentiating between migraine and other chronic pain disorders, and for assessing its response with treatment, respectively. Accuracies of 91.4%, 84.2% and 73.1% were obtained in the three diagnostic studies respectively (Table III).

Yang *et al* (2018)[45] used AlexNet and Inception module-based GoogleNet CNN models to diagnose and classify migraine based on the pre-processed resting-state fMRI data and the three indices ALFF, Regional Homogeneity (ReHo) and Regional Functional Correlation Strength (RFCS) extracted from it. GoogleNet CNN model was found to have a higher accuracy of 99.25% (Table III).

In the study conducted by Zhang *et al* (2016)[46], along with fMRI (ALFF, ReHo and RFCS) data, gray matter maps were also created using sMRI. 116 features were selected for each map and fed to a multi-kernel SVM model. An accuracy of 83.67% was obtained (Table III).

Schwedt *et al* (2015)[47] used 4 classifiers (Table III) to classify migraineurs into chronic and episodic and differentiate them from HCs, as well as to test the currently used threshold of 15 headache days/month for differentiating chronic from episodic migraine. Using sMRI scans and PCA, principal components for the cortical area, thickness, and volume features were used as input data. DQDA was found to have the highest accuracy of 86.3% (HC vs chronic migraine) in all the classification schemes.

Li *et al* (2020)[48] used a new method based on neighbourhood rough set and PCA for feature extraction from resting state functional MR scans. KNN model was most accurate (100%) at binary classification (migraine vs HC) (Table III).

Jorge-Hernandez *et al* (2014)[49] and Meng *et al* (2018)[50] performed feature extraction based on graph theory using fMRI (T1, EPIBOLD) and magnetoencephalogram (MEG) as input variables respectively. After feature extraction, the images were classified into migraineurs vs HCs. In the study by Jorge-Hernandez *et al*, multiple ML algorithms were evaluated (Table III) and the highest accuracy was achieved using ANN (92.86%). In the study by Meng *et al*, an accuracy of 81.25% was achieved using CNN.

Two studies (Garcia-Chimeno *et al* and Chong *et al*) (Table III) employed both clinical data and MRI scans as features for classification and diagnosis of migraine. Garcia-Chimeno *et al* (2017)[51] recruited HCs, subjects with sporadic migraine and chronic migraine with medication overuse. They were administered a set of questionnaires assessing the extent of pain, mental health and IQ, and diffusion tensor MRI. They used three classification algorithms (Table I) and then employed four feature selection algorithms to improve classification accuracy, taking it as high as 98% with SVM and NB.

Chong *et al* (2021)[52] also used a combination of clinical questionnaires and imaging data (T1-weighted and diffusion tensor MRI) for classification, achieving an average accuracy of 97.1% for identifying migraineurs using an LR algorithm (Table III).

Risk of Bias and Applicability Assessment

QUADAS-2 has four domains for risk of bias assessment

(patient selection, index test, reference standard and flow and timing) and three for applicability concerns (patient selection, index test, reference standard) (Fig. 3).

There were a total of four studies (11.8%) with an overall low risk of bias – three of these however, had a high applicability concern in the patient domain[29,30,32]. Holsteen *et al*[31] was the only study which had an overall low-risk of bias as well as low applicability concerns.

Twenty-three out of the 34 studies had 'high'-risk of bias in the patient selection domain as per QUADAS-2, the most frequent cause being a case-control study design. Not mentioning the sampling method or an objective inclusion/exclusion criteria also increase the risk of bias in this domain, as well as raise applicability concerns. Applicability concerns for the present review was considered 'high' in the patient domain if subjects less than 18 years old were included[29,30,32,33].

The studies that did not mention the validation method used for their models were given 'unclear' risk of bias in the index test domain[19-22,38-40,43,48]. Applicability concerns in the index test domain were low for all 34 studies.

The studies that did not mention a recognised reference criteria were considered having 'unclear' risk of bias and applicability concern in the reference standard domain since subjects may have been misdiagnosed as having migraine patients[22,27,28,33,36,39,48-51].

Risk of bias in the flow and timing domain was considered 'unclear' if all subjects were not administered a reference standard or if it was not the same for all[22,36,39,40,49-51].

Discussion

Headache is the most common presenting neurological symptom in primary care[7]. Migraine is a significant contributor to global disease burden and disability. It has a complex pathophysiology which includes channelopathies as well as various neurovascular phenomena and poses a diagnostic dilemma for physicians owing to its varied and non-specific clinical presentation. Some radiological features like small regions of cerebral infarcts and white matter hyperintensities are also seen in other neurological conditions.

AI can help to identify medical data from multiple sources[15]. In recent times, several new diagnostic questionnaires have been validated, e.g., ID Migraine[53], HUNT-4[54], a web-based questionnaire by Min Kim[55] *et al,* etc. Feature selection algorithms can help select clinical attributes from such questionnaires and modalities most relevant in the diagnosis of migraine, as done in the study by Garcia-Chimeno *et al*[51]. AI can reduce inter-observer and intra-observer variation, and save time and effort.

To our knowledge, this is the first systematic review reporting the use of AI in the diagnosis of migraine in adults. Thirty-four papers were included in this review spanning close to a hundred AI models. A meta-analysis was not possible due to marked heterogeneity in study design, input data and reporting of performance parameters.

Two studies in this review reported a best accuracy of 100%- Khayamnia *et al*[33] using clinical attributes in SVM and Li *et al*[48] using fMRI in kNN. In comparison, the highest accuracy among studies using EEG was 93.3% by Akben *et al* (2012)[19]. The two studies (Chong *et al*[52] and Garcia-Chimeno *et al*[51]) which used both clinical data and MRI scans for classification of migraine got accuracies as high as 97.06% and 98% respectively.

The median accuracy achieved by the studies included in this review was highest for those employing radiological data (92.13%) and lowest for those using clinical attributes (81%) for diagnosing migraine. However, it must be noted that all studies with low-risk of bias used clinical data for diagnosis. This highlights the need for developing and training of more models using clinico-demographic or questionnaire-based data since that is the primary mode of migraine diagnosis currently[8] and also the most viable diagnostic avenue to be pursued; considering patient convenience and expenses incurred, and the lack of availability of other modalities; especially in low-resource settings.

There is increasing interest in the possible applications of AI in the field of medicine. However, its application comes with challenges. Most studies in this review employed relatively small data sets whereas the development of an accurate algorithm relies on larger ones. Thus, we recommend use of bigger, more diverse data sets. Additionally, the AI models developed should be open source to make external validation possible. These measures will boost accuracy and ensure generalisability. Further, systematic and uniform reporting should be ensured to minimise omission of important information. Appropriate study designs should be employed to reduce risk of bias and increase reliability of the conducted studies. The need of the hour is to develop a model for the integration of AI in workflow. Such recommendations were made by only two studies in our review[27,36].

AI models have the potential to minimise inequalities in healthcare. However, developing countries face a unique challenge in terms of the application of this new technology in low-resource settings. Training of clinicians would also be required to be able to use this technology effectively. In order to address these issues and other potential challenges, more studies need to be conducted in such settings, with use of indigenous datasets.

There also exist ethical concerns regarding ownership and use of the data for developing AI models. These concerns should be addressed by developers of the software and all stakeholders.

Strengths of this review

All English-language peer-reviewed articles from across the world were included in this review. Clinical setting for patient selection was not a bar in the inclusion or exclusion of a study. Many types of models (Fig. 1) using various types of input data were assessed. Risk of bias for the included studies was assessed using the standardised QUADAS-2 tool.

Limitations of this review

A quantitative synthesis of results was not possible due to the heterogeneity, high-risk of bias and small sample size of a significant number of studies included in this review. Accuracy was chosen as the primary outcome measure as other metrics were reported infrequently. However, accuracy may be influenced by the quality of the dataset. We excluded studies that were not in the English language and thus may have missed out on some potentially significant findings reported in these articles. Rarer forms of migraine and subjects below the age of 18 years, though a small subset, were not included in our review.

Other uses of AI in Migraine

AI has also been employed in other aspects of migraine like delineation of pathophysiology, prognostication, pharmacotherapy and cost analysis[56–58]; but these studies were beyond the scope of the present systematic review.

Conclusion

This review aims to highlight recent advances in the diagnosis of migraine using machine learning. It is a step towards building comprehensive data driven diagnostic models for migraine. Future studies should use larger, more diverse samples to achieve greater accuracy and generalisability while paying attention to ethical implications. Concerted efforts are necessary to ensure that these models progress from their current experimental status to the point of deployment in actual clinical settings to improve patient care.

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ORIGINAL ARTICLE

JIACM 2024; 25 (3): 100-05

Serum Magnesium as a Prognostic Indicator in the Intensive Care Unit

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Introduction

Magnesium is present in the intracellular fluid of all living cells and is the second most plentiful intra cellular cation after potassium. It is a co-enzyme for several enzymes and is essential for energy metabolism, regulation of cellular pathways and synthesis of DNA and RNA. So, magnesium abnormalities are likely to have an impact on morbidity and mortality in critically ill patients, but often go undiagnosed in the intensive care unit (ICU)[1-4].

Hypomagnesaemia is expected to develop in 20% to 65% of critically ill patients[3]. It is often associated with other electrolyte abnormalities such as hypokalaemia, hypocalcaemia and hypophosphataemia[2-5]. Factors contributing to magnesium deficiency in critical care settings are reduced absorption due to altered gastrointestinal activity, malnutrition, renal loss and diabetes[3,6-14].

Magnesium abnormalities in critically ill patients have been found to cause an increased requirement for ventilatory support because hypomagnesaemia causes muscle weakness and respiratory failure which leads to difficulty in weaning patients from the ventilator[1-14]. Hypomagnesaemia is found to be an important predictor of poor patient outcome in critically ill patients[15].

Hence, in an ICU set up, monitoring of serum magnesium levels along with other electrolytes could have an important prognostic as well as therapeutic implication[1,13-14,16].

Objectives

To determine serial values of serum magnesium in critically ill patients and correlate them with:-

a. Severity of illness as assessed by the Sequential Organ Failure Assessement (SOFA) score.

b. Outcome of the patient in terms of duration of ICU stay, need and duration of mechanical ventilation and mortality.

Material and Methods

A prospective observational study was carried-out in the medical ICU at Nizam's Institute of Medical Sciences over a period of one year from December 2021 to November 2022 after approval from the institutional ethics committee. A total of 83 patients in the age group 18 to 70 years were included in the study. After taking informed consent, the data of each patient was collected in a proforma which included age, gender, detailed history and examination.

Specifically, patients were assessed and followed-up for:-

1. SOFA Score (Table I)
2. Length of stay in ICU
3. Need for ventilatory support
4. Duration of ventilatory support
5. Outcome in terms of mortality

Serum magnesium levels were estimated by COBAS C501 clinical chemistry analyser. Other relevant investigations were carried-out based on the clinical condition of the patient.

Patients with renal failure with serum magnesium more than 4 mg/dL and patients on magnesium supplementation before admission into acute medical care unit were excluded from our study.

Statistical Analysis

Data was entered in MS excel and analysed using Stata 13 and Epi info. Data was analysed by mean, standard deviation, Chi-square test. A p value of <0.05 was considered statistically significant. In this study 95% confidence interval was employed.

Correlation between serum magnesium levels and mortality, mechanical ventilator support, duration of stay in ICU, and SOFA score were assessed by chi-square test. Receiver operating characteristic (ROC) curve analysis was done to assess diagnostic performance of serum magnesium levels in predicting requirement of mechanical ventilation and outcome of the patient in terms of mortality.

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Table I: Assessing the sequential organ failure assessment (SOFA) score of the patient[17].

	0	1	2	3	4
Glasgow Coma Scale Score	15	14 - 13	12 - 10	9 - 6	Less than 6
p02/fio2 mmHg	>400	<400	<300	<200	<100
Platelet Count (lac/mm)	>1.5	<1.5	<1	<0.5	<0.2
Serum Bilirubin (mg/dL)	<1.2	1.2 - 1.9	2 - 5.9	6 - 11.9	>12
Cardiovascular (vasopressor dosage in ug/kg/min)	MAP >70 mmHg	MAP <70 mmHg	Dopamine <5, or dobutamine (any dose)	Dopamine >5, or epinephrine < 0.1, Norepinephrine < 0.1	Dopamine >15, or epinephrine >0.1, or Norepinephrine >0.1
Serum creatinine	<1.2	1.2 - 1.9	2 - 3.4	3.5 - 4.9	>5
Urine output (mL/d)				<500	<200

Results

A total of 83 patients were included in the study. 47 (56.6%) were males and 36 (43.4%) were females. The mean age (Years) was 48.64 ± 16.40 years. Baseline characteristics are given in Table II.

Table II: Patient characteristics in the study.

Characteristics	
Age (mean)	48.64 ± 16.40 years
Gender	
Males	47 (56.6%)
Females	36 (43.4%)
Comorbid conditions	
Diabetes mellitus	29 (34.9%)
Hypertension	30 (36.1%)
Coronary artery disease	10 (12.0%)
Primary medical conditions	
Sepsis	45 (54.2%)
Heart failure	18 (21.7%)
Acute pancreatitis	5 (6%)
Diabetic ketoacidosis	8 (9.6%)
Pneumonia	10 (12%)
Duration of ICU stay	
Mean (SD)	9.81 (6.50) days
Median	7 days
Range	2 - 40 days
Mechanical ventilation (MV) requirement	39 (47%)
Duration of MV requirement	
Mean (SD)	7.90 (5.90) days
Median	6 days
Range	2 - 34 days
Outcome	
Discharge	55 (66.3%)
Mortality	28 (33.7%)

Hypomagnesaemia was present in 37 (44.6%) patients and hypermagnesaemia was present in 14 (16.9%) patients. Magnesium level was normal in 32 (38.6%) patients. 2 (2.5%) patients who had normal serum magnesium levels on day 1, developed dysmagnesaemia on day 3 and day 6 respectively. 18 (22.2%) patients, who had abnormal serum magnesium levels on day 1, were found to have normalisation of serum magnesium levels spontaneously.

Hypomagnesaemia was most commonly observed in the age group of 61 - 70 years with a female preponderance. Hypermagnesaemia was most commonly observed in the age group of 61 - 70 years and in male patients.

Among the patients with hypomagnesaemia and hypermagnesaemia on day 1, the mean (SD) SOFA scores were 8.76 (2.88) and 10.29 (3.20) respectively. Mean (SD) SOFA score in those with normal serum magnesium was 3.81 (2.78). This was found to be statistically significant with a p value <0.001 (See Fig. 1).

Among the study subjects with persistent hypomagnesaemia on day 3, the mean SOFA score was 8.28 and it was 10.31 in those with hypermagnesaemia. In contrast, in patients with normal magnesium levels on day 3, the mean SOFA score was 4.59, which was significantly lower. Similar results were seen in patients having persistent hypomagnesaemia and hypermagnesaemia on day 6, where the mean SOFA score was 9.30 and 10.50, respectively, as compared to 6.1 for patients with normomagnesaemia.

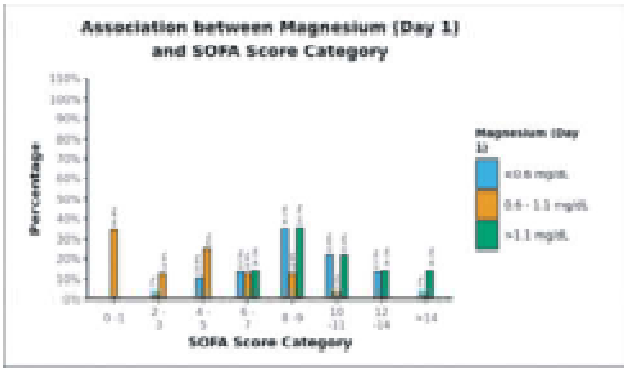

Fig. 1: *Association between SOFA score and serum magnesium levels (day 1).*

The mean duration of ICU stay in the hypomagnesaemia group was 12.30 days and in the hypermagnesaemia group was 11.14 days. The average length of stay for those with normal magnesium was 6.32 days. There was a statistically significant difference between the groups in terms of duration of ICU stay (P value is 0.016).

In our study group, 39 (64.3%) patients required mechanical ventilation. Among these patients, 28 (71.8%) patients had hypomagneasemia, 9 (23%) patients had hypermagnesaemia and 2 (5.12%) patients had normomagnesaemia. There was significant association between Day 1 serum magnesium levels and requirement of mechanical ventilation with a p value of <0.001 (See Fig. 2).

The mean duration of mechanical ventilation requirement was 8.79 days in patients with hypomagnesaemia and 5.89 days in patients with hypermagnesaemia in our study. This was higher than patients with normomagnesaemia whose mean requirement was 4.5 days.

In our study, out of 37 patients with hypomagnesaemia (Day 1), 20 (54.1%) had mortality while 17 (45.9%) were discharged. In those with hypermagnesaemia (Day 1), 6 (42.9%) patients were discharged and 8 (57.1%) patients had mortality. All patients with normal magnesium levels on day 1 recovered. This was statistically significant with a p value of < 0.001 (See Fig. 3).

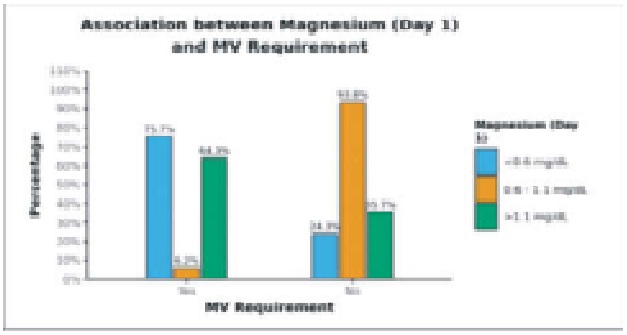

Fig. 2: *Association between serum magnesium levels (day 1) and mechanical ventilation requirement.*

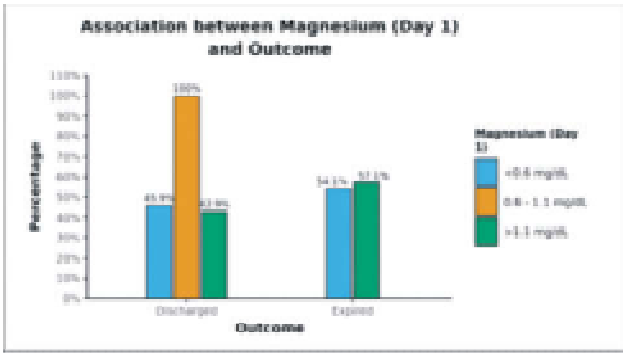

Fig. 3: *Association between day 1 serum magnesium level and outcome.*

We assessed association between trend of serum magnesium levels during ICU stay with outcome of study population in terms of mortality. 32 patients had persistent magnesium abnormalities throughout their stay. Mortality rate in this group was 68.8%. Among the 18 patients whose magnesium levels improved spontaneously, 13 (72.2%) improved and only 5 (27.8%) died. 2 (2.5%) patients who developed dysmagnesaemia on day 3 and day 6 during ICU stay improved. Serum magnesium levels remained normal in 29 (35.8%) patients during ICU stay and all of them were discharged. Thus, we observed a statistically significant association between the trend in serum magnesium levels and outcome in our study. (p value is <0.001) (See Fig. 4).

ROC curve analysis was done to assess diagnostic performance of serum magnesium levels in predicting mechanical ventilation requirement and outcome in terms of mortality. In our study we observed that serum magnesium levels on days 1, 3 and 6 at a cut-off values of </= 0.59 mg/dL, </= 0.61mg/dL and </= 0.59 mg/dL had sensitivity of 72%, 68% and 53% and specificity of 82%, 77% and 86% in predicting mechanical ventilation requirement. Day 1 and day 3 serum magnesium levels (<0.59 mg/dL and <0.61mg/dL respectively) significantly predicted mechanical ventilation requirement.

We observed that serum magnesium levels on days 1,3 and 6 at cut-off values of </= 0.57 mg/dL, </= 0.60 mg/dL and </= 0.6 mg/dL had sensitivity of 61%, 70% and 65% and specificity of 82% , 70% and 72 % in predicting mortality. Day 3 serum magnesium level was more sensitive than day 1 and day 6 serum magnesium levels in predicting the outcome in terms of mortality.

In our study we evaluated the association between serum magnesium abnormalities and co-morbid conditions in the study population. The prevalence of hypomagnesaemia was 48% and 46.6% in study subjects with diabetes mellitus and hypertension, respectively. Whereas the prevalence of hypermagnesaemia was 10% and 16% in study subjects

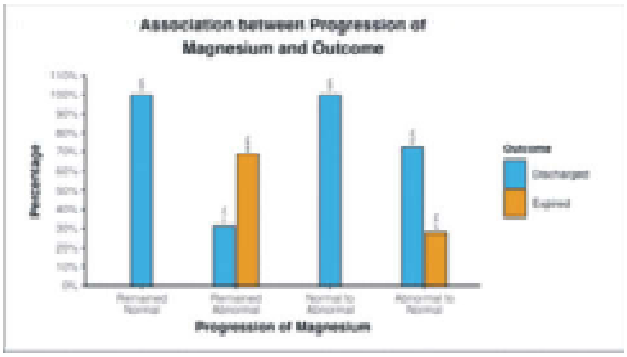

Fig. 4: *Association between trend of serum magnesium levels during ICU stay and outcome of study population.*

Table III: Comparison of present study with similar studies.

Study	Mortality Rate		Mean Duration of stay (Days)		
	HypoMg	HyperMg	NormoMg	HypoMg	HyperMg
	NormoMg	HypoMg	HyperMg	NormoMg	HypoMg	HyperMg	NormoMg
Present Study	54.1%	57.1%	25%	12.3	11.4	6.34
	71.7%	23.2%	5.1%	8.76	10.29	3.81
R Sudha *et al*[19]	39%	-	25%	-	-	-
	60%	-	43%	-	-	-
Safavi *et al*[13]	55%	-	35%	9.16	-	5.71
	58.6%	-	41.4%	10.8	10.8	7.58
Tasnuva Saiful *et al*[18]	37.5%	25%	20%	7.45	8.67	6.83
	-	-	-	-	-	-
Gonuguntla *et al*[20]	51.3%	23.1%	29.3%	Did not vary	Did not vary	High
	Did not vary	High	Low	High	High	Low
	High					

Note: HypoMg - Hypomagnesaemia; HyperMg - Hypermagnesaemia; NormoMg - Normomagnesaemia; SOFA - Sequential Organ Failure Assessment.

with diabetes mellitus and hypertension. This was found to be higher than patients with other co-morbidities but was not statistically significant.

We observed that hypomagnesaemia was more common than hypermagnesaemia in the presence of other electrolyte abnormalities. The prevalence of hypomagnesaemia was higher in patients with hyponatraemia, hypokalaemia, hypercalcaemia and hypophosphataemia. Whereas the prevalence of hypermagnesaemia was higher in the study subjects with hyperkalaemia, hyperphosphataemia and hypocalcaemia.

Discussion

In our study, out of 83 patients admitted in ICU, hypomagnesaemia was present in 44.6% patients, hypermagnesaemia was present in 16.9% patients and in 38.6% of the patients the serum magnesium levels were normal. Similarly, in studies done by Saiful *et al*[18] and Sudha *et al*[19], the prevalence of hypomagnesaemia was 53.33% and 45%, respectively. Prevalence of hypermagnesaemia was 13.33% and 6%, respectively. Normomagnesaemia was seen in 33.33% and 49% of the patients, respectively.

Hypomagnesaemia was most commonly observed in the age group of 61 - 70 years with a female preponderance. Hypermagnesaemia was most commonly observed in the age group of 61 - 70 years and in male patients in our study. These findings were in contrast to those in a study by Saiful *et al*[18], where hypomagnesaemia and hypermagnesaemia were mostly observed in patients above 70 years of age and more commonly in males. In a study by Sudha *et al*[19] hypomagnesaemia was prevalent mostly in age group of 51 - 60 years.

Our study showed that patients in ICU with hypomagnesaemia at admission had a mean SOFA score of 8.76 and those with hypermagnesaemia had a mean SOFA score of 10.29. These findings, when compared to patients with normal magnesium levels at admission, in whom the mean SOFA score was 3.81, were found to be significantly higher (p value <0.05). In our study we found that patients who had hypomagnesaemia and hypermagnesaemia at admission in ICU , as well as persistent dysmagnesaemia on day 3 and 6, had higher SOFA scores when compared with patients with normal magnesium levels, thus predicting a higher mortality rate in patients with serum magnesium abnormalities. This is in accordance with the study by Safavi *et al*[13] which showed higher mean SOFA score (10.8) in both hypomagnesaemia and hypermagnesaemia group when compared with patients with normal magnesium levels (7.58). A study in the Indian scenario by Gonuguntla *et al*[20], found that patients with hypomagnesaemia had higher SOFA scores than those with normal magnesium levels. However, in contrast with our study, they found that mean SOFA scores in patients with hypermagnesaemia were lower than those with normomagnesaemia.

Our study showed that mortality rate was higher in patients with hypomagnesaemia and hypermagnesaemia, that is 54.1% and 57.1%, respectively. Gonuguntla *et al*[20] had similar mortality (51.3%) in their patients with hypomagnesaemia but had lower mortality (23.1%) in their patients with hypermagnesaemia.

Unique to our study is the serial measurement of serum magnesium levels on days 3 and 6. Thirty-two patients had persistent magnesium abnormalities throughout their stay. Mortality rate in this group was high (68.8%). Among the 18 patients whose magnesium levels improved, 13 (72.2%) recovered and only 5 (27.8%) died. This was statistically significant with a p value of less than 0.001. These results suggest the importance of frequent monitoring of serum magnesium levels to assess the prognosis of patients admitted in ICU and the necessity to correct abnormal serum magnesium levels in these patients, however further intervention studies on magnesium correction in ICU patients are required.

In our study , the mean duration of ICU stay was 12.30 days and 11.14 days in study subjects with hypomagnesaemia and hypermagnesaemia, respectively, which was significantly higher when compared to patients with normal

magnesium levels, in whom, the mean duration of ICU stay was 6.34 days. This was in concordance with the results of a study done by Saiful *et al*[18] and Safavi *et al*[13] . Gonuguntla *et al*[20] had similar results with hypomagnesaemia patients requiring a longer ICU stay but not with hypermagnesaemia patients.

Patients with serum magnesium abnormalities – hypomagnesaemia and hypermagnesaemia had higher requirement of mechanical ventilation support as well as longer duration of mechanical ventilation. This observation could be due to respiratory muscle weakness and respiratory failure[1-14]. These results were in line with the results of a study done by Sudha *et al*[19] Safavi *et al*[13].

Our study showed that patients with hypomagnesaemia and hypermagnesaemia had a mean duration of mechanical ventilation requirement for 8.79 days and 5.89 days, respectively. The mean duration of mechanical ventilation requirement was 4.5 days in patients with normal serum magnesium levels, which was significantly lower when compared to patients with dysmagnesaemia. These results were consistent with the results of similar studies done by Safavi *et al*[13] and Munoz *et al*[21] which showed a longer duration of mechanical ventilation support in study population with hypomagnesaemia. In a study done by Sudha *et al*[19] patients with hypomagnesaemia and hypermagnesaemia had longer duration of mechanical ventilation requirement (See Table III).

In our study, we found day 1 serum magnesium level had more sensitivity and was the best parameter in terms of diagnostic accuracy in predicting mechanical ventilation requirement when compared to day 3 and 6 serum magnesium levels. Day 1 serum magnesium level was the best parameter in terms of diagnostic accuracy in predicting mortality. Day 3 serum magnesium level was more sensitive than day 1 and day 6 serum magnesium levels in predicting mortality.

Our study showed a higher prevalence of serum magnesium abnormalities in patients with diabetes mellitus, hypertension and sepsis but this was not statistically significant.

We also observed that magnesium abnormalities were associated with other electrolytes disturbances especially potassium. Thus, these electrolyte abnormalities should prompt investigation of serum magnesium and correction as required.

Conclusion

Serum magnesium abnormalities are frequently encountered in ICU patients. Both hypomagnesaemia and hypermagnesaemia are associated with higher mortality and morbidity in terms of longer duration of ICU stay and requirement of mechanical ventilation. This is substantiated by the association between dysmagnesaemia and higher SOFA score, which is a known prognostic indicator in ICU patients. Hence, serum magnesium is a simple, economical and accessible investigation that can be used for prognostication in ICU patients.

Furthermore, improving trend of serum magnesium levels is associated with better outcomes suggesting a therapeutic implication.

Limitations

Our study has a limitation of smaller sample size. In this study we measured total serum magnesium levels. Ionized magnesium is a more sensitive test that could have strengthened this study. This study included patients admitted only in medical intensive care unit but not trauma and post-operative patients. This is only an observational study and not an interventional study as serum magnesium levels were not corrected in patients with dysmagnesaemia.

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MEDICAL COUNCIL OF INDIA (MCI)/NATIONAL MEDICAL COMMISSION (NMC) GUIDELINES FOR AUTHORS (AMENDED), 2020

As per notification No. MCI-12(2)/2019-Med. Misc./189334 dated 12 February, 2020 published in Extraordinary Gazette of Govt. of India, the MCI/NMC has made changes to amend the "Minimum Qualifications for Teachers in Medical Institutions Regulations, 1998". These will be part of "Minimum Qualifications for Teachers in Medical Institutions (Amendment) Regulations, 2019" and shall come into force from the date of their publication in the Official Gazette.

1. Original papers, meta-analysis, systematic reviews, and case series that are published in journals included in Medline, Pubmed Central, Citation index, Sciences Citation index, Expanded Embase, Scopus, Directory of Open access journals (DoAJ) will be considered.
2. The author must be amongst first three or should be the Corresponding author.

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ORIGINAL ARTICLE

JIACM 2024; 25 (3): 106-10

Association of HbA1c with Severity and Outcome of Acute Coronary Syndrome in Patients of Type 2 Diabetes Mellitus

Suman Sharma, Akanksha Singh**, Sumit Sharma***, AK Varshney*****

Abstract

Background: Diabetes is a major risk factor for acute coronary syndrome (ACS) and is associated with a poor prognosis in patients with an ACS. This study was conducted to analyse the association of HbA1c with severity of ACS in diabetic patients and the outcome post-ACS.

Material and Methods: Study was conducted at Department of Medicine and Cardiology in PGIMER, Dr Ram Manohar Lohia Hospital, New Delhi from November 2012 to February 2014. Consecutive diabetic patients who had ACS were selected. Study group consisted of 60 patients. Severity of ACS and the outcome post-ACS were analysed in different groups according to HBA1c levels. Severity of ACS was analysed by Killip class, TIMI score, 2D-ECHO findings and coronary angiography. Outcomes included in-hospital events (arrhythmias, CHF, pulmonary oedema, hypovolemic shock, reinfarction), re-hospitalisation and mortality within hospital stay and within one month of event. Statistical software package SPSS version 20.0 was used for analysis of data.

Results: Patients were divided into 2 groups according to HbA1c level, i.e., group 1 with HbA1c <8.5% and group 2 with HbA1c ≥8.5%. Severity of ACS was assessed by Killip classification, TIMI score and coronary angiography. In HbA1c group 2, the proportion of patients with Killip class 4 (45%) were significantly more in comparison to proportion of patients (5%) in HbA1c group 1 (p value <0.001). The proportion of patients with high-risk TIMI were significantly more in HbA1c group 2 (95%) in comparison to HbA1c group 1 (22.5%) (p value <0.001). The proportion of patients in HbA1c group 2 who had complications (85%) were significantly more in comparison to proportion of patients (27.5%) with complications in HbA1c group 1 (p value <0.001). In HbA1c group 2, the proportion of patients (45%) with re-hospitalisation/death within 1 month of event were significantly more in comparison to proportion of patients (17%) with re-hospitalisation/death in HbA1c group 1 (p value - 0.023).

Conclusion: In conclusion, HbA1c was an independent factor influencing the severity of ACS. Poor control of diabetes as shown by higher levels of HbA1c is associated with higher severity of ACS and more complications post-ACS.

Key words: Diabetes, acute coronary syndrome, HbA1c.

Introduction

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia, together with impaired metabolism of glucose and other energy-yielding fuels such as lipids and proteins. The number of people suffering from diabetes mellitus worldwide is increasing at an alarming rate, with a projected 366 million in 2030 in comparison to 191 million in 2000[1].

Diabetes is associated with both microvascular and macrovascular complications. Macrovascular complications start taking place long before the symptoms of diabetes appear[2]. It accelerates the process of atherosclerosis by the formation of advanced glycation end products, which increases endothelial dysfunction[3].

Hyperglycaemia is an independent risk factor for acute coronary syndrome syndrome (ACS)[4]. The term ACS includes ST elevation myocardial infarction, Non-ST elevation myocardial infarction and unstable angina. Epidemiologic evidence indicates that diabetes is a major risk factor for ACS and its burden contributed by diabetes is on the rise[5]. People with type 2 diabetes have a two-fold increased risk of ACS within the first five years of diagnosis, in comparison to the general population[6].

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The risk of having ACS in diabetic patients is equal to the risk in a non-diabetic individual having previous ACS[7]. The risk of death from coronary heart disease associated with type 2 diabetes is about 50 per cent more in women than in men[8].

Diabetes is associated with a poor prognosis in patients with an ACS having more acute glycometabolic disturbances which imparts a negative impact on outcome[9].

Thus, this study was conducted to assess the severity of ACS in diabetic patients and the outcome post-ACS.

The objectives of this study were: 1) To measure HbA1c in type 2 diabetes mellitus patients having a first episode of ACS, 2) Assessment of severity of ACS in patients of type 2 diabetic patients, 3) To study outcomes of ACS in type 2 diabetes patients.

Material and Methods

The study was conducted at Departments of Medicine and Cardiology in PGIMER, Dr Ram Manohar Lohia Hospital, New Delhi from November 2012 to February 2014. Consecutive ACS patients were selected from the patients attending the Medicine or Cardiology departments at Dr RML Hospital, New Delhi. The study group consisted of 60 patients. Valid written informed consent was taken from all patients prior to inclusion in the study.

Inclusion criteria was newly or previously diagnosed type 2 diabetes patients having first episode of ACS.

Exclusion criteria were: 1) Previous history of congestive heart failure, 2) Recurrent episode of ACS, 3) Congenital heart disease or known cardiomyopathy. 4) Valvular heart disease. 5) Patient with known systolic dysfunction (LVEF <50%). 6) Echo findings of old scar or previous wall motion abnormality.

Acute myocardial infarction was diagnosed when symptoms were consistent with increase in cardiac enzymes – creatine kinase MB fraction >2 times upper limit of normal range or total creatine phosphokinase >2 times upper limit of normal range and/or positive troponin I or T results. ST segment elevation acute myocardial infarction was defined as persistent ST-segment elevation of ≥1 mm in 2 contiguous electrocardiographic leads or the presence of a new left bundle branch block in the setting of positive cardiac enzyme results.

Non-ST-segment elevation myocardial infarction was defined as occurrence of acute myocardial infarction in the setting of positive cardiac enzyme results with or without accompanying electrocardiographic changes other than ST-segment elevation[11].

Unstable angina was defined as cardiac enzymes negative for myocardial infarction and electrocardiographic changes: transient ST-segment elevation of ≥1 mm in 2 contiguous leads; ST-segment depression of ≥1 mm; new T-wave inversion of ≥1 mm; or pseudo normalisation of previously inverted T-waves[11].

Measurement of HbA1c was done according to the method used in our hospital. Bayer's $A1_c$ NOW$^+$ Monitor kit was used to assess HbA1c level.

Left ventricular ejection fraction was calculated by 2D-echocardiography and was assessed by modified Simpson's method from apical two chamber and four chamber views. LVEF was stratified as - 45 to 55% (mild), 35 to 45% (moderate), <35% (severe) dysfunction[12].

The severity of ACS was studied in the form of single vessel, double vessel or triple vessel disease, Killip13 class and TIMI score.

Killip classification was done as follows: class 1- no CHF, class 2-rales and /or increased JVP, class 3-acute pulmonary oedema, class 4-cardiogenic shock.

Outcomes studied included in-hospital events (arrhythmias, CHF, pulmonary oedema, hypovolemic shock, reinfarction), re-hospitalisation and mortality doing hospital stay and within one month of the ACS event.

Statistical analysis

All the data collected was entered in MS-Excel and statistical software package SPSS version 20.0 was used for analysis of data. Chi square test and Fischer exact test was used as test of association for qualitative variables. Statistical significance was accepted RA $p \leq 0.05$.

Results

Total patients included in the study were 60. A total of 37 (61.7%) patients were male and 23 (38.3%) were female. A total of 78% subjects were already diagnosed cases of diabetes and 21.7% subjects were newly diagnosed at the time of the event.

Patients were divided into 2 groups according to HbA1c level ie group 1 with HbA1c <8.5% and group 2 with HbA1c ≥8.5%.

Fig. 1 Shows distribution of patients according to age.

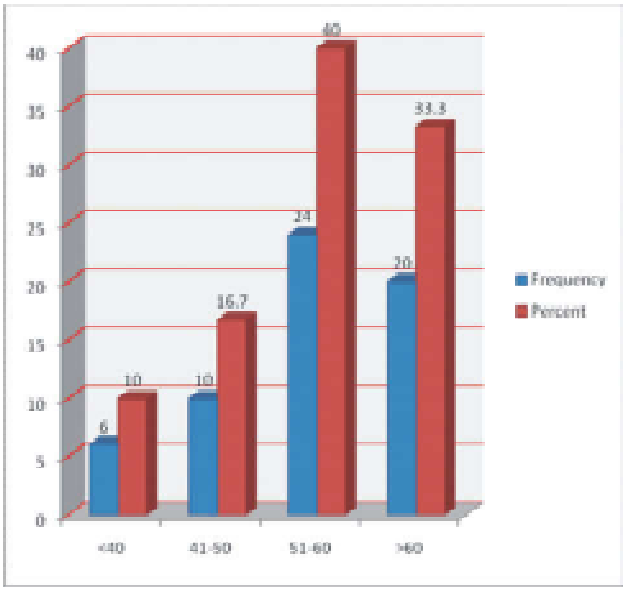

Fig. 1: *Distriution of patients according to age (n = 60).*

Table I: Association of HbA1c levels with Killip class (N = 60).

Killip class	HbA1c group 1 (<8.5%)	HbA1c group 2 (≥8.5%)	p value
1	22 (55%)	1 (5%)	**<0.001**
2	10 (25%)	6 (30%)	
3	6 (15%)	4 (20%)	
4	2 (5%)	9 (45%)	
Total	40	20	

Pearson's chi-square test.

Table I shows the association of HbA1c with Killip class. In HbA1c group 2 (i.e., HbA1c ≥8.5%), the proportion of patients in Killip class 4 (45%) were significantly more in comparison to proportion of patients in Killip class 4 in HbA1c group 1 (HbA1c less than <8.5%), i.e., 5%. (p value = <0.001).

Table II: Association of levels of HbA1c with TIMI score (N = 60).

TIMI score	HbA1c Group 1	HbA1C Group 2	p value
Low-risk (<4)	31 (77.5%)	1 (5%)	**<0.001**
High-risk (>4)	9 (22.5%)	19 (95%)	
Total	40	20	

Fischer's exact test.

Table II shows association of TIMI score with HbA1c. The proportion of patients with high-risk TIMI were significantly more in HbA1c group 2 (95%) in comparison to HBA1c group 1 (22.5%) (p value = <0.001).

Table III: Association of HbA1c with LVEF finding on 2D-ECHO (N = 60).

LVEF	HbA1c Group 1	HbA1c Group 2	p value
>55% (normal)	1 (2.5%)	1 (5%)	**0.002**
45 to 55% (mild)	1 (5%)	6 (30%)	
35 to 45% (moderate)	21 (52.5%)	11 (55%)	
<35% (severe)	17 (42.5%)	2 (10%)	
Total	40	20	

Fischer's exact test.

Table III shows association of HbA1c with LVEF finding on 2D-ECHO. Ejection fraction categories were divided in following way- EF >55% (Category 1), 45 - 54.9% (Category 2), 35 - 44.9% (Category 3) and <34.9% (Category 4). Maximum proportion of patients had LVEF of 35 - 45% in both HbA1c groups (p value: 0.002).

Table IV: Association of HbA1c with distribution of arrhythmia in study group (N = 60).

Arrythmia	HbA1c group 1	HbA1c group 2	p value
No	38 (95%)	13 (65%)	**0.004**
Yes	2 (5%)	7 (35%)	
Total	40	20	

Fischer's exact test.

Table IV shows association of HbA1c with arrhythmia events. Bradyarrhythmias and tachyarrhythmias were included in arrythmias. Proportion of patients who had arrhythmia in HbA1c group 2 (35%) were significantly more than proportion of patients in HbA1c group 1 (5%) who had arrhythmia (p value = 0.004).

Table V: Association of HbA1c with number of coronary vessels involved (findings of coronary angiography) (N = 60).

No. Of Coronaries involved	HbA1c Group 1	HbA1c Group 2	p value
0	1 (2.5%)	1 (5%)	**<0.001**
1	25 (62.5%)	0	
2	9 (22.5%)	11 (55%)	
3	5 (12.5%)	8 (40%)	
	40	20	

Fischer's exact test.

Table V shows association of HbA1c with number of coronary vessels involved on coronary angiography. In HbA1c group 2, maximum proportion of patients had double vessel disease (55%). Whereas in HbA1c group 1, maximum proportion of patients had single vessel disease (62.5%). The results were statistically significant (p value - <0.001).

Table VI: Association of HbA1c with complications occurring post-ACS (N = 60).

Complications	HbA1C group 1	Hba1c group 2	p value
No	29 (72.5%)	3 (15%)	**<0.001**
Yes	11 (27.5%)	17 (85%)	
	40	20	

Fischer's exact test.

Table VI shows association of HBA1c with complications that occur post-ACS. Heart block, cariogenic shock, heart failure etc were included as complications post-ACS. The patients who had at least one complication were included in the category of complication post-ACS.

The proportion of patients in HBA1c group 2 who had complications (85%) were significantly more in comparison to proportion of patients (27.5%) with complications in HbA1c group 1 (p value = <0.001).

Table VII. Association of HBA1c with outcomes of ACS within one month of event (N = 60).

Events	HbA1c group 1	HbA1c group 2	p value
No rehospitalisation/death within 1 mth	33 (82.5%)	11 (55%)	**0.023**
Rehospitalisation/death within one mth	7 (17.5%)	9 (45%)	
	40	20	

Pearson's Chi-square test.

Table VII shows association of HbA1c with outcomes of ACS within one month of event.

Outcomes studied were rehospitalisation (due to reinfarctions, arrhythmia, and congestive heart failure) or death post-ACS within one month of event.

In HbA1c group 2 the proportion of patients (45%) with rehospitalisation/death were significantly more in comparison to proportion of patients (17%) with rehospitalisation/death in HbA1c group 1 (p value = 0.023).

One patient died in HbA1c group 2.

Discussion

Total patients included in the study were 60. A total of 37 (61.7%) patients were male and 23 (38.3%) were female. Severity of ACS was assessed by Killip classification, TIMI score and coronary angiography.

In HbA1c group 2, the proportion of patients with Killip class 4 (45%) were significantly more in comparison to proportion of patients (5%) in HbA1c group1. Cubbon *et al*[16] showed similar observation of Killip class in patients with fresh ACS in diabetic patient *versus* non-diabetic patients with established past history of CVD.

TIMI score depicts risk of mortality in ACS patients and tells severity of event. The proportion of patients with high-risk TIMI were significantly more in HbA1c group 2 (95%) in comparison to HbA1c group 1 (22.5%).

Maximum proportion of patients had LVEF of 35 - 44% in both HBA1c groups. Vinita *et al*[17] also had similar finding in patients with acute cardiac stress, i.e., LVEF <50% was seen more in diabetics with HbA1c ≥7% in comparison to diabetics with HBA1c <7% (<0.0001).

In HbA1c group 2, maximum proportion of patients had double vessel disease (55%). Whereas in HbA1c group 1, maximum proportion of patients had single vessel disease(62.5%). In study conducted by Vinita *et al*[17] amongst patients with acute cardiac stress, triple vessel disease was seen in a significantly higher proportion of patients with poor glycaemic control (HbAlc > or = 7%) compared to patients with HbAlc level <7% (p value <0.001).

Post-ACS outcomes were analysed by inhospital events (arrhythmias, CHF, pulmonary oedema, hypovolaemic shock, reinfarction), rehospitalisation and mortality within hospital stay and within one month of event.

The proportion of patients in HbA1c group 2 who had complications (85%) were significantly more in comparison to proportion of patients (27.5%) with complications in HbA1c group 1. Complications like re-infarction were also seen more in diabetics with HbA1c ≥7% in study done by Vinita *et al*[17] (p value <0.032). Vinita *et al*[17] also showed that complications like heart failure was also seen more in diabetics with HbA1c ≥7% (p value <0.001).

In HBA1c group 2, the proportion of patients (45%) with re-hospitalisation/death were significantly more in comparison to proportion of patients (17%) with rehospitalisation/death in HbA1c group 1.

The strength of our study was that we studied both clinical and imaging laboratory parameters to assess the association of HBA1c with severity and outcome of ACS. Limitations of the study were a small sample size and short follow-up period.

In conclusion, HbA1c was an independent factor influencing the severity of ACS. Poor control of diabetes as shown by higher levels of HbA1c is associated with higher severity of ACS and more complications post-ACS.

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ANNOUNCEMENT

Mrs. Uma Bansal - Prof. B.C. Bansal Best Paper Award (Journal -2024)

Best Original Article – "Evaluation of Platelet Indices with Uncomplicated Essential Hypertension"- Dr. Aanchal Mangal, Dr. Yad Ram Yadav, Dr. Pawan Kumar, Dr. Sanjiv Maheshwari, Department of General Medicine, Jawahar Lal Medical College, Ajmer - 302015, (Rajasthan).

Best Review Article – "Hydroxychloroquine in Obstetrics: Newer Perspectives" – Dr. Nazia Parveen, Dr. Sandhya Jain, Department of Obstetrics and Gynaecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110095.

Best Case Report – "The Bug Story: Melioidosis with Candidaemia" – Dr. Anusha Uddandam, Dr. Nandakrishna B, Dr. Vasudev Acharya, Dr. Cynthia Amrutha Sukumar, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal – 576104 (Karnataka).

ORIGINAL ARTICLE

JIACM 2024; 25 (3): 111-15

Cardiac Manifestations in Patients with Dengue Fever: A Prospective Study at a Tertiary Care Centre in Western Uttar Pradesh

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Abstract

Background: Dengue fever, a mosquito-borne viral infection, can lead to significant cardiac complications. This study aimed to investigate the prevalence, characteristics, and clinical significance of cardiac manifestations in dengue patients at a tertiary care centre.

Methods: We conducted a prospective observational study on 385 confirmed dengue patients admitted to our institution. All patients underwent clinical evaluation, electrocardiography, and echocardiography. Cardiac biomarkers were measured in patients with suspected myocardial involvement.

Results: Cardiac manifestations were observed in 100 patients (26%, 95% CI: 21.7 - 30.3%). The most common findings were sinus bradycardia (12%), myocarditis (8%), and pericardial effusion (4%). Elevated cardiac biomarkers were found in 6% of patients. Severe dengue cases had a higher incidence of cardiac involvement compared to non-severe cases (42% vs. 20%, p <0.001). Patients with cardiac manifestations had longer hospital stays (median 7 days versus 5 days, p <0.001).

Conclusion: Cardiac manifestations are common in dengue fever, with approximately one-fourth of patients showing some form of cardiac involvement. Close cardiac monitoring is crucial, especially in severe dengue cases, to improve patient outcomes.

Key words: Dengue, sinus bradycardia, myocarditis, pericardial effusion.

Introduction

Dengue fever, caused by the dengue virus (DENV), is a major global health concern affecting millions of people annually[1,2]. The World Health Organisation (WHO) estimates that 390 million dengue infections occur each year, with about 96 million manifesting clinically[3]. While traditionally known for its haematological complications, growing evidence suggests significant cardiac involvement in dengue patients[4-6].

The dengue virus, a member of the Flaviviridae family, consists of four distinct serotypes (DENV-1 to DENV-4), with a potential fifth serotype (DENV-5) identified in 2013[7]. Infection with one serotype provides lifelong immunity against that particular serotype but only partial and temporary protection against other serotypes. Secondary infection with a different serotype often leads to more severe disease manifestations[1].

The spectrum of cardiac manifestations in dengue ranges from subtle electrocardiographic changes to severe myocarditis and even fulminant heart failure[8,9]. Recent studies have reported varying prevalence rates of cardiac involvement in dengue, ranging from 15% to 50%[10-13]. This wide range may be attributed to differences in study populations, severity of dengue cases, and diagnostic criteria used for cardiac involvement.

The pathogenesis of cardiac involvement in dengue is not fully understood but is thought to involve multiple mechanisms. These include direct viral invasion of cardiomyocytes, cytokine-mediated injury, immune-mediated mechanisms, and metabolic disturbances[1,14]. The expanded dengue syndrome, a term coined to describe atypical manifestations of dengue, includes various cardiac complications such as myocarditis, pericarditis, and arrhythmias[15].

Despite the growing recognition of cardiac involvement in dengue, the exact burden and characteristics of cardiac manifestations remain unclear, particularly in tertiary care settings where more severe cases are managed. Furthermore, the clinical significance of these cardiac manifestations, in terms of patient outcomes and long-term prognosis, is not well established.

This study aimed to investigate the prevalence, types, and clinical significance of cardiac manifestations in patients with dengue fever admitted to a tertiary care centre. By providing a comprehensive assessment of cardiac involvement in dengue, we hope to contribute to improved

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patient management and outcomes.

Material and Methods

Study Design and Setting: We conducted a prospective observational study at our hospital which is a tertiary care centre. The study included 385 patients aged ≥18 years with laboratory-confirmed dengue infection. Dengue was confirmed by either positive NS1 antigen or IgM antibody test. Patients with pre-existing cardiac conditions such as coronary artery disease, valvular heart disease, or cardiomyopathy were excluded to avoid confounding the assessment of dengue-related cardiac manifestation. The study protocol was approved by the Institutional Ethics Committee (IEC). Written informed consent was obtained from all participants or their legal representatives.

Clinical and Laboratory Evaluation: All patients underwent a detailed clinical examination upon admission and daily thereafter. Patients were classified according to the 2009 WHO dengue classification as non-severe dengue (with or without warning signs) or severe dengue[16].

Laboratory investigations included:

1. Complete blood count (daily)
2. Liver function tests (admission and as clinically indicated)
3. Renal function tests (admission and as clinically indicated)
4. Serum electrolytes (admission and as clinically indicated)
5. Coagulation profile (admission and as clinically indicated)

Cardiac Evaluation: All patients underwent comprehensive cardiac evaluation, which included:

1. 12-lead electrocardiography (ECG): Performed daily during hospitalisation.
2. Transthoracic echocardiograph: Performed on admission and repeated if clinically indicated.
3. Cardiac biomarkers: Troponin I and NT-pro BNP were measured in patients with suspected myocardial involvement based on clinical features, ECG changes, or echocardiographic abnormalities.

Cardiac manifestations were defined as the presence of one or more of the following:

- ECG abnormalities: Sinus bradycardia (heart rate <60 beats per minute), ST-segment or T-wave changes, conduction disturbances, or arrhythmias.
- Echocardiographic abnormalities: Left ventricular systolic dysfunction (ejection fraction <50%), diastolic dysfunction, pericardial effusion, or regional wall motion abnormalities.
- Elevated cardiac biomarkers: Troponin I >99th percentile of the upper reference limit or NT-pro BNP >125 pg/mL.
- Clinical features of heart failure or myocarditis.

Myocarditis was diagnosed based on the presence of at least two of the following criteria:

1. Cardiac symptoms (chest pain, dyspnoea, palpitations).
2. New-onset ECG changes (ST-segment elevation or depression, T-wave inversion, conduction disturbances).
3. Elevated cardiac biomarkers.
4. Echocardiographic evidence of new-onset systolic or diastolic dysfunction.

Data Collection: Demographic data, clinical features, laboratory results, and cardiac evaluation findings were recorded using a standardised case report form. All data were entered into a secure electronic database with double-entry verification to minimise errors.

Statistical Analysis: Assuming a prevalence of cardiac manifestations of 15 - 50% based on previous studies, with a precision of 5% and a confidence level of 95%, the required sample size was calculated to be 385. Data were analysed using SPSS version 25.0. Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) depending on the distribution of data. The chi-square test or Fisher's exact test was used to compare categorical variables between groups (patients with and without cardiac manifestations, severe and non-severe dengue). Student's t-test or Mann-Whitney U test was used for continuous variables, as appropriate. A p-value <0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to identify independent predictors of cardiac manifestations in dengue patients. Variables with a p-value <0.1 in univariate analysis were included in the multivariate model.

Results

Demographics and Clinical Characteristics: Of the 385 patients enrolled, 210 (54.5%) were male, and the mean age was 36.7 ± 14.3 years. According to the WHO classification, 285 (74%) patients had non-severe dengue, and 100 (26%) had severe dengue. The median duration of fever at presentation was 4 days (IQR: 3-5 days) (Table I).

Table I: Demographics and clinical characteristics of the study participants.

Characteristic	Value
Total patients	385
Male	210 (54.5%)
Female	175 (45.5%)
Mean age (years)	36.7 ± 14.3
Non-severe dengue	285 (74%)
Severe dengue	100 (26%)
Median fever duration (days)	4 (IQR: 3-5)

The most common presenting symptoms were fever (100%), headache (82%), myalgia (78%), and arthralgia (65%). Warning signs were present in 180 (46.8%) patients, with abdominal pain (30%) and persistent vomiting (25%) being the most frequent.

Prevalence of cardiac manifestations: Cardiac manifestations were observed in 100 patients (26%, 95% CI: 21.7 - 30.3%). The prevalence was significantly higher in patients with severe dengue compared to non-severe dengue (42% *versus* 20%, p <0.001).

Types of cardiac manifestations: Various cardiac manifestations seen have been mentioned in Table II. Some patients had multiple cardiac manifestations. Sinus bradycardia was the most common ECG abnormality, consistent with previous studies[17,18]. The median heart rate in patients with sinus bradycardia was 54 beats per minute (IQR: 50 - 58).

Table II: Types of cardiac manifestations in Dengue fever.

Manifestation	Frequency
ECG Abnormalities	
Sinus bradycardia	46 (12%)
ST-T changes	19 (5%)
Conduction disturbances	8 (2%)
Arrhythmias	4 (1%)
Echocardiographic Abnormalities	
Left ventricular systolic dysfunction	23 (6%)
Diastolic dysfunction	15 (4%)
Pericardial effusion	15 (4%)
Regional wall motion abnormalities	8 (2%)
Elevated cardiac biomarkers	
Troponin I elevation	19 (5%)
NT-pro BNP elevation	23 (6%)
Clinical myocarditis	31 (8%)

Myocarditis, diagnosed based on clinical features, biomarker elevation, and echocardiographic findings, was observed in 8% of patients. This rate is similar to those reported in other studies[19,20]. Among patients with myocarditis, the mean left ventricular ejection fraction was 42 ± 6%.

Temporal pattern of cardiac manifestations: ECG abnormalities were often observed early in the course of illness, with sinus bradycardia typically occurring between days 3 and 7 of fever. Myocarditis and elevated cardiac biomarkers were more commonly seen during the critical phase (days 4 - 6) or early recovery phase of dengue (Fig.1).

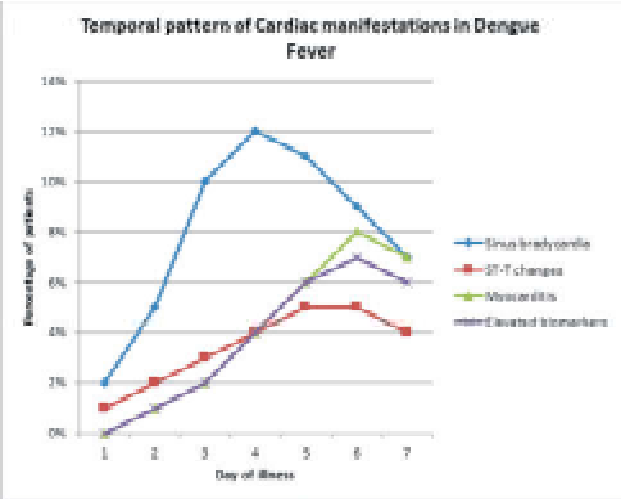

Fig.1: *Temporal pattern of cardiac manifestations in Dengue fever.*

Factors associated with cardiac manifestations: In multivariate analysis, several factors were independently associated with the presence of cardiac manifestations as shown in Table III.

Table III: Factors associated with cardiac manifestations.

Factor	Odds Ratio	95% CI	p-value
Severe Dengue	2.8	1.7 - 4.6	**<0.001**
Age >40 years	1.9	1.2 - 3.0	**0.006**
Presence of warning signs	1.7	1.1 - 2.7	**0.02**
Platelet count <50,000/μL	1.6	1.0 - 2.5	**0.04**

CI: Confidence Interval

Clinical Outcomes: Patients with cardiac manifestations had a longer hospital stay compared to those without (median 7 days *versus* 5 days, p <0.001). Three patients (0.8%) died during the study period, all of whom had severe myocarditis with cardiogenic shock.

Among patients with myocarditis, 26 (84%) showed improvement in left ventricular function at the time of discharge. Five patients (16%) had persistent left ventricular

dysfunction and were scheduled for follow-up echocardiography.

Discussion

Our study found that approximately one-fourth of dengue patients admitted to a tertiary care center experienced cardiac manifestations. This prevalence is consistent with previous studies, which have reported rates ranging from 15% to 50%[10-13]. The wide range in reported prevalence may be due to differences in study populations, severity of dengue cases, and diagnostic criteria used.

Sinus bradycardia was the most common ECG abnormality observed, which aligns with findings from other studies[17,21]. This relative bradycardia in dengue has been attributed to viral-induced autonomic dysfunction[22]. The exact mechanism remains unclear but may involve increased vagal tone or direct effects of inflammatory mediators on the sinoatrial node[21]. ST-T changes were also frequently observed, which could indicate myocardial involvement or electrolyte disturbances common in dengue[21]. These ECG changes were often transient and resolved with clinical improvement. However, their presence should prompt further cardiac evaluation to rule-out more significant myocardial involvement.

Myocarditis was diagnosed in 8% of our patients, which is within the range reported in previous studies[19,20]. The pathogenesis of myocarditis in dengue is not fully understood but may involve direct viral invasion of cardiomyocytes, cytokine-mediated injury, or immune-mediated mechanisms[1,14]. A study by Weerakoon *et al* demonstrated histopathological evidence of myocarditis in fatal dengue cases, supporting the concept of direct viral invasion[22].

The higher prevalence of cardiac manifestations in severe dengue cases (42% *versus* 20% in non-severe cases) underscores the importance of cardiac monitoring in these patients. This finding is consistent with other studies that have reported more frequent and severe cardiac involvement in dengue haemorrhagic fever and dengue shock syndrome[23,24]. The increased cardiac involvement in severe dengue may be related to the more pronounced inflammatory response and endothelial dysfunction seen in these cases[1].

Pericardial effusion was observed in 4% of patients, similar to rates reported in other studies[25,26]. While usually small and self-limiting, pericardial effusions can occasionally be large enough to cause haemodynamic compromise[6]. The development of pericardial effusion in dengue is thought to be related to increased vascular permeability and plasma leakage characteristic of severe dengue[14].

Our study identified several factors associated with an increased risk of cardiac manifestations, including severe dengue, age >40 years, presence of warning signs, and thrombocytopenia. These factors can help clinicians identify patients who may benefit from more intensive cardiac monitoring and earlier intervention.

The temporal pattern of cardiac manifestations observed in our study provides valuable insights into the natural history of cardiac involvement in dengue. The early occurrence of sinus bradycardia suggests that it may be a result of autonomic dysfunction rather than direct myocardial injury. In contrast, myocarditis and elevated cardiac biomarkers were more commonly seen during the critical phase or early recovery phase, possibly reflecting the peak of the inflammatory response and immune-mediated injury.

The majority of patients with myocarditis in our study showed improvement in left ventricular function by the time of discharge. This finding is consistent with other studies that have reported a generally favourable prognosis for dengue-associated myocarditis[19,20]. However, the persistence of left ventricular dysfunction in a small proportion of patients highlights the need for follow-up evaluation to assess for long-term cardiac sequelae.

The mortality rate in our study was low (0.8%), but all deaths occurred in patients with severe myocarditis, underscoring the potential lethality of this complication. This finding is consistent with other studies that have identified myocarditis as a significant risk factor for mortality in dengue[27,28].

Limitations of the study

Our study has several strengths, including its prospective design, large sample size, and comprehensive cardiac evaluation of all patients. However, there are also some limitations to consider. First, our study was conducted at a single tertiary care center, which may limit its generalisability to other settings, particularly primary care or community-based practices. Second, we did not perform cardiac magnetic resonance imaging (CMR), which could have provided more detailed information on myocardial involvement and tissue characterisation. CMR has been shown to be more sensitive than echocardiography in detecting subtle myocardial changes in viral myocarditis[29]. Additionally, we did not conduct long-term follow-up of patients with cardiac manifestations, which would have provided valuable information on the persistence or resolution of cardiac abnormalities. Future studies should consider incorporating CMR and long-term follow-up to address these limitations.

Conclusion

While the prevalence of cardiac manifestations in our cohort of dengue patients was lower than expected, it remains a significant clinical concern affecting approximately one-fourth of patients. The discrepancy between our findings and previous studies highlights the need for further research to understand regional variations and temporal trends in dengue-related cardiac complications. Clinicians should maintain a high index of suspicion for cardiac involvement, particularly in severe dengue cases, and consider routine cardiac evaluation in these patients. Future multi-center studies with standardised definitions and advanced cardiac imaging techniques are needed to better characterise the true burden of cardiac complications in dengue fever.

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ORIGINAL ARTICLE

JIACM 2024; 25 (3): 116-20

Testing the Tormenting Trio-A Study of Thyroperoxidase(TPO) Activity, Serum Ferritin and Thyroid Diseases among Pregnant Women

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Abstract

Background: Limited literature has explored the connection between Hypothyroidism and Iron deficiency anaemia. Some studies have noted that Iron deficiency can reduce thyroid function by reducing Thyroid peroxidase (TPO) enzyme activity[1-4]. None of the studies have been done to evaluate TPO enzyme activity in Hypothyroidism and Iron deficiency anaemia patients except few studies done in rodents[4]. Hence, we tried to do a qualitative and quantitative analysis of TPO enzyme activity among iron deficient hypothyroid, iron deficient euthyroid, iron normal hypothyroid and iron normal euthyroid pregnant women.

Methods: This was a cross-sectional study conducted among 500 pregnant women at JSS Hospital, a tertiary care hospital in Mysuru. Following strict aseptic protocols, approximately 5 mL of venous blood was collected and analysed for levels of Haemoglobin (Hb), Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3), Thyroxine (T4), Anti-Thyroid Peroxidase (Anti-TPO) antibody and Serum Ferritin. Then pregnant women were divided into 4 groups-iron deficient hypothyroid, iron deficient euthyroid, normal iron hypothyroid and normal iron euthyroid pregnant women. Quantitative analysis of TPO enzyme was done by luminometric method for all pregnant women and was compared between above groups.

Results: Out of 500 women, 9 were excluded because of pre analytical error, hence there were 491 pregnant women in the study. Among 491 pregnant women,156 (31.77%) were hypothyroid and 7 (1.42%) had thyrotoxicosis. The results showed that 55% of euthyroid subjects and 61% of hypothyroid subjects had normal levels of serum ferritin, while 44.7% of euthyroid subjects and 38% of hypothyroid subjects had lower levels of serum ferritin. The results did not show any correlation between the serum ferritin levels and thyroid status. Comparative analysis of TPO enzyme activity among iron sufficient and iron deficient euthyroid showed elevated TPO enzyme activity in iron deficient euthyroid subjects. However, among the iron sufficient and iron deficient hypothyroid subjects, the TPO activity was similar. Similarly, comparison between iron deficient euthyroid and hypothyroid also did not show any significant changes in the TPO enzyme activity.

Conclusion: Contrary to expectations, TPO enzyme activity was not reduced in iron-deficient hypothyroid subjects. Further studies are warranted to elucidate the intricate relationship between TPO enzyme activity, serum ferritin levels, and thyroid status among pregnant women, as well as its potential impact on the overall growth and development of the foetus.

Key words: Iron deficiency anaemia, hypothyroidism, ferritin, thyroid peroxidase, thyroid stimulating hormone.

Introduction

Thyroid diseases and iron deficiency anaemia are very common diseases affecting pregnant women worldwide. Despite anaemia occuring frequently with thyroid diseases, it is often underestimated and their relationship is not well understood[1]. Various reasons including decreased erythropoietin production, vitamin B12, folate and concomitant iron deficiency due to decreased absorption from the gut can lead to anaemia among hypothyroid subjects[1].

Thyroperoxidase (TPO) is an essential enzyme responsible for catalyzing the iodination of tyrosine residues within thyroglobulin, thereby facilitating the formation of monoiodotyrosine and diiodotyrosine, which subsequently undergo coupling to produce T3 and T4, namely thyroxine or triiodothyronine[2]. The TPO gene is situated on chromosome 2p25, spanning 17 exons. Transcription of the TPO gene yields a 3kb mRNA, which translates into a 110 kDa glycosylated hemo-protein, known as the TPO enzyme[3]. Initially referred to as thyroid peroxidases (ThOX), this enzyme plays a pivotal role in thyroid hormone synthesis[3].

Iron is an important component of the TPO enzyme and plays a major role in the synthesis and metabolism of thyroid hormones[4]. Deficiency of iron is known to decrease the efficacy of TPO enzyme and affect thyroid hormone metabolism[5]. Maternal and foetal complications occur when pregnant women suffer from these diseases[6,7].

Despite the well-documented relationship between iron

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levels and TPO enzyme activity, no studies, to date, have investigated the activity of TPO in individuals with hypothyroidism and iron deficiency anaemia. Recent research, primarily conducted in rodent models, has aimed to address this gap. Therefore, the current study endeavours to assess TPO enzyme activity among pregnant women categorised into iron-deficient hypothyroid, iron-deficient euthyroid, iron-sufficient hypothyroid, and iron-sufficient euthyroid groups. To the best of our knowledge, this study represents the first attempt to report TPO activity in both euthyroid and hypothyroid human subjects.

Material and Methods

The study was a cross-sectional investigation conducted between January 2018 to June 2020 at JSS Hospital, a tertiary care teaching and research hospital attached to JSS Medical College at Mysuru, Karnataka. Inclusion criteria-pregnant women aged 18 - 45 years (n = 500) in first trimester of pregnancy were recruited into this study. Informed written consent was taken from all women. Ethics clearance was obtained from the Institutional Ethics Committee of JSS Medical College, JSS Academy of Higher Education and Research.

Exclusion criteria-pregnant women who had any past or present history of thyroid dysfunction/disease, family history of thyroid disease, previous head or neck irradiation, usage of drugs such as levothyroxine, methimazole, iodide, lithium, amiodarone and corticosteroids, patients diagnosed with autoimmune and connective tissue diseases. Detailed history and clinical examination were recorded in a clinical proforma.

Venous blood of about 5 mL was drawn under aseptic conditions and subjected for analysis of haemoglobin (Hb), Thyroid stimulating hormone (TSH), Triiodotyrosine (T3), Tetraiodotyrosine (T4), Anti-TPO antibody and Serum Ferritin level. Levels of T3, T4, TSH and AntiTPO Antibody were measured by chemiluminescence method. Serum Ferritin was estimated by Chemiluminescence Immunoassay in Roche COBAS 6,000 integrated analyser. According to American Thyroid Association and National Guidelines[8], a TSH value >2.5 mIU/L but less than or equal to 10 mIU/L with normal T4 was considered to be subclinical hypothyroidism, but, TSH value >10 mIU/L irrespective of T4 concentration, and TSH value >2.5 with low T4 concentration were considered to be overt hypothyroidism. Individuals with a serum ferritin concentration <20 µg/L were considered as iron deficient. Based on the level of serum ferritin and thyroid status (euthyroid or hypothyroid), the pregnant women were divided into 4 groups viz., iron deficient hypothyroid, iron deficient euthyroid, iron sufficient hypothyroid and iron sufficient euthyroid pregnant women.

Quantitative analysis of thyroid peroxidase enzyme: Estimation of TPO activity was carried-out by luminometric method as detailed by Barae Jomaa *et al*[9]. In brief, serum containing 0.1 to 0.2 mg/mL total protein was incubated with 1.0 M glycine-NaOH (pH9.0) and 1.0 mM EDTA for 30 min with gentle shaking at 37 ° C after which the reaction was initiated by the addition of 20 µL of luminol mix containing 1 M glycine-NaOH (pH 9.0), 1 mM EDTA and 400 µM luminol. Following a 4.0 sec delay, 5.0 µL of 80 mM H_2O_2 was added, and the luminescence was measured as relative luminescence units (RLUs) integrated over 10.0 sec using a PerkinElmer Enspire Multimode Plate Reader (luminol kit-Thermoscientific company, USA).

Statistical analysis

Data collected was entered in Microsoft Excel and analysed using GraphPad Prism version 8. Descriptive statistical measures like percentage, mean and standard deviation were calculated. Paired T-test and Two-way ANOVA (confidence interval 95) for subgroups (comparing TPO enzyme activity with thyroid levels and ferritin level > and <50 ng/mL) was used to calculate the statistical significance at 'p' value of <0.05.

Results

Out of 500 subjects in the study, 9 were excluded because of pre-analytical error, hence data of the remaining 491 pregnant women was analysed. Most of them, 403 (82%) were in age group 21 - 30 years, the majority - 363 (74.75%) belonged to the urban category, 481 (98%) were literate, 228 (46%) were primigravida and 263 (53%) were multigravida. 227 (46%) had normal BMI, 107 (21%) were overweight, 65 (12%) were obese and 92 (18%) were underweight.

The mean TSH was 2.37 ± 3.17 mIU/L, mean T3 was 1.45 ± 0.72 ng/dL and mean T4 was 9.29 ± 2.53 µg/dL among 491 pregnant women.

Among the 491 subjects, 335 had normal thyroid levels (euthyroid) while 156 subjects were considered hypothyroid based on the T3, T4 and TSH levels.

Further, 128 (29.22%) had iron deficiency, 82 (18.72%) had iron deficiency anaemia and rest had normal Hb and ferritin.

1. **Serum Ferritin levels in iron-sufficient and iron-deficient euthyroid as well as hypothyroid patients**

   Serum ferritin level of 491 pregnant women was

analysed. Serum ferritin level in euthyroid women ranged from 0.86 µg/L to 282 µg/L. Ferritin levels less than 20 µg/L were considered as iron deficient. Among the 491 subjects, 335 had normal thyroid levels (euthyroid) while 156 subjects were considered hypothyroid based on the T3, T4 and TSH levels. Among the 335 euthyroid subjects, 185 subjects had normal ferritin levels ranging from 20.8 µg/L to 282 µg/L, while 150 subjects had lower levels of ferritin which ranged from 0.86 µg/mL to 20 µg/L. Among the hypothyroid subjects (n = 156) 96 subjects had normal ferritin levels ranging from 20 µg/L to 240 µg/L while 60 subjects had lower levels of ferritin ranging from 1.69 µg/L to 19.97 µg/L. The results showed that 55% of euthyroid subjects and 61% of hypothyroid subjects had normal levels of serum ferritin, while 44.7% of euthyroid subjects and 38% of hypothyroid subjects had lower levels of serum ferritin.

2. TPO enzyme activity in normal and hypothyroid subjects with correlation to ferritin levels.

TPO enzyme activity was measured in iron sufficient euthyroid and hypothyroid as well as iron deficient euthyroid and hypothyroid women. Quantitative analysis of TPO enzyme was done in different groups. Median TPO enzyme value in iron deficiency hypothyroid group was 225, iron deficiency euthyroid group was 295, normal iron hypothyroid group was 185 and normal iron euthyroid group was 220.

Comparative analysis of TPO enzyme activity among iron sufficient and iron deficient euthyroid women showed elevated TPO activity in iron deficient euthyroid women. However, among the iron sufficient and iron deficient hypothyroid women, the TPO activity was similar. However, for further confirmation, the TPO enzyme activity was compared among euthyroid and hypothyroid

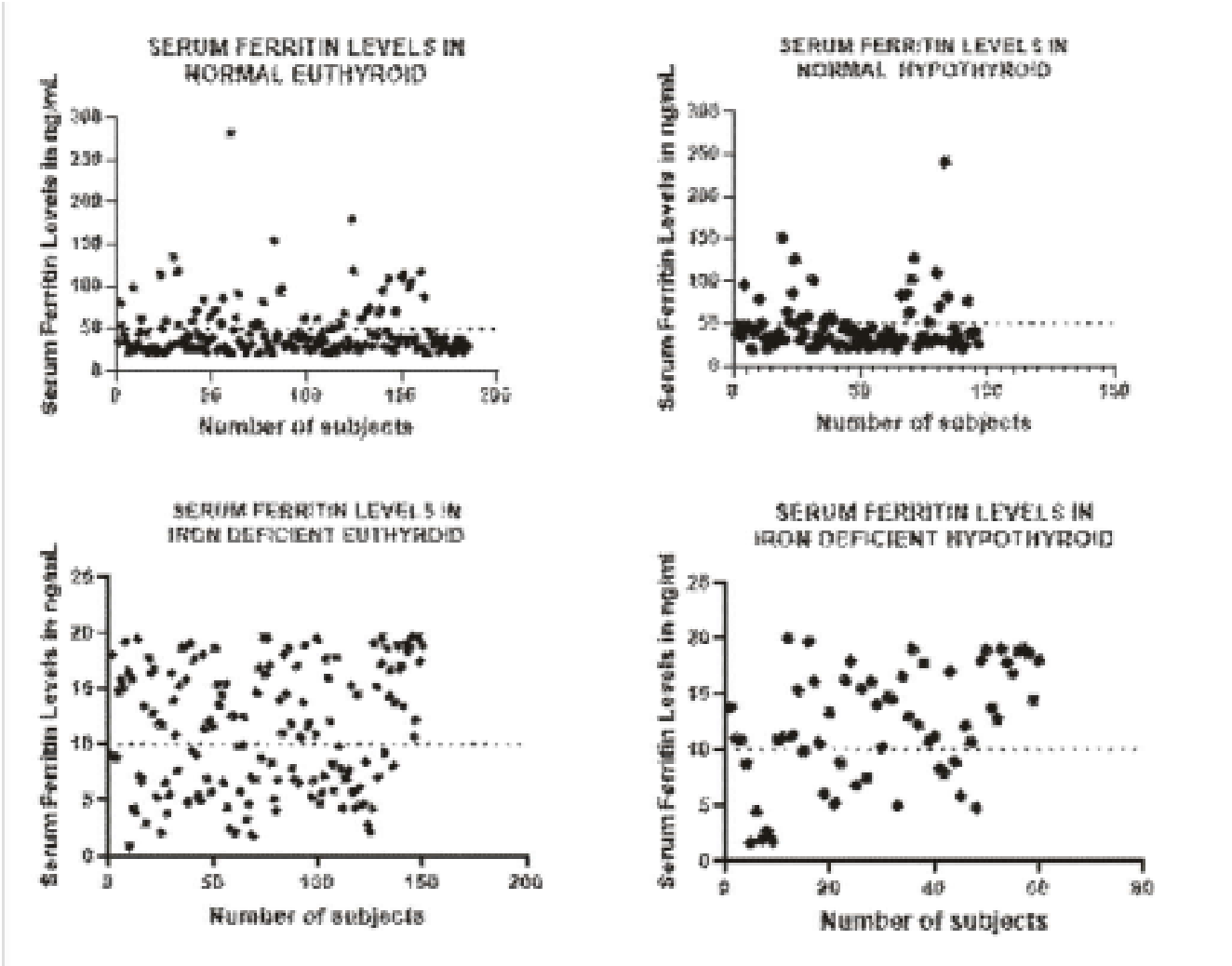

Fig. 1: *Serum ferritin levels in normal iron euthyroid and hypothyroid women as well as iron deficient euthyroid and hypothyroid women.*

women with normal levels of ferritin, which did not show significant differences. Similarly, comparison between Iron deficient euthyroid and hypothyroid women also did not show any significant changes in the TPO enzyme activity as illustrated in Fig. 3.

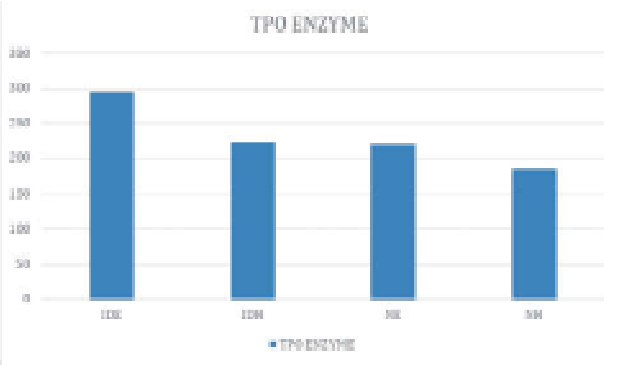

Fig. 2: *TPO Enzyme levels in normal iron euthyroid and hypothyroid women as well as iron deficient euthyroid and hypothyroid women.*

Discussion

Numerous studies have established a direct correlation between iron levels and thyroid gland function[11,12]. Iron deficiency has been shown to directly impact circulating levels of thyroid hormones T3 and T4[11,12]. A recent study published by Pooja *et al* studied the relationship between iron deficiency and thyroid hormone levels in pregnant women. The correlation and regression analysis revealed a significant negative association of TSH and a positive association of FT4 with ferritin, iron, and Hb[13]. However, the data of the current study showed varied levels of serum ferritin in euthyroid and hypothyroid subjects with no significant correlation.

Additional evidence from other studies hypothesize that iron deficiency affects thyroid hormone levels by reducing the

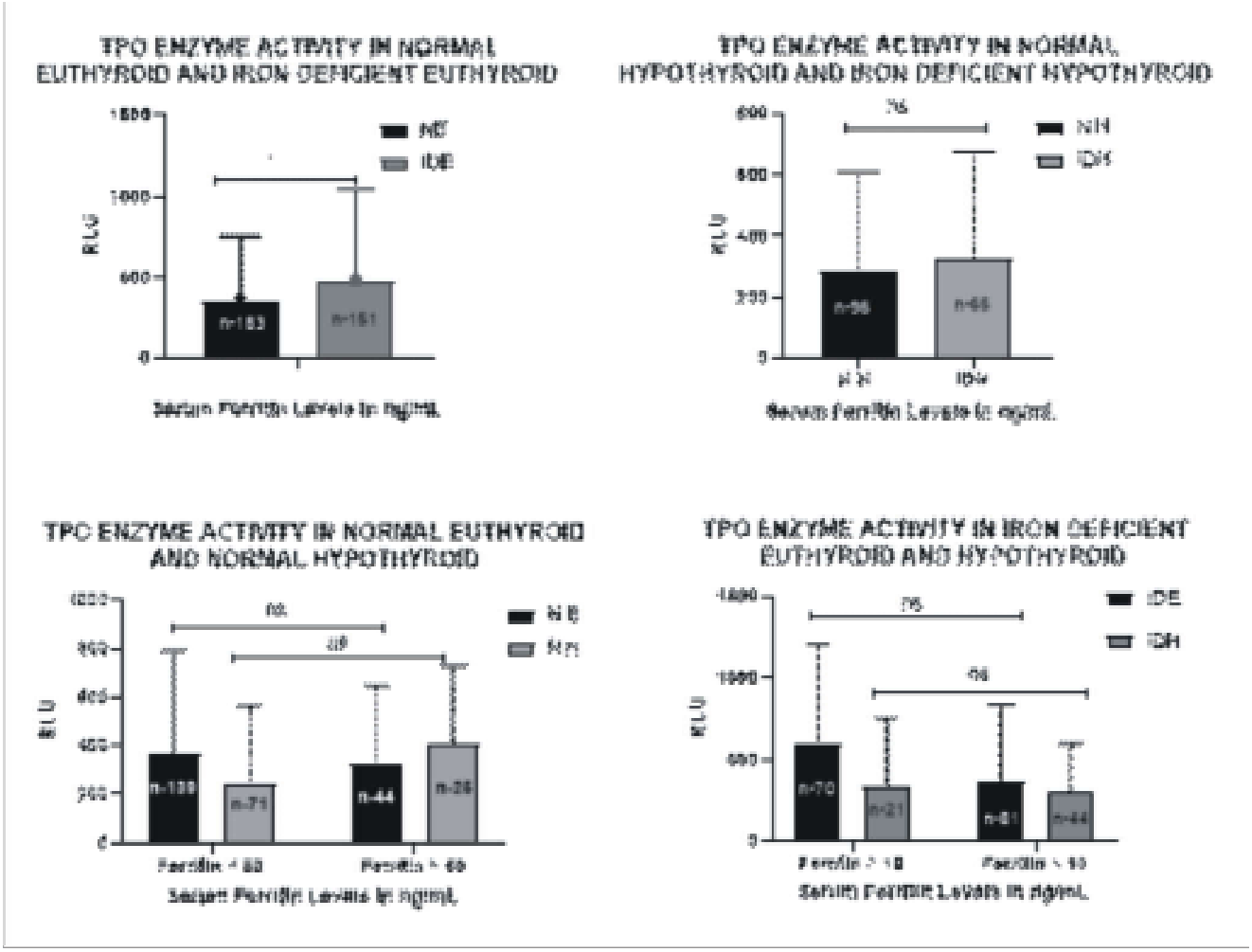

Fig. 3: *Comparative assessment of the activity of TPO in iron sufficient euthyroid and hypothyroid women, as well as iron deficient euthyroid and hypothyroid women. Paired T-test (graph 1 and 2) and Two-way ANOVA (graph 3 and 4 independent variables – ferritin levels and thyroid status is compared with dependent variable TPO enzyme activity) was used to calculate the statistical significance at 'p' value of <0.05.*

activity of the TPO enzyme[14,15,16]. Human thyroid peroxidase (TPO), encoded by the TPO gene located on chromosome 2p25, is subject to regulation by various factors[3]. The TPO mRNA, comprising 17 exons, predominates in human thyrocytes and encodes the 933-amino acid TPO-1 protein. Additionally, alternative splicing generates multiple truncated versions of TPO. TPO-1, a dimeric glycoprotein with a covalently linked heme, features a large N-terminal extracellular region (ectodomain) projecting into the follicular lumen, alongside a short transmembrane domain and intracellular C-terminal region[3].

In the present study, evaluation of TPO enzyme activity among iron sufficient and iron deficient euthyroid and hypothyroid showed significance only among iron sufficient and iron deficient euthyroid. However, no significant correlation was observed among iron sufficient and iron deficient hypothyroid subjects. A study done by Zimmerman *et al*, showed iron deficiency reduces TPO enzyme activity in rats[4]. We couldn't find human studies to compare our study. Potential reasons for these discrepant observations are (a) low sample size; (b) differences in the TPO activity estimation methods, viz., Chemiluminescence versus Fluorimetric methods, c) most women had Subclinical Hypothyroidism rather than Overt Hypothyroidism and (d) sample collection, processing and storage as the exposure of collected samples to light is known to influence the serum ferritin level. Further studies considering these potential influencing factors are needed to conclusively establish a relation between serum ferritin and thyroid status of the individuals.

Conclusion

Contrary to expectations, TPO enzyme activity was not reduced in iron-deficient hypothyroid subjects. Further studies are needed to elucidate the intricate relationship between TPO enzyme activity, serum ferritin levels, and thyroid status in pregnant women, as well as their impact on the overall growth and development of children.

Acknowledgements: We would like to acknowledge Dr Mahesh M, Professor of Medicine, Dr Madhu B, Professor of Community Medicine and Dr Stavelin, Statistician for their help in the study.

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REVIEW ARTICLE

JIACM 2024; 25 (3): 121-29

Urine Analysis: The Neglected Art

Mukesh K Sarna, Rahul**, Abhishek Sanadhya**, Sudha Sarna***, Chinmay***

Introduction

Urinalysis is comprehensive analysis of a urine sample that involves examining its physical, chemical, and microscopic properties. The physical examination assesses the visual characteristics and concentration of urine. Chemical analysis is employed to uncover and measure crucial constituents of urine, primarily through the utilisation of dipstick technologies. Microscopic examination is the third primary element of urinalysis. Although it is time-consuming, it is crucial for diagnosing conditions including urinary tract infections and kidney damage. Urinalysis is an invaluable tool for healthcare professionals. It is mostly utilised for evaluating the genitourinary system. Furthermore, it can assist in diagnosing specific systemic conditions, such as diabetes mellitus or pregnancy-induced hypertension.

Urine formation

There are 3 main steps of urine formation:-

1. **Glomerular Filtration:** The first stage in the production of urine. Through an inert mechanism, fluid and solute are propelled over a membrane by hydrostatic pressure without energy. The volume of fluid filtered every minute is known as the Glomerular Filtration Rate (GFR). It is governed by the net pressure that drives filtration, the total surface area accessible for filtration, and the permeability of the filtration membrane. The normal range for the glomerular filtration rate (GFR) is 120 - 125 millilitres per minute.
2. **Reabsorption:** There are four segments, each segment has unique absorptive properties. The name of first segment is proximal convoluted tubule (PCT). In normal circumstances, the proximal convoluted tubule (PCT) effectively reabsorbs amino acids, glucose nearly 100% as well as 65% of sodium (Na) and water. The PCT cells have the highest amount of absorptive capacity. The descending limb's (of the Loop of Henle) main function is to speed up the osmosis process, which allows water to be reabsorbed. This technique can work because aquaporins are widely distributed. In ascending limb (of the Loop of Henle) there is a narrow segment where sodium moves passively down its concentration gradient. A symporter reabsorbs chlorides, sodium and potassium together in the thick section of the ascending limb. The electrochemical gradient aids in the passive paracellular diffusion that reabsorbs the magnesium and calcium ions in this limb. The last stage of reabsorption occurs in a collecting tubule that is situated right after the distal convoluted tubule (DCT). Here, mainly active sodium transport occurs at the basolateral surface during reabsorption.
3. **Secretion:** The main function of tubular secretion is to get rid of substances that have an affinity for plasma proteins, such as metabolites and medications. Additionally, undesirable substances that were passively reabsorbed, like uric acid and urea, are eliminated through tubular secretion. One aspect of tubular secretion function is the removal of extra potassium via aldosterone regulation at the DCT and collecting duct. When the blood pH drops below normal, H+ ions are secreted. Bicarbonate is secreted and chloride ions are reabsorbed when blood pH rises above normal. Ammonia, creatinine, and several other organic acids and bases are excreted.

Indications for Urinalysis

General Health Screening

It is a fundamental component of a comprehensive health evaluation aimed at identifying any health problems at an early stage. Preoperative assessment: To identify any preexisting conditions that may impact the results of surgery.

Evaluation of Symptoms

Urinary Symptoms: Dysuria (painful urination), haematuria (presence of blood in urine), increased frequency of urination, urgent need to urinate, or alterations in urine colour and smell. Systemic Symptoms: Unexplained pyrexia, exhaustion, unintended weight loss, or oedema, which may suggest renal or systemic ailment.

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Diagnosis of Specific Conditions

Urinary Tract Infections (UTIs) can be diagnosed by detecting the presence of bacteria, white blood cells (WBCs), and nitrites. Kidney diseases, such as glomerulonephritis, nephrotic syndrome, and acute kidney damage, are characterised by the presence of proteinuria, haematuria, and casts. Diabetes Mellitus is characterised by the presence of glucose and ketones in urine. Liver diseases are characterised by the presence of bilirubin and urobilinogen. Bladder and kidney stones: Crystals and blood in the urine.

Monitoring of Chronic Conditions

Chronic Kidney Disease (CKD) requires regular monitoring for the presence of proteinuria, hematuria and alterations in urine concentration.

Diabetes: Monitoring glucose levels, ketones, and symptoms of diabetic nephropathy (such as microalbuminuria).

Hypertension: To assess for renal impairment and the presence of protein in urine (proteinuria).

Pregnancy-Related Indications

Prenatal screening involves the routine analysis of urine samples during pregnancy to detect the presence of infections, proteinuria (abnormal amounts of protein in the urine), and gestational diabetes. Pre-eclampsia: Monitoring proteinuria as a marker for pre-eclampsia.

Medication Monitoring

Nephrotoxic Drugs: Vigilantly monitoring for renal impairment in individuals receiving medications recognised to impact kidney function.

Diuretics: Monitoring the equilibrium of electrolytes and the functionality of the kidneys.

Detection of Metabolic Disorders

Screening for inborn errors of metabolism involves the analysis of metabolic products such as amino acids, organic acids, and sugars.

Gout: Identification of uric acid crystals.

Assessment of Fluid and Electrolyte Status

Dehydration is characterised by urine that is concentrated and has a high specific gravity, electrolyte imbalances, such as low potassium levels (hypokalaemia) or high potassium levels (hyperkalaemia).

Follow-up on Abnormal Findings

Purpose of Previous Abnormal Urinalysis: To track and assess any alterations or resolution of previously identified irregularities.

Substance Abuse Screening

Drug Testing: Identification of illegal drugs and substances.

Procedure and Process of collection

Urine is a volatile fluid that undergoes immediate changes in its composition upon elimination through micturition. Precise acquisition, retention, and manipulation are essential for preserving the integrity of the specimen.

Urine samples obtained from the first void or "morning urine sample" are regarded as most accurate for testing. It is recommended to analyse urine during the first hour after collection since certain components of urine, such as casts, cells and crystals, might degenerate over time. If it is not feasible, the sample should be stored at a temperature of 4 degrees for a maximum duration of 24 hours; this will effectively retard the process of decomposition. Urinalysis cannot be conducted on specimens that are more than 24 hours old. There are two approaches to acquire a urine sample: invasive and non-invasive techniques.

Non-invasive Techniques

The procedure of spontaneous voiding is widely utilised in clinical practice due to its simplicity and popularity. Prior to taking the sample, it is important to explain the patient ways to reduce the risk of contamination from genital microbiota using the "clean-catch" method. Typically, the kits used for urine collection consist of a clean container with a cover and sterile moist towels to clean the urethral area before to collection. Afterwards, the patient should initially release a little quantity of urine and then take a sample of urine while it is flowing in the middle of the stream. For precise analysis, it is recommended that patients collect just 15 mL - 30 mL of urine. Therefore, it is advisable to inform patients not to completely fill the containers in most situations. Ultimately, the container is sealed meticulously to avoid any contamination of its lid or rim. The specimen must be appropriately labeled either before or immediately after it is collected, and it should not be placed on the collecting table.

Invasive Techniques

The process of invasive urine collection is necessary in cases where patients are unable to void urine voluntarily, experience incontinence, or have external urethral ulcers that raises the risk of contamination.

Both of these techniques carry a risk of contamination, hence leading to urinary tract infections.

1. Urethral catheterisation is the process of inserting a urinary catheter into the urethral meatus following prior washing using appropriate equipment. The requirement for a sterile syringe may vary depending on the type of catheter being used. When patients already have a catheter in place, it is important to avoid taking the samples from the urinary bag because it is considered to be contaminated.
2. The suprapubic needle aspiration of the bladder is the most common invasive and unpleasant technique among those listed before. It has the potential to produce false-positive findings for protein, red blood cells (RBCs), and white blood cells (WBCs) due to contamination with blood. They are typically used in cases when it is difficult to collect samples or when earlier approaches have resulted in persistent contamination, which is often the case with young children. The primary benefit is that it reduces the likelihood of receiving a contaminated sample by circumventing the urethra. Prior to the procedure, skilled personnel must ascertain the location of the bladder through inspection. It is advisable to provide the patient with fluids and wait for proper identification or utilise the guidance of ultrasound if it is accessible. Following thorough cleansing with the help an antiseptic solution and numbing the skin at a distance of 5 cm above the pubic symphysis, a tiny needle (specifically, a spinal needle of 22-gauge and 10 cm in length for adults) is inserted at an angle of around 60 degrees at the previously marked location. In adults, the needle is directed somewhat caudal, while in children, it is directed slightly cephalic, depending on the anatomic placement. Typically, the needle will penetrate the abdomen bladder after inserting it around 5 cm in adults. Ultimately, urine is extracted by use of a sterile syringe.

Normal Urine Composition

Parameters	Values
Volume	600 - 2000 mL
Specific gravity	1.003 - 1.030
Osmolality	300 - 900 mOsm/kg
pH	4.6 - 8.0
Glucose	<0.5 gm/dL
Proteins	<150 gm/dL
Urobilinogen	0.5 - 4.0 mg/dL
Prophobilinogen	0 - 2 mg/dL
Creatinine	14 - 26 mg/kg (men), 11 - 20 mg/kg (women)
Urea nitrogen	12 - 20 mg/dL
Uric acid	250 - 750 mg/dL
Sodium	40 - 220 mEq/L
Potassium	25 - 125 mEq/L
Chloride	110 - 250 mEq/L
Calcium	50 - 150 mg/dL
Red, Epithelial and white cells	<1 - 2/hpf

Urine Examination

A comprehensive urinalysis comprises three distinct components or evaluations: chemical, physical and microscopic.

The physical assessment assesses volume, colour, transparency, odour, and density. The chemical analysis detects the pH, presence of RBCs, WBCs, proteins, glucose, bilirubin, ketone bodies, and nitrites. Microscopic examination involves identifying casts, cells, crystals, and microbes.

Physical examination

Colour

Normal: Clear or translucent

Clinical Associations:

- Amber: Pigments found in bile Brown/Black (Tea-coloured): The colouration can be caused by several substances such as bile pigments, chloroquine, homogentisic acid (associated with alkaptonuria), levodopa, fava beans, methaemoglobin, methyldopa, metronidazole, myoglobin, nitrofurantoin, primaquine, and senna.
- Pink/Red: Beets, blackberries, chlorpromazine, food dyes, haematuria, haemoglobinuria, menstrual contamination, phenolphthalein, myoglobinuria, porphyrins, rhubarb, senna, thioridazine, rifampin, uric acid crystals. If a urine sample changes colour to red when left undisturbed, it indicates the presence of porphobilinogen, which is elevated in cases of acute porphyrias.
- Dark Yellow: Indicates a concentrated sample, which may be due to factors such as dehydration or exertion.
- Orange colour can be caused by bile pigments, rifampin, carrots, phenazopyridine, nitrofurantoin, phenothiazines, and vitamin C.
- Green/Blue: The substances that might cause a green or blue colour are amitriptyline, biliverdin, cimetidine, indicans, indomethacin, methocarbamol, methylene blue, promethazine, propofol, indigo carmine, and *Pseudomonas* urinary tract infection.

Odour

Normal: "Urinoid"

Clinical Associations: Cystine decomposition is characterized by the emission of a sulfuric odor. When cystine is subjected to dehydration or exposed to prolonged room temperature, it releases a strong smell.

Diabetes Mellitus: Honey/fruity

Diabetic Ketoacidosis: Characterised by a fruity or sweet odor.

Gastrointestinal-bladder Fistula: Odor resembling feces

Maple syrup Urine Disease: Also known as "burnt sugar"

Extended bladder retention: Ammoniacal

Infection of Urinary Tract: Having a strong or unpleasant odour

Treatment and Nutrition: Prescribed medications include onions, garlic, and asparagus as part of the diet.

Specific Gravity/Osmolality (O)

Normal: 1.002 - 1.035 (usually 1.016 to 1.022)

Osmolality = 50 - 1200 mOsm/kg (usually 275 - 900 mOsm/kg) (Both parameters are lab dependent)

Clinical Associations

High values of urinary osmolality can be caused by several factors such as contrast media, dehydration, reduced blood supply to the kidneys (due to heart failure, shock, or renal artery stenosis) diarrhoea, vomiting, glycosuria, excessive sweating, liver failure, and syndrome of inappropriate antidiuretic hormone also known as SIADH.

Causes of low values include acute tubular necrosis, acute adrenal insufficiency, aldosteronism, diuretic use, diabetes insipidus, excessive fluid consumption (psychogenic polydipsia), decreased renal function, interstitial nephritis, hypercalcaemia, hypokalaemia, and pyelonephritis.

False elevation of results of urine osmolality can be caused by dextran solutions, intravenous (IV) radio – contrast media, and proteinuria.

False depression of urine osmolality might be due to by the presence of alkaline urine.

Volume

Normal: 0.5 to 1.5 mL/kg/hour or 600 mL - 2,000 mL daily in adults (typically 1,000 - 1,600 mL/day)

Clinical Associations

Anuria (urine output less than 100 mL/day) and oliguria (urine output less than 500 mL/day) can be caused by severe dehydration due to haemorrhage, vomiting, diarrhoea, or profuse sweating. It can also be caused by renal disease, renal obstruction, or renal ischaemia due to heart failure or hypotension.

Polyuria, defined as the production of urine exceeding 2,500 mL - 3,000 mL per day, can be caused by various factors such as diabetes mellitus, diabetes insipidus, diuretic use, alcohol or caffeine use, increased water intake, or administration of saline or glucose intravenous therapy.

Chemical Examination

pH

Normal: 4.5 to 8 (usually 5.5 to 6.5)

The measurement of urine pH is crucial and offers valuable information on the functioning of the tubules. Typically, urine has a slightly acidic pH due to metabolic processes. If the urinary pH is higher than 5.5 and there is systemic acidemia (serum pH less than 7.35), it indicates renal failure caused by the inability to eliminate hydrogen ions. Contrarily, the primary reason for alkaline urine is a stagnant urine sample caused by bacterial growth and the decomposition of urea, which releases ammonia. Measuring urine pH is useful for diagnosing and treating urinary tract infections and the formation of calculi or crystals.

Clinical Associations

High values of urine alkalinity can be caused by various factors. The most prevalent cause is stale or old urine specimens. Other factors include hyperventilation, the presence of urease-producing bacteria, renal tubular acidosis, a vegetarian diet, and vomiting.

High urinary acidity can be caused by various factors such as dehydration, diabetes mellitus, diabetic ketoacidosis, diarrhoea, emphysema, high protein diet, cranberry juice, hunger, potassium depletion, drugs (such as mandelic acid and methionine), and a potential inclination towards the development of kidney or bladder stones.

Proteins

Normal: less than or equal to 150 mg/day of proteinuria (usually less than 30 mg/day of albuminuria) or 10 mg/dL.

Clinical Associations

Between 30 and 300 mg/day of albuminuria is indicative of glomerular damage, early renal disease, and the likelihood that the condition may worsen.

Additional Associations: Fanconi syndrome, Wilson disease,

pyelonephritis, multiple myeloma, congestive heart failure, and physiological circumstances (heat, fever, hypothermia, orthostatic proteinuria, and dehydration).

- False-positive: Quaternary ammonia compounds, phenazopyridine, and concentrated or alkaline urine.
- False-negative: Urine that is acidic or diluted, with albumin as the predominant protein.

Blood Cells

Erythrocytes having peroxidase activity are mostly detected by the blood dipstick test, while haemoglobin and myoglobin can also catalyse this process. Consequently, the presence of haematuria, myoglobinuria, or haemoglobinuria is indicated by a positive test result.

Normal: Negative (usually) or less than or equal to 5 RBCs per mL (lab-dependent value)

Clinical Associations

Numerous conditions, including renal calculi, glomerulonephritis, pyelonephritis, malignancies, trauma, anticoagulants, intense exercise, and exposure to toxic substances, can result in haematuria.

Haemoglobinuria can occur due to several factors such as haemolytic anaemias, trauma to red blood cells, intense physical activity, transfusion responses, severe burns, and infections like malaria.

Myoglobinuria can be caused by several factors such as muscle injuries, (e.g., rhabdomyolysis), extended unconsciousness, convulsions, drug addiction, severe effort, alcoholism or overdose, and muscle wasting illnesses.

A number of conditions, including dehydration, exertion, haemoglobinuria, menstrual blood, and myoglobinuria, might result in false-positive readings. False-negative results can occur with the presence of captopril, increased specific gravity, acidic urine, proteinuria, or vitamin C.

Glucose

Glycosuria occurs when the amount of glucose filtered by the kidneys is greater than the kidneys' ability to reabsorb it. This usually happens when the concentration of glucose in the blood is around 180 mg per dL.

Normal: Not Present

Clinical Associations

Conditions that can lead to diabetes mellitus include Cushing's syndrome, Fanconi syndrome, and pregnancy. Additionally, the administration of glucose through an infusion can also contribute to the development of diabetes mellitus.

Glucosuria with normal plasma glucose levels, without any other symptoms of Fanconi syndrome, is caused by a harmless condition known as renal glycosuria. This condition is the result of a mutation in the sodium glucose associated transporter. False-positive results can occur with the presence of ketones or levodopa. False-negative results can occur when there are increased levels of uric acid, specific gravity, or vitamin C.

Ketone bodies

As a result of increased fat metabolism, these substances may be observed in urine. The highest quantity is found in β Hydroxybutyric acid, followed by acetoacetic acid and acetone. A strong fruity odour may be noticable when there is a significant quantity present. The assays usually used to detect ketone bodies rely on the formation of a purple substance when nitroprusside and alkali are present. These tests will undergo a chemical reaction with acetone or acetoacetic acid, but not with β-hydroxybutyric acid. L-Dopa can yield a spurious positive outcome when subjected to nitroprusside-based assays. There is a method using ferric chloride that produces inaccurate positive findings for both L-dopa and salicylates. Ketone bodies are commonly found in the urine of adults after episodes of diabetic ketoacidosis or prolonged fasting.

Microscopic examination

Crystals

Crystals are optically active objects with a distinct geometric form resulting from the three-dimensional organisation of their atoms and molecules. Amorphous material, also known as a deposit, lacks a distinct shape and is typically observed as clusters or conglomerates of granules.

The crystals found in acidic urine include uric acid, calcium oxalate, cystine, and leucine. Crystals in urine with a high pH level have a composition that includes triple phosphate (consisting of ammonium, magnesium, and phosphates) and calcium carbonate.

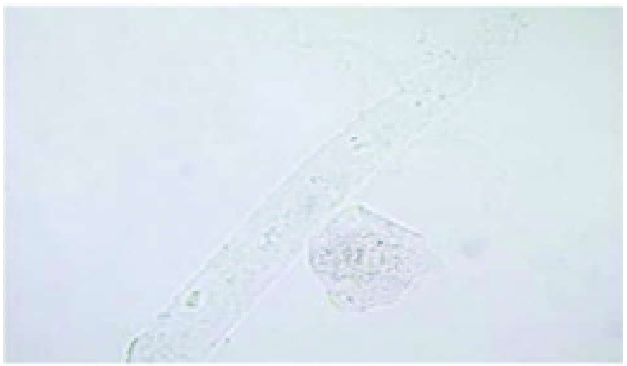
Casts

Urinary casts are cylindrical clusters of particles that develop in the distal nephron and are expelled in urine. Casts are of two main types: Noncellular substances can be of four types: granular, waxy, hyaline and fatty.

Cellular components: Erythrocytes, leukocytes, renal tubular epithelial cells.

Hyaline casts

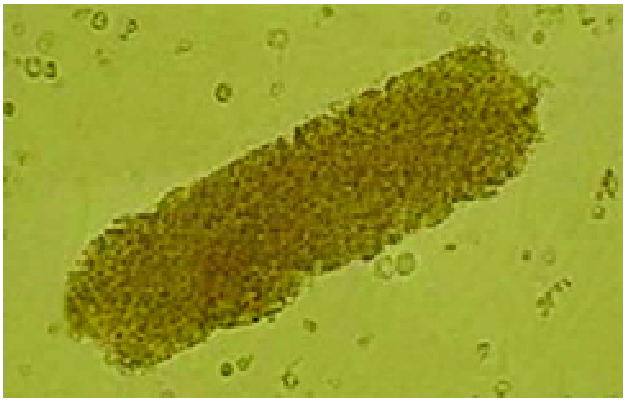
The most prevalent type of casts are made up of solidified



Tamm-Horsfall mucoprotein. These casts have a smooth texture and a refractive index that closely matches the surrounding fluids. They may be observed in individuals who are in good condition, but their numbers may increase during periods of dehydration, physical activity, or when using diuretic drugs.

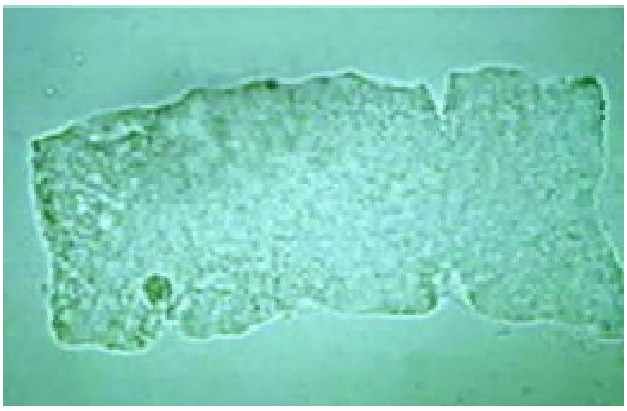
Granular casts

Granular casts form as a result of either the breakdown of cellular casts or the direct clumping together of plasma proteins or immunoglobulin light chains. They possess a textured look that varies in character from fine to coarse. These are observed during intense physical activity, chronic kidney disease, acute tubular necrosis, and other similar conditions.



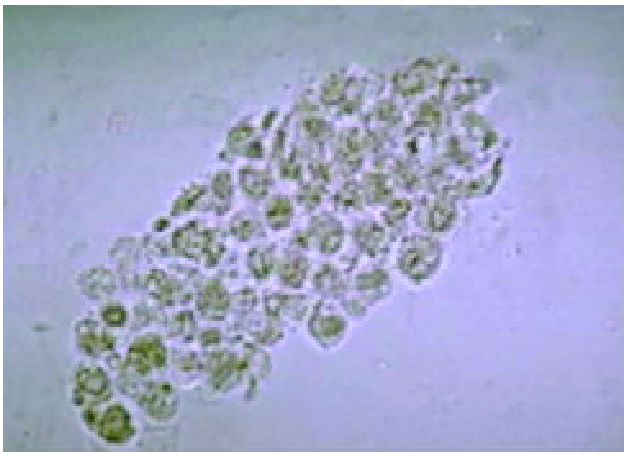
Waxy casts

Waxy casts are the end result of the deterioration of cellular casts. They exhibit a higher degree of refractivity. These types of casts are observed in cases of tubular injury that are of a more prolonged nature, as opposed to granular or cellular casts which are associated with severe chronic renal illness and renal amyloidosis. These casts are alternatively referred to as renal failure casts.



Fatty casts

Fatty casts are created from the degradation of epithelial cells that contain a high amount of lipids. These lipid droplets are found inside the protein matrix of the cast and can be identified by the presence of refractile lipid droplets. They are commonly observed in disorders such as tubular degeneration, nephrotic syndrome, and hypothyroidism.



Red blood cells casts

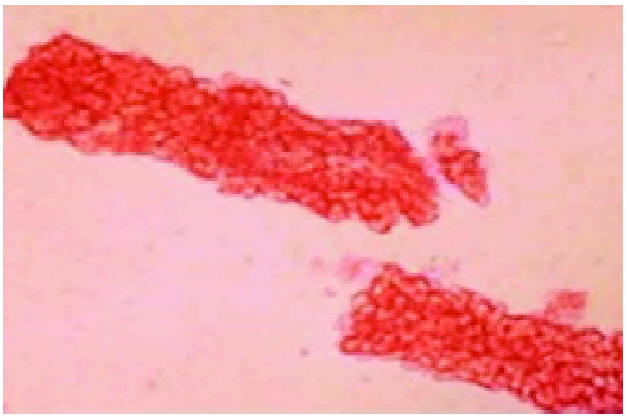
The occurrence of red blood cells within the cast is consistently pathological and highly suggestive of glomerular injury. They are commonly linked to nephritic disorders.

White blood cell casts

Casts include whole blood cells, typically neutrophils, either inside or on their surface. Suggestive of inflammation or infection. These casts are characteristic of acute pyelonephritis.

Renal tubular epithelial cell casts

The casts consist of renal epithelial cells. These types of

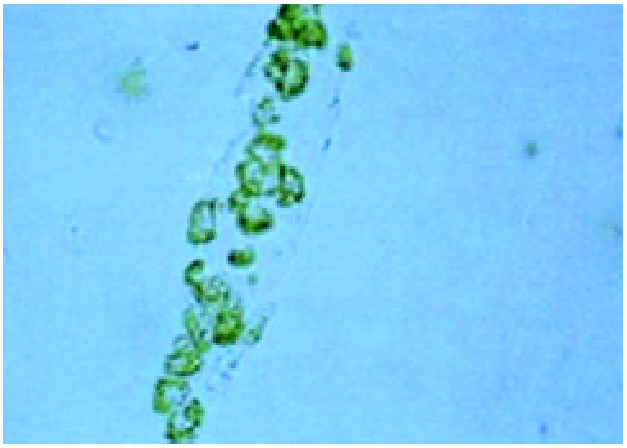


casts are observed in illnesses such as renal tubular necrosis, viral diseases (such as CMV nephritis), and kidney transplant rejection.

Organisms in urine

Bacteria, Yeasts, *Trichomonas* and Eggs of *Schistosoma haematobium* may be focued during urine analysis in various infections.

Summary of common urinary findings



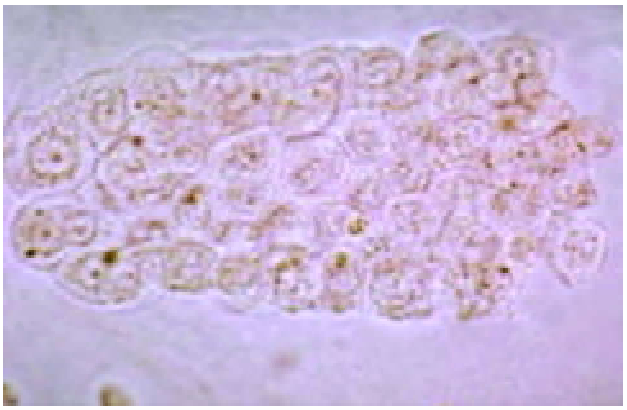


Table I.

Physical Examination	
Colour	Yellow: Normal urine. Dark yellow: Dehydration or concentrated urine. Red or pink: Haematuria (blood in urine). Cloudy: Infection (pus) or crystals.
Odour	Normal: Mild ammonia-like odour. Foul-smelling: Infection (e.g., UTI).
Chemical Examination	
pH	Low (acidic): Urinary tract infections, metabolic acidosis. High (alkaline): Urinary tract infections with urea-splitting bacteria, metabolic alkalosis.
Specific Gravity	High: Dehydration, concentrated urine. Low: Diabetes insipidus, renal tubular necrosis.
Protein	Nephrotic syndrome, glomerulonephritis
Glucose	Diabetes mellitus.
Ketones	Diabetic ketoacidosis, starvation.
Bilirubin	Liver disease, biliary obstruction.
Blood	Haematuria (infection, kidney stones, trauma).
Microscopic Examination	
Red Blood Cells (RBCs)	Increased: Haematuria (glomerulonephritis, kidney stones).
White Blood Cells (WBCs)	Increased: Urinary tract infection (pyelonephritis).
Epithelial Cells	Increased: Renal tubular injury or inflammation.
Crystals	Types (e.g., calcium oxalate, uric acid): Kidney stones, crystalluria.
Microbiological Examination	
Culture	Positive growth: Bacterial or fungal infection (UTI).
Parasites	Parasitic infection (e.g., Schistosoma haematobium).
Additional Tests	
Drug Screening	Positive: Exposure to toxins (e.g., heavy metals).
Toxicology Screening	Positive: Exposure to toxins (e.g., heavy metals).
Interpretation and Reporting	Results integrated with clinical symptoms and history. Diagnosis and treatment recommendations provided.

Urinary Findings in common Renal Diseases

Table II.

Urinary examination findings	Renal disease suggested
Haematuria with dysmorphic red blood cells, red blood cell casts, varying degrees of albuminuria	Proliferative glomerulonephritis (e.g., IgA nephropathy, ANCA-associated vasculitis, lupus nephritis)
Multiple granular and epithelial cell casts with free epithelial cells	Acute tubular necrosis in a patient with underlying acute kidney injury
Heavy albuminuria with minimal or absent haematuria	Nonproliferative glomerulopathy (e.g., diabetes, amyloidosis, membranous nephropathy, focal segmental glomerulosclerosis, minimal change)
Isolated pyuria	Infection (bacterial, mycobacterial) or tubulointerstitial disease
Abnormal kidney function with normal dipstick and sediment containing few cells, no casts, and no or minimal	– Prerenal acute kidney injury due to either volume contraction or an effective decrease in circulating volume (e.g., heart failure, liver

proteinuria	disease) – Hypercalcaemia – Light chain cast nephropathy in multiple myeloma – Tumour lysis syndrome – Vascular disease that produces glomerular ischaemia but not infarction (e.g., hypertensive emergency, scleroderma, thrombotic microangiopathies) or that affects extraglomerular vessels (e.g., cholesterol atheroemboli, polyarteritis nodosa) – Urinary tract obstruction

ANCA: Antineutrophil cytoplasmic antibody; IgA: immunoglobulin A.

Urinary findings in common systemic diseases

Table III.

Urinary findings in common systemic diseases

Disease	Urinary findings	Disease	Urinary findings
Diabetes Mellitus	Glycosuria, Ketonuria, Proteinuria	**Rhabdomyolysis**	Dark coloured urine, Myoglobinuria
Hypertension	Proteinuria, Haematuria	**Phaeochromocytoma**	Metanephrines and Catecholamines
Chronic Kidney Disease (CKD)	Proteinuria, Casts, Haematuria	**Liver Disease**	Urobilinogen, Bilirubinuria
Urinary Tract Infections (UTIs)	Pyuria, Bacteriuria, Haematuria	**Fabry Disease**	Proteinuria, Lipiduria
Systemic Lupus Erythematosus (SLE)	Proteinuria, Haematuria, Casts	**Paget's Disease of Bone**	Hydroxyproline
Multiple Myeloma	Bence-Jones proteins, Proteinuria	**Wilson's Disease**	Aminoaciduria

Why is it a neglected art?

Urinalysis is an invaluable, non-intrusive, and cost-efficient diagnostic procedure that offers crucial insights into a broad spectrum of medical disorders. The neglect of Urine examination can be ascribed to a variety of issues, such as developments in technology, deficiencies in training, economic pressures stemming from historical changes, gaps in education, intricacies of the healthcare system and changes in healthcare practices. To tackle these issues, it is necessary to adopt a well-rounded approach that acknowledges the lasting significance of urinalysis, incorporates it into contemporary diagnostic methods, and guarantees that healthcare systems and professionals appreciate and employ this indispensable tool efficiently.

Interpretation Challenges: Precise comprehension and expertise is necessary for the accurate interpretation of urine data. If practitioners do not have sufficient training, they may not fully understand the nuances of interpreting these results, which could result in reduced trust in the test.

Focus on Immediate Results: Contemporary healthcare frequently gives priority to prompt diagnostic outcomes in order to accelerate patient treatment. Although urinalysis can yield rapid findings, it may be considered less pressing in comparison to tests that are regarded as offering more promptly actionable information.

Training and Emphasis in Medical Education: Medical courses sometimes prioritise advanced diagnostic techniques over fundamental ones. Consequently, the reduced emphasis on urinalysis in medical education may result in medical students and professionals receiving inadequate training, which in turn leads to a deficiency in their knowledge and recognition of the diagnostic capabilities of urinalysis.

Laboratory Dependency and Centralisation: Contemporary healthcare heavily depends on centralised laboratory testing. While urinalysis can be conducted promptly and effectively at the point of care or in a clinic, there might be an inclination towards laboratory-validated assays, which might cause a delay in obtaining findings and diminish the perceived significance of urinalysis.

Skill Retention and Clinical Expertise: With the advancement of medical practice, there is a risk that the specific skills needed for thorough interpretation of urinalysis may not be maintained or cultivated. Over time, this can result in a decrease in its utilisation and the proficiency required to accurately evaluate its outcomes.

Cultural Factors and Patient Preferences: Additionally, cultural variables and patient preferences might also have an influence. Certain individuals may experience discomfort when asked to provide urine samples, resulting in a preference for alternative diagnostic techniques. Healthcare practitioners must acknowledge these concerns and enlighten patients about the significance of urinalysis.

Historical Shifts in Medical Practices: Urinalysis served as a key diagnostic method for clinicians. With the advancement of medical knowledge, there has been a change in attention towards more advanced technology, resulting in a progressive decrease in the importance placed on conventional methods such as urinalysis. This historical transition has resulted in a lasting pattern of insufficient usage.

Variability in Test Quality and Standardisation: There is considerable variation in the quality and standardisation of urinalysis among different laboratories and healthcare settings. Fluctuating quality control can result in inconsistencies in test outcomes, eroding trust in the exam and contributing to its disregard.

Preventive versus curative healthcare systems frequently prioritise treatment rather than prevention. Urinalysis is

essential in preventive medicine as it can identify initial indications of illnesses. Nevertheless, the importance of this preventive feature may be underestimated in a healthcare system that prioritizes curative interventions.

Data Integration and Health Records: Integrating urine data into electronic health records (EHR) and decision-making algorithms may be less reliable than other tests. This oversight can lead to the neglect of urinalysis in clinical decision-making processes.

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CASE SERIES

JIACM 2024; 25 (3): 130-32

From Plate to Paralysis: A Rare Encounter with Food-Borne Botulism

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Abstract

Background: Botulism is a rare but fatal neuroparalytic syndrome, caused by a neurotoxin produced by bacteria of the genus Clostridium. Food-borne botulism is caused by ingestion of pre-formed botulinum neurotoxin. This syndrome courses initially with symmetrical cranial nerve palsy, may progress to descending flaccid paralysis and ultimately to respiratory arrest. Intensive management and antitoxin administration are crucial for treatment. Here, we present a case report involving five family members with varying degrees of severity of food borne botulism.

Cases description: Five members of a family, a 38-year-old lady with her three sons and one daughter came to Accident and Emergency (A and E) department with nausea, vomiting, and varying degrees of weakness after 13 hours of ingestion of common food (Kadhi Rice). It gradually progressed to bilateral symmetrical ophthalmoparesis and descending paralysis with varying severity amongst them. The mother and her 17-year-old son required mechanical ventilation. All of them recovered with conservative and supportive management with the mother having residual generalised weakness. A diagnosis of food-borne botulism with acute descending paralysis was made clinically.

Conclusion: Although a rare entity, recognising botulism based on the clinical picture is relatively easy. It is important to maintain a high clinical suspicion to avoid diagnostic delay with increased risk of sequelae and death. Anti-botulinum toxin is not required in every case of botulism, making intensive care support the corner stone of management.

Key words: Botulinum, food borne, descending paralysis, antitoxin, BoNTs.

Introduction

Botulism is a rare but fatal neuroparalytic syndrome, caused by a neurotoxin produced by bacteria of the genus *Clostridium*. Food-borne botulism is caused by ingestion of preformed botulinum neurotoxin. A reported case of food-borne botulism represents a public health emergency because of the potential severity of the disease and the possibility of mass exposure to the contaminated product. The first food-borne botulism case in India was reported in 1996 by Chaudhry *et al*[1] which was caused by a neurotoxigenic *Clostridium butyricum*. This syndrome courses initially with gastrointestinal symptoms like nausea and vomiting, followed by symmetrical cranial nerve palsies, may progress to descending flaccid paralysis and ultimately lead to respiratory arrest. The effective management of this condition hinges significantly on intensive care and the timely administration of antitoxin. Here, we present a case series of 5 family members, with varying severity of food-borne botulism.

Cases Description

Five members of a family, a 38-year-old lady with her four children presented to A and E department at Pandit B. D. Sharma PGIMS, Rohtak on 20 January 2024 with nausea, and vomiting episodes and varying degrees of weakness after 13 hours of ingestion of common food (Kadhi Rice, a curd-based dish). All the family members initially showed similar gastrointestinal symptoms characterised by multiple episodes of non-bilious, non-projectile, watery vomiting.

Case 1

The 38-year-old lady experienced throat heaviness 5 - 6 hours after the onset of vomiting. This progressed to difficulty in swallowing and speaking, accompanied by blurring of vision. Subsequently, she developed weakness in both the upper limbs, which extended to her lower limbs.. On examination in the emergency department, her Glasgow Coma Scale (GCS) score was E4V1M1. She had bilateral flaccid paralysis (Power 0/5 in all 4 limbs) with absent deep tendon and superficial reflexes, complete ophthalmoplegia, mild bilateral ptosis, and absent direct and consensual light reflexes in both pupils. Also, her corneal and gag reflexes were absent. She started having chest tightness and shortness of breath with oxygen saturation dropping to 80%

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on room air within 30-45 minutes. She was intubated and put on ventilator in the intensive care unit (ICU) . After three days, she was extubated but continued to have 4/5 power in all four limbs at two-months follow-up.

Case 2

17-year-old son had dizziness, difficulty in swallowing, blurring of vision, and weakness in his upper limbs, followed by weakness in his lower limbs. At presentation, he had a GCS of E4V1M1 and an oxygen saturation of 90%. He also had bilateral flaccid paralysis with absent reflexes and complete ophthalmoplegia. He also required mechanical ventilation in the ICU amd recovered after three days.

Case 3

12-year-old son presented with acute descending weakness, characterised by flaccid paralysis in all four limbs followed by development of bilateral dilated, non-reacting pupils, and ophthalmoplegia . On presentation, he had a GCS of E4V1M1 and oxygen saturation of 82%. He also required mechanical ventilation and recovered after three days.

Case 4

18-year-old son developed a feeling of neck heaviness about an hour after vomiting. He experienced heaviness and weakness in both arms followed by weakness in both the lower limbs. On presentation, he had difficulty in raising his arms above his head and holding objects. He was able to bear weight but had slight knee buckling upon standing. Despite these symptoms, he did not experience any chest tightness, swallowing or breathing difficulty. The boy was vitally stable but had bilateral decreased tone and 4/5 power in all four limbs with mild bilateral ptosis. He was managed conservatively and showed clinical improvement within two days.

Case 5

15-year-old daughter also experienced mild heaviness in both upper limbs followed by difficulty in raising her arms above the head. There were no problems with swallowing or speaking. Neurologically, she had 4/5 power in her upper limbs, 5/5 power in lower limbs with normal pupillary and deep and superficial reflexes. She was managed conservatively.

There was no history of loose stools, any unknown bite, fever, bladder-bowel involvement in any of the member. All the routine investigations including serum electrolytes were normal. Based on the history of common food intake, afebrile gastrointestinal complaints, clustering in a family, normal potassium levels, acute flaccid descending paralysis with bilateral symmetrical cranial nerve palsy of varying severity, a clinical diagnosis of food-borne botulism was made.

Discussion

Botulism is a rare neuroparalytic disease mediated by *Clostridium botulinum*, an anaerobic, gram-positive, spore-forming bacterium. It is caused by botulinum neurotoxin (BoNTs) which is produced by bacteria under low oxygen conditions and certain combinations of storage temperature and preservative parameters. There are 7 distinct forms of botulinum toxin, types A-G. Four of these (types A, B, E and rarely F) cause human botulism. The toxin is one of the most lethal and potent neurotoxin known to humans. Food-borne botulism occurs when *C. botulinum* grows and produces toxins in food prior to consumption with case fatality being 5 - 10 %[2]. The botulinum toxin has been found in a variety of foods, including low-acid preserved vegetables, such as green beans, spinach, mushrooms, and beets; fish, including canned tuna, fermented, salted, and smoked fish; and meat products, such as ham and sausage. Following ingestion, the toxin permeates the bloodstream via the mucosa of the jejunum or ileum, ultimately spreading within the neuromuscular cholinergic synapse[3]. BoNTs specifically attach to motor neurons and autonomic cholinergic nerves. Within the peripheral cholinergic synapse, the toxin establishes an irreversible and highly selective affinity with the presynaptic receptors.

The typical manifestation of food-borne botulism involves a sudden onset of bilateral cranial neuropathies accompanied by symmetric descending weakness, typically starting between 6 and 72 hours after ingestion[4]. The cranial nerve impairment encompasses symptoms such as blurred vision (resulting from fixed pupillary dilation and affliction of cranial nerves III, IV, and VI), diplopia, nystagmus, ptosis, dysphagia, dysarthria, and facial weakness (bulbar palsy). The progression of muscle weakness typically follows a descending pattern, starting from the trunk and upper extremities to the lower extremities. Respiratory challenges, such as dyspnoea, may arise due to diaphragmatic paralysis, upper airway compromise, or a combination of both, often necessitating intubation and mechanical ventilation[5].

Notably, like in our case, most patients initially present to the emergency department with predominant gastrointestinal symptoms followed by onset of pronounced neurological changes. A systematic review also showed nausea was reported 36% of the time by patients with foodborne botulism and vomiting was reported in 50% of the patients[6].

The first case of food borne botulism was reported in India in 1996; 34 students of a residential school in rural Gujrat complained of abdominal pain, nausea, chest pain, and difficulty in breathing. Patients reported that 24 hours before onset of symptoms, they had eaten ladoo (a local sweet), curd, buttermilk, sevu (crisp made of gram flour), and pickle. Anaerobic culture of left over sevu yielded *C. butyricum*[1]. Similarly, Agarwal *et al*[7] in 2004 reported food-borne botulism in 2 members of a family with a history of eating canned meat products, along with preserved curd.

Botulism should be suspected in a patient who is responsive, afebrile with normal or low heart rate with acute symmetric cranial nerve palsy (typically bulbar palsies) followed by bilateral flaccid paralysis of voluntary muscles and respiratory arrest. It has a distinct clinical profile, but its differential diagnosis includes conditions such as snake bite, myasthenia gravis, Lambert-Eaton myasthenic syndrome, Tick paralysis, Guillain-Barré syndrome, Miller-Fisher variant, and poliomyelitis but they have distinguishing features that help differentiate them from botulism. Other potential confounding conditions include magnesium intoxication, diphtheria, organophosphate poisoning, or brainstem infarction. A careful examination and consideration of these factors are essential for accurate diagnosis and appropriate management.

Confirmation of botulism diagnosis relies on identifying toxins in serum, stool, vomitus, or the implicated food source. However, this process involves several days for the growth and identification of the causative organism. Stool examination in our cases showed gram-positive cocci with no identification of organism. Stool culture reports which were obtained later did not show any growth of *Clostridium* on anerobic culture. Thus, syndrome-based clinical suspicion and diagnosis is of utmost importance. It is important to note that the decision to administer antitoxins should be based on a presumptive clinical diagnosis, and any delay in diagnosis should not impede the initiation of therapy.[3]

Antitoxin stands as the primary therapeutic intervention for botulism but intensive care in ICU holds the key for survival. Antitoxins exclusively neutralise circulating toxins but have no effect on toxins already bound to nerve terminals, emphasizing that supportive management is the key to management. We managed our case in intensive care with supportive management with persistent mild residual paralysis in 1 patient.

Conclusion

Botulism can cause a variety of symptoms, ranging from minor gastroenteritis to symmetrical cranial nerve palsies, to descending weakness and rapid respiratory arrest and death. Rapid neurologic dysfunction and respiratory difficulties start between 6 and 72 hours after ingestion. Overall Botulism is a clinical diagnosis and a high degree of clinical suspicion is needed in any patient who is responsive, afebrile with acute gastrointestinal symptom, acute symmetric cranial nerve palsy or descending flaccid paralysis. Anti-botulinum toxin is not required in every case of botulism, making intensive care support the corner stone of management.

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CASE SERIES

JIACM 2024; 25 (3): 133-37

Hyperhomocysteinaemia and Hypercoagulability: A Case Series from Darjeeling

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Abstract

Hyperhomocysteinaemia (HHcy) is a common metabolic disorder that predisposes to a procoagulant state and has emerged as an established risk factor for IHD, ischaemic stroke and DVT. Serum Vitamin B12 and folate concentrations play significant role in pathogenesis, as both are important co-factors in the methionine cycle. Nutritional deficiencies and enzyme defect in the methionine homocysteine pathway contributes to HHcy. We report here 4 cases of HHcy (AMI 1, ischaemic Stroke 2 and DVT 1), all in the age group of 18 to 40 years. We propose that HHcy is grossly under-reported in our country and all cases with ischemic pathology in younger age should be screened for HHcy.

Key words: Hyperhomocysteinaemia, methionine, vitamin B12.

Introduction

Hyperhomocysteinaemia (HHcy) is a common metabolic disorder characterised by systemic elevation of the thiol amino acid, homocysteine, formed as an intermediate of the methionine cycle[1]. Deficiencies of cofactors of the methionine cycle such as vitamin B6, B12, and folate, or defects of enzymes such as cystathionine beta-synthase (CBS) or methylenetetrahydrofolate reductase (MTHFR), contribute to the genesis of HHcy. HHcy is associated with premature atherosclerosis, endothelial dysfunction and arterial and venous thrombosis[2].

Case 1

BR, an 18-year-old, non-diabetic, non-hypertensive non-smoker male, vegetarian, student from Kalimpong, West Bengal, India, was admitted with chest pain of 7 hours duration. The chest pain was sudden in onset, constricting in nature, radiating to left arm, aggravated with activities, associated with profuse sweating and was not relieved with oral analgesics. The patient had no history of fever, palpitation, dyspnoea, cough or haemoptysis, denied any past or current addictions, and had no family history of sudden cardiac death. We received the patient in respiratory distress with pulse rate of 98/minute regular, and BP 110/74 mmHg over the right upper arm in supine position. He was tachypnoeic with respiratory rate of 26/min with normal SpO_2 in room air. ECG revealed lateral wall AMI without AF and the patient was thrombolysed with Tenecteplase (Fig. 1A). Repeat ECG after 1 hour showed >50% reduction of ST elevation. 2D ECHO showed hypokinetic postero-lateral wall, moderate systolic dysfunction with LVEF 41%. Coronary angiography revealed unremarkable D1/D2, thrombotic plaque at proximal D1, dominant RCA and totally occluded distal LCX (Fig. 1B). Blood tests suggested macrocytic anaemia and elevated serum homocysteine with decreased serum vitamin B12 levels (Table I). Other causes of a hypercoagulable state were ruled-out. We arrived at a final diagnosis of posterolateral AMI in a young male with HHcy and macrocytic anaemia due to vitamin B12 deficiency. Patient was treated with parenteral vitamin B12 supplementation 1000 µg IM weekly for 6 weeks, then monthly, along with folic acid supplementation. He had an uneventful recovery and is currently under regular follow-up.

Case 2

MT, 30-year-old non-diabetic, non-hypertensive, alcoholic male smoker, presented with sudden onset right-sided hemiparesis, simultaneously involving proximal and distal limbs. The weakness rapidly progressed to complete paralysis, within a span of 30 minutes without headache, fever, vomiting, convulsion, diplopia, or vertigo. The patient had slurring of speech and deviation of mouth towards the left side. There was no family history of stroke or sudden cardiac death. On arrival, his pulse was 96/minute, regular, and normal in volume, with no special character, all peripheral pulses well palpable, and no radioradial or radio femoral delay. The BP was 128/84 mmHg measured at left upper arm supine position, respiration 20/min, and Spo2 99% in room air. Neurological examination revealed complete right-sided hemiparesis. NCCT brain showed no hemorrhage (Fig 1C). Our stroke thrombolysis team was activated and thrombolysis was performed with

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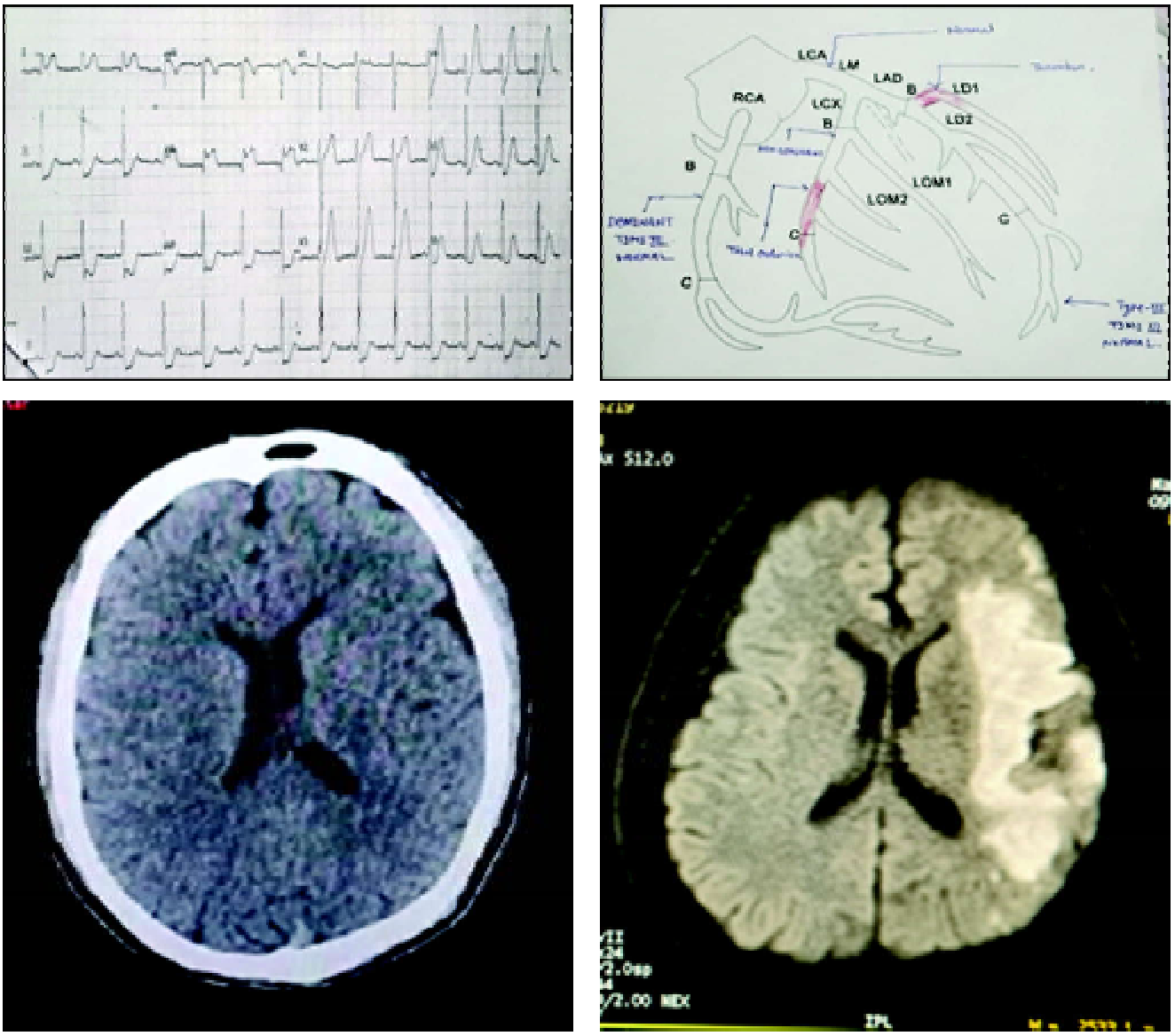

Fig. 1: *Showing investigation findings of contributing cases. 1A: ECG from Case 1 showing STEMI involving anterior wall; 1B: Diagrammatic representation of coronary angiography findings of Case 1; 1C: NCCT brain from Case 2, prethrombolysis; 1D: MR DWI showing large left MCA territory infarct from Case 3.*

Tenecteplase. Two hours after thrombolysis, the NIHSS score reduced from 12 to 7, and was zero after 24 hours of thrombolysis. Carotid artery Doppler showed a 5.5 x 3.0 mm non-occlusive thrombus in the left ICA, which was confirmed by MR angiography. Blood tests documented ANA seronegativity and elevated homocysteine levels with normal blood levels of protein C, protein S and antithrombin III (AT III) (Table I). ECG 12 lead showed sinus rhythm. The upper GI endoscopy was non-contributory. We considered a final diagnosis of complete right-sided hemiparesis due to atheroembolic stroke on the background of HHcy and normal vitamin B12 level, possibly due to an enzyme defect or deficiency in the methionine homocysteine metabolism cycle (Fig. 2). The patient was treated with antiplatelet therapy and is presently on physical rehabilitation care.

Case 3

RT, a 28-year-old non-diabetic, non-hypertensive, non-smoker, non-alcoholic male from Darjeeling, presented with right-sided hemiparesis of acute onset, along with slurring of speech and deviation of mouth towards left side, 2 days back. He had no headache, fever, vomiting, convulsion, diplopia, vertigo, or sensory symptoms. There was no positive family history of stroke or sudden cardiac death. Initial assessment revealed normal vital parameters including pulse 90 bpm regular, BP 120/74 mmHg. Neurological examination revealed right-sided complete

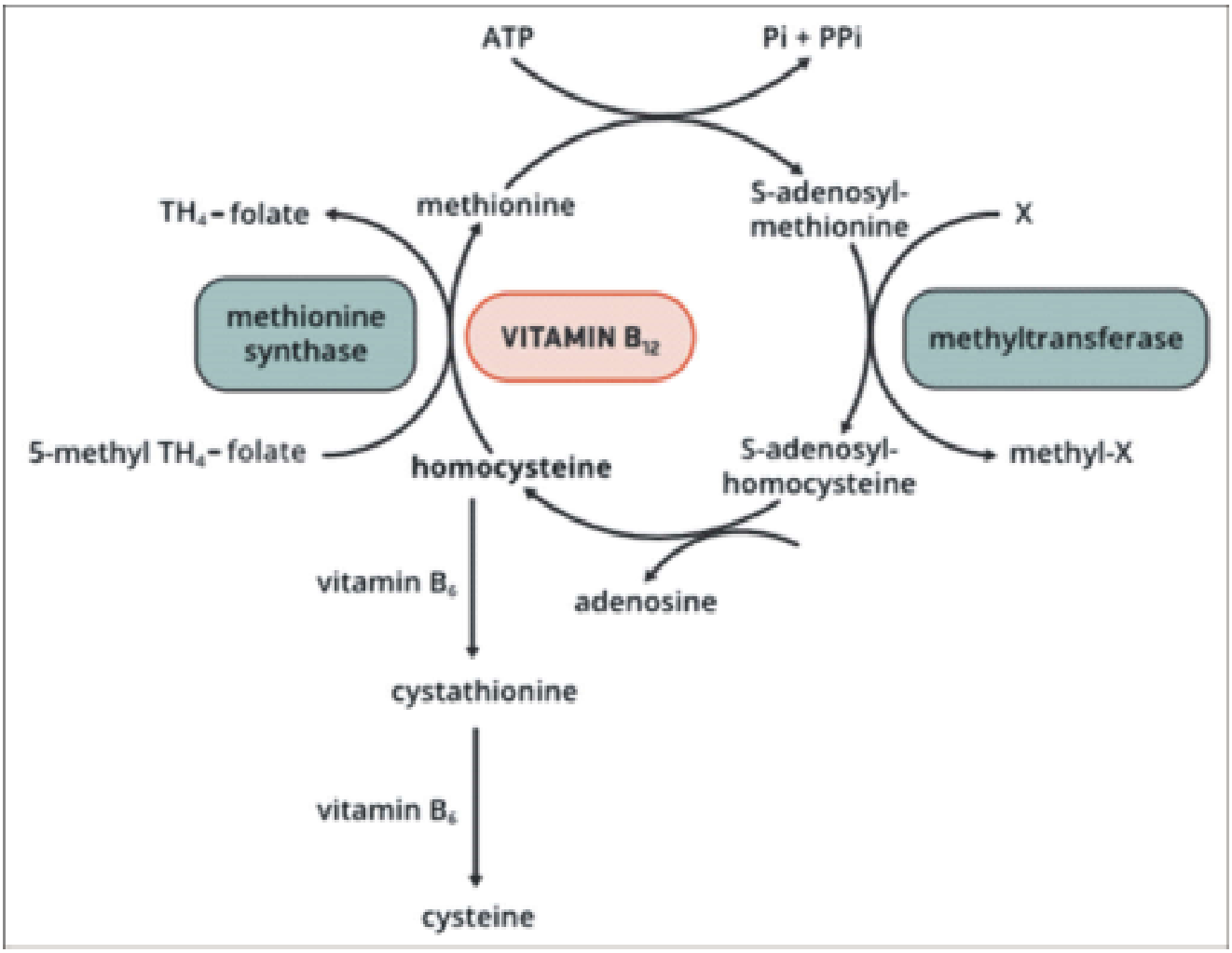

Fig. 2: *Methionine homocysteine metabolism cycle.*

hemiparesis with characteristic UMN features. CT scan revealed hypodensity in left temporo-parietal region, suggestive of acute infarct. MRI brain revealed large acute infarct involving left MCA territory (Fig. 1D). MR angiography and carotid artery Doppler were normal. ECG 12 lead showed sinus rhythm. Blood tests were normal, except for high EPO level characteristic of residence at high altitude, and macrocytosis arising out of diminished serum vitamin B12 and folate levels, along with elevated homocysteine. Other causes predisposing to hypercoaguability were ruled-out (Table I). He was diagnosed to be a case of ischaemic stroke in young with HHcy contributing to a hypercoaguable state. The patient received aspirin, rosuvastatin, B12 and folate supplementation and was discharged with follow-up at the Physical Medicine and Rehabilitation Department.

Case 4

AS, a 40-year-old non-diabetic, non-hypertensive, non-smoker, non-alcoholic, vegetarian female presented with recurrent right-sided lower limb swelling for last 2 years. She had a pulse rate of 104/minute regular, with good volume and all peripheral pulses being well palpable. All other vital parameters were normal. Doppler study revealed an echogenic thrombus at right popliteal vein extending up to right common femoral vein. Doppler of all other limbs, as well as the ECG and echocardiography, was normal. Blood biochemistry including tests for protein C, protein S and AT III was normal, except for high homocysteine and reduced vitamin B12 (Table I). We entertained a diagnosis of recurrent DVT of right popliteal vein without evidence of embolic sequel, on the background of HHcy leading to a thrombophilic state.

Discussion

The essential amino acid methionine is usually present in diet far in excess of physiological needs. Excess methionine

is degraded by the methylation cycle to homocysteine, which can be remethylated back to methionine or catabolised by transulfuration to cysteine. In this metabolic cycle, activation of methionine generates S-adenosylmethionine (SAM), which serves as the "universal methyl donor" for numerous methylation reactions. The recycling of Homocysteine back to methionine requires the enzyme methionine synthase (also known as 5-methyltetrahydrofolate-homocysteine methyltransferase), along with folate in the form of 5-methyltetrahydrofolate as the methyl donor and vitamin B12 in the form of methylcobalamin as a cofactor (Fig. 1).

Table I: Laboratory data with normal values.

	Normal value	Case 1	Case 2	Case 3	Case 4
BMI	18.5 - 23 kg/m^2	19.4	22.2	20.7	21.5
Hb	13 - 15 g/dL	11.0	14.8	16.9	9.8
MCV	80 -100 μm^3	103	92	100	112
WBC	4,000 - 10,000/μL	13,300	7,000	6,100	9,800
Platelet count	150 - 500/μm	218	206	95	187
FBS	<100 mg/dL	85	93	98	105
TSH	0.7 - 5.2 mIU/L	1.6	2.1	1.8	2.4
Creatinine	0.6 - 1.2 mg/dL	0.5	0.9	0.5	0.7
LDL Cholesterol	<100 mg/dL	52	81	55	104
Triglyceride	50 - 150 mg/dL	36	163	109	134
Uric Acid	3.6 - 7 mg/dL	4.7	4.0	8.7	6.2
Serum Protein	6.0 - 8.3 mg/dL	7.4	6.8	7.0	7.2
Serum Albumin	3.5 - 5.5 mg/dL	4.2	3.9	4.1	5.0
Serum B12	120 - 914 pg/mL	67.83	239	106	51
Serum Folate	3.1 - 19.9 ng/mL	4.82	6.2	2.0	3.2
Homocysteine	3.3 - .2 μmol/L	30.82	48.54	>50.00	41
Lipoprotein (a)	0 - 30 mg/dL	18.35	9.5	25.5	20
Protein C	65 - 135 IU/dL	92.4	97.2	110.6	104.7
Protein S	60 - 160 IU/dL	77.2	87.3	105.8	95.8
Antithrombin III	80 - 130%	96%	102%	113%	88%
ANA	Negative	Negative	Negative	Negative	Negative
APLA	Negative	Negative	Negative	Negative	Negative
ANCA	Negative	Negative	Negative	Negative	Negative
24 hour urinary protein	<30 mg	12	23	27	14
Echocardiography		Hypokinetic postero - with LVEF 41%	No RWMA with LVEF 68%	No RWMA with LVEF 65%	No RWMA with LVEF 70%

It is now well accepted that elevations of homocysteine in the blood arise from genetic defects in homocysteine transsulfuration or re-methylation, or in the transport, delivery or metabolism of cofactors, B12 and folate being the most clinically important. Cystathionine β-synthase deficiency leading to impaired metabolism of homocysteine, MTHFR deficiency leading to impaired 5-methyl tetrahydrofolate generation subsequently leading to reduced availability of methyl groups for the remethylation of homocysteine, and disorders of vitamin B12 absorption, transport, and metabolism, are the primary causes of HHcy in clinical settings[3]. In this series of 4 cases of HHcy, 3 patients had B12 deficiency (Cases 1, 3 and 4), and the remaining patient had clinical suspicion of an enzyme defect (Case 2). Case 3 also had associated folate deficiency which might be contributory to the genesis of HHcy. We excluded prothrombotic states due to protein C and protein S deficiency, dyslipidaemia and hypothyroidism, as well as those arising from common autoimmune settings (Table I).

Elevated plasma homocysteine is associated with an increased risk of myocardial infarction, stroke, and venous thromboembolism.[4] A meta-analysis found that for every 2.5 μmol/L increase in plasma total homocysteine, the risk of myocardial infarction increases by about 10% and the risk of stroke increases by about 20%[5]. It has been suggested that HHcy may be a late stage predictor of CVD, implying elevated homocysteine levels may not be a primary risk factor for atherosclerosis and CVD, but may increase the risk of clinical disease in those with an atherosclerotic background[6].

The issue of elevated plasma homocysteine levels as predisposition to cerebrovascular disease appears less distinct in the world literature. In the British Regional Heart Study of 5665 men aged 40 to 59 years, baseline homocysteine levels in those who suffered a first stroke during 12.8 years of follow-up were significantly higher. In the same study it was observed that comparison of homocysteine levels of 15.4 μmol/L or more with levels less than 10.3 μmol/L yielded a multivariate relative risk of stroke of 4.7[7]. Accordingly it may be concluded that HHcy is likely to confer a significantly high-risk of stroke.

Elevated homocysteine has a documented association with unprovoked, deep vein thrombosis (DVT) and pulmonary embolism (PE)[8]. In a study of 60 patients with DVT from Turkey, mean homocysteine was significantly higher in patients over the age of 40 years[9]. In our series, all patients were between 18 to 40 years and the questionable issue of homocysteine elevations with age, does not appear to influence our findings.

Considering hypercoagulable states seems clinically judicious when encountering stroke, CVD or DVT in young. Thomas proposed the mnemonic CALMSHAPES to remember the clinically important hypercoagulable states: Protein C deficiency, Antiphospholipid syndrome, factor V Leiden mutation, Malignancy, protein S deficiency,

hyperhomocysteinaemia, antithrombin III deficiency, prothrombin G2021A mutation, factor eight excess, and Sticky Platelet syndrome[10]. With better understanding and refined diagnostics, all these are being picked up more frequently in recent years.

Conclusion

We conclude that HHcy confers an independent predisposition to a hypercoagulable state, and in the appropriate metabolic milieu, can lead to premature prothrombotic clinical events, as exemplified by our cases. Increasing physician awareness to consider this often neglected procoagulant risk factor is the central purpose of this case series.

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CASE REPORT

JIACM 2024; 25 (3): 138-40

Rare Presentation of Dermatomyositis with Haemophagocytic Lymphohistiocytosis

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Abstract

22-year-old male presented with fever, yellowing of the eyes and urine, rash, and had been unable to move since a week. Per-abdomen examination revealed splenomegaly. An evaluation of the nervous system revealed proximal myopathy more in lower limbs than the upper limbs. Routine laboratory tests revealed pancytopenia, abnormal liver function tests, elevated ferritin, elevated triglycerides, and reduced fibrinogen. Mixing studies revealed presence of inhibitors. Anti-MI 2 antibodies, Anti-KU antibodies, and SRP-borderline were positive in the myositis profile. Dermatomyositis was the underlying cause in the Haemophagocytic-lymphohistiocytosis (HLH) diagnosis. Although rare (4%), the connection of HLH with inflammatory myositis is deadly (77% mortality).

Key words: Haemophagocytic-lymphohistiocytosis, dermatomyositis, clotting factor deficiency.

Case report:

A student, aged 22, who had been experiencing body rashes, difficulty walking, a fever, and jaundice for a week presented to our emergency room. The patient first had difficulty in walking, but was able to do so with assistance. Over the course of a week; however, the patient's weakness worsened and he eventually became bedridden. He also reported a rash that spread to the torso ((Fig. 1), upper (Fig. 2) and lower limbs, which worsened over the course of two weeks. He also had a low-grade fever which had been present for 6 months, but had gotten worse over the last 2 weeks. The patient's eyes and urine had yellow discolouration since the past six months. There were no sensory or cranial nerve impairments. He had no concomitant conditions, wasn't a smoker or alcoholic, and ate a variety of foods.

Upon general inspection, erythematous rashes covered the upper, and lower limbs, and trunk, alongwith icterus and pallor. A thorough neurological evaluation revealed no cranial nerve impairments or sensory involvement and normal higher mental function. In the motor assessment, tone was normal, power was 2/5 in the lower limbs' proximal muscles and 4/5 in the upper limbs' and lower limbs' distal muscles. There was discomfort in the muscles. We were contemplating along the lines of inflammatory myositis. Laboratory tests revealed a haemoglobin level of 3.7 g/dL, a total white cell count of 2210/mm^3 predominately composed of neutrophils, and a platelet count of 25,000/

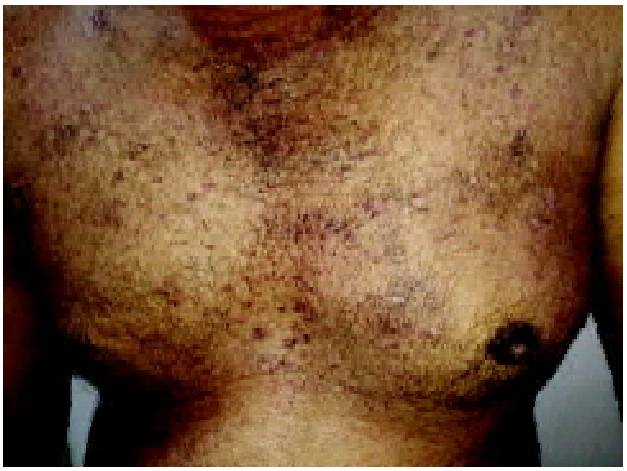

Fig. 1: *A rash spread over the torso.*

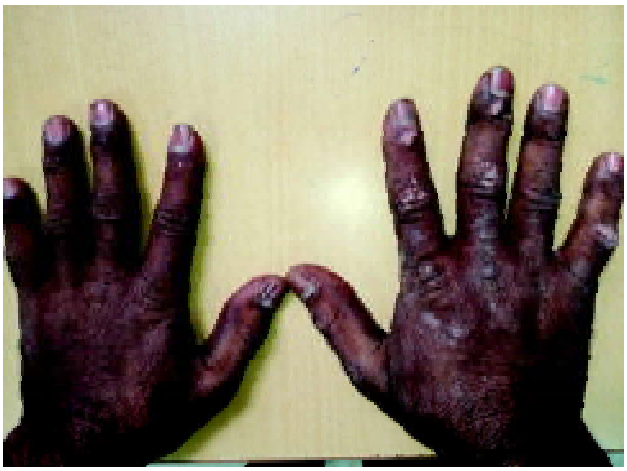

Fig. 2: *Gottron's papules over knuckles.*

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mm^3. Total bilirubin was 1.55 mg/dL and direct bilirubin was 1.50 mg/dL. Three times above average liver enzyme levels were observed. The aPTT with more than 3 minutes, PT/INR was 24.3/1.7. LDH was increased. He had a normal CK-MB. There was a small increase in CK-NAC. Triglycerides were 250 mg/dL and serum ferritin was 40,000 μg/L. Prior to admission, a bone marrow biopsy revealed normal haemopoietic cells as well as a small number of epitheloid and myeloid band formations, rendering it inconclusive. Anti-MI 2 antibodies, Anti-KU, and SRP-borderline were positive in the myositis profile. The results of a mixing study, which adjusted both the APTT and the PT, revealed presence of inhibitors. Steroids were started for the patient. Cyclosporine was added since the response was subpar. The patient was supported with PRBCs, FFPs, and RDPs transfusion. Because fibrinogen was low, cryoprecipitate was administered. Because of the patient's persistently low platelet count and increased PT and APTT, we were unable to perform a bone marrow biopsy. Patient was lost for follow-up after that.

Discussion

HLH is a hyper-inflammatory syndrome that can be primary or develop as a result of autoimmune conditions, infections, cancer, or other factors[1,2]. Despite improvements in the diagnostic evaluation of febrile[3] patients, HLH continues to be a potentially lethal disease entity and is difficult to diagnose. The pathogenesis includes excessive macrophage activation and dysregulated immune activation. The hallmarks of the immunologic abnormalities in HLH are the excessive production of proinflammatory cytokines, unchecked activation of T-cells, and macrophages and diminished natural killer cell and cytotoxic cell activities[5]. An excessive cytokine storm caused by macrophage activation in the host results in tissue damage and organ malfunction. Host factors or environmental chemicals may cause an excess of pro-inflammatory or inadequate anti-inflammatory responses, which in turn cause this cytokine storm[1]. As a result, HLH that develops in the presence of an underlying infection is referred to as reactive or secondary haemophagocytic syndrome or secondary HLH, while HLH that develops in the presence of an underlying rheumatologic disease, such as rheumatoid arthritis, is referred to as macrophage activation syndrome (MAS).

In individuals with juvenile idiopathic arthritis, SLE, adult-onset Still's disease, or other autoimmune disorders, case reports describing MAS have been recorded, but not with dermatomyositis[4,5,6]. All HLH cases should be classified based on origin and pathophysiology, according to human and murine studies, because therapy approaches for each case may differ[7]. However, all aetiologies result in an overproduction of ferritin. Immunosuppressive therapy is used in conjunction with vigorous treatment of the underlying illness to treat secondary HLH.

Clinicians across the world use the HLH-2004 standard protocol[8]. In lymph node and bone marrow biopsy samples, it is challenging to identify haemophagocytosis in the early stages of disease[9]. It is a frequent misperception that haemophagocytosis must be detected on immunological tissue or bone marrow biopsies in order to diagnose HLH[10,11]. Haemophagocytosis is not actually necessary for diagnosis[10,11]. Instead, a diagnosis must be made by determining whether an HLH-associated gene mutation exists or by fulfilling five of the following eight criteria: fever 38.5° C, splenomegaly, hypertriglyceridaemia, haemophagocytosis in the bone marrow, spleen, lymph nodes, or liver, low or absent natural killer cells, ferritin >500 ng/mL, elevated soluble CD25, and peripheral blood cytopenias.

Six of these criteria were met by our patient; thus we classified our case as HLH secondary to dermatomyositis[12]. The patient also exhibited a common factor pathway deficit, which was on intriguing co-morbidity.

Conclusion

The intriguing part of this case was that HLH secondary to Dermatomyositis was coupled with common pathway factor deficiency. HLH should be considered in all patients with inflammatory myopathies accompanied by cytopenias, aberrant LFTs, and high ferritin levels.

Declaration of patient consent: The authors certify that they obtained all appropriate patient consent forms. In the forms the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Sit by my side, do not plunder

An accidental apple falling in front of Newton,
Made him to think about gravitational force,
Same apple to a French lead him to discover phlogin,
Molecule of century for diabetes kidney and heart.
Much before Leopold seeing dad percussing wine bottle,
Propagated idea of using percussion in clinical medicine,
Woodpecker searching safe nest for her eggs,
Assessed with her beak hollow wood beneath.
Laennec watched the way kids talked each other,
Developed new technique of auscultation,
Precursor of stethoscope removing that sore,
No need keeping ears close to chest anymore.
A fungus overgrown in petri dish in a lonely lab,
Alexander Fleming discovered penicillin,
Far east Bose watching Mimosa reacting to touch,
Proved plants too are living thriving and growing.
A wire tied around stem of an inclining big tree,
Months later enveloped by its epithelial tissue,
This is how healing takes place in our body & tissues,
So said an Ortho Professor to his eager disciples.
Hibiscus buds detached from their stalk,
Blooming into bright red flowers hours after,
Tuberose attracting herds of humming bees,
Though kept aside from their mother stock.
Which is that powerhouse making them to blossoms,
Who prompted bees to collect nectar from bloom ?
All this reflects omnipresence of omnipotent,
Building block of that chip we are made of.
Peeled skin of arjuna tree countryside,
Telling aloud its utility in heart ailments,
People plucking red periwinkle flowers,
Others collect black plums for high sugar.
Umpteen hints dropped by mother nature,
So many clues containing ills without pills,
My dear remedies in plenty look and search,
Sit by my side do not plunder no besmirch.

– Dr Shridhar Dwivedi,
Senior Consultant Cardiologist,
National Heart Institute, New Delhi

CASE REPORT

JIACM 2024; 25 (3): 141-43

A Rare Case of Dyselectrolytaemia – Adult Onset Bartter Syndrome

Shashidhar KC, Savitha V**, Ganesh****

Abstract

Bartter syndrome (BS) is a rare autosomal recessive disorder affecting salt reabsorption in the thick ascending limb of the loop of Henle. This report highlights clinicopathological findings and genetic studies of classic BS in a 43-year-old male patient who presented with persistent hypokalaemia, hypocalcaemia and hypercalciuria with low cognitive abilities and sensorineural hearing loss, diagnosed as Bartter syndrome. Genetic analysis of the patient was done which did not reveal any mutations of NKCC2 SLC12A1, KCNJ1, CLCNKA, CLCNKB and MAGE-D2. This case represents an atypical presentation of classic BS in an adult patient. Clinical and laboratory findings with persistent dyselectrolytaemia in the form of hypokalaemia, hyponatraemia, hypocalcaemia with hypercalciuria with mild sensorineural deafness and low cognitive abilities were important for diagnosis of this case.

Key words: Hypokalaemia; hypocalcaemia, hypercalciuria, sensorineural hearing loss, low cognition.

Introduction

Bartter syndrome (BS) is a rare renal tubulopathy that was first described by Bartter in 1962. The condition is characterised by polyuria, hypokalaemia, metabolic alkalosis, and hyper-reninaemic-hyperaldosteronism with normal or slightly low blood pressure due to renal loss of sodium and hyperplasia of the juxtaglomerular apparatus (JGA). The condition is also referred to as salt-wasting nephropathy[1]. The prevalence of BS is 1 in 1,000,000, compared with 1 in 40,000 for Gitelman syndrome (GS)[3]. The classification depends on the severity of the symptoms and the type of genetic mutation. Clinically, BS can be classified into two variants, antenatal/neonatal BS and classic BS, according to the onset of age. Genetically, BS can be classified into five variants according to the type of gene mutation[2]. Type V BS presents as classic BS, which is characterised by polyuria, polydipsia, and a tendency for dehydration, hypocalcaemia, hypomagnesaemia and hypercalciuria. Patients with classic BS might have symptoms in the first two years of life, but most cases are usually diagnosed at school-age or in adolescence. However, age of onset and clinical severity is highly variable[5].

Here, we present a case of late-onset BS, with typical hypokalaemia, hypomagnesaemia, hypocalcaemia, and hypercalciuria with low cognitive ability since birth and mild sensorineural hearing loss, corresponding to the features of type V BS.

Case report

A 43-year-old male patient presented to A and E with persistent vomiting, pain abdomen and altered sensorium since 3 days with no history of fever and no prior comorbidities.

He was a labourer by occupation with lower socio-economic status. His mother gave a history of mild deafness from childhood (around 10 years) and was intellectually challenged since childhood. He was a reformed alcoholic left, 2 years back and a chronic smoker with 1 pack beedis per day. There was no significant family history with and an unremarkable prenatal history. He was previously diagnosed to have suspected Wernicke's encephalopathy/Viral encephalitis but was not on follow-up. There was no use of diuretics, laxatives or nephrotoxic drugs.

On examination, the patient was moderately built and nourished with no signs of pallor, icterus, cyanosis, clubbing, lymphadenopathy or oedema and vitals were stable.

On evaluation, he had a normocytic normochromic anaemia with neutrophilic leukocytosis. Renal function tests showed hyponatraemia and hypokalaemia, for which correction was given. ABG showed hypochloraemic metabolic alkalosis with Ph 7.56, bicarbonate - 36 mmoL/lt. LFT was within normal limits. Serology for HIV, HBsAg, and Anti-HCV were non-reactive. Urine routine was normal. Amylase and lipase were within normal limits. USG abdomen and pelvis showed mild increase in renal cortical echogenicity of both kidneys with maintained corticz – medullary differentiation. 2D ECHO was normal. CT Brain was done as he had altered sensorium and showed chronic infarct in posterior limb of

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left internal capsule with age disproportionate cerebral atrophy. MRI Brain showed mild diffuse cerebral atrophy – disproportionate to age. RFT was monitored regularly. Patient had persistent hypokalaemia and correction was given for the same. On the 4th day of hospitalisation he developed tetany (Trousseau's sign and Chvostek's sign were positive). Serum calcium and magnesium were low and correction was given for the same. Upon re-evaluating the history and examination, the patient gave a history of polyuria and polydipsia since 1 year. Release reflexes were present (glabellar tap and palmomental reflexes). His serum calcium, magnesium, electrolytes were monitored regularly and correction was given for the same. Spot urine calcium, magnesium, sodium and potassium were within normal limits. 24-hour urinary calcium, sodium, and magnesium were high. 24-hour urinary potassium was within normal limits. Input and output monitoring was done daily. Upper gastrointestinal endoscopy was done which showed gastric erosions and treatment was given for the same. On suspicion of adult onset Bartter syndrome, Tab Indomethacin 75 mg once daily was introduced following which the patient improved significantly, both clinically and biochemically. Genetic analysis was done which did not reveal any mutations of NKCC2 *SLC12A1, KCNJ1, CLCNKA, CLCNKB* and *MAGE-D2*. After 1 month, his reports were serum pH: 7.326, serum bicarbonate: 21.7 mmoL/L, serum potassium: 4.3 mEq/L. Subsequently, repeat calcium, magnesium, electrolytes are within normal limits and polydipsia and polyuria had recovered.

Discussion

Bartter syndrome was first described by Bartter *et al* in 1962[1]. Bartter syndrome can be inherited or acquired. Inherited Bartter syndrome is divided into five subtypes: types I-IV are due to a loss of function mutations and type V due to gain of function mutation. Types I, II, and IV are usually called antenatal Bartter syndrome while type III is called adult-onset/classical Bartter syndrome. Type V Bartter syndrome can be distinguished from all other types by the presence of hypocalcaemia and hypomagnesaemia. In addition to this, there are several acquired causes of Bartter syndrome, including autoimmune disorders like Sjogren syndrome, Hashimoto thyroiditis, scleroderma, and several drugs like aminoglycosides, loop diuretics, amphotericin, etc[4].

Bartter syndrome is classified into different subtypes according to the gene mutations involved: type I BS is caused by mutations in NKCC2 (*SLC12A1*); type II BS is caused by mutations in ROMK (*KCNJ1*)18; type III BS is caused by mutations in CLC-Kb (*CLCNKB*)19; type IVa BS is caused by mutations in barttin (*BSND*) 20 and type IVb BS is caused by mutations in CLC-Ka and CLC-Kb (*CLCNKA* and *CLCNKB)*. All these four types are recessive disorders. An additional distinct subtype of BS, considered as type V BS by many investigators, is ascribed to gain-of-function mutations of *CASR* and is characterised by an autosomal dominant hypocalcaemic hypercalciuria. More recently, mutations in melanoma-associated antigen-D2 (*MAGE-D2*) have been implicated in a transient form of antenatal BS, also referred to as type V BS according to some reports. This newly recognised form of BS is characterised in most cases by a very early onset of severe polyhydramnios and complete resolution of symptoms after birth[6].

Types I, II, and IV have a neonatal presentation, while in type III, the symptoms begin in the first 2 years of life, but diagnosis is made later, at school age or adolescence.

The pathophysiology of Bartter syndrome is related to defect in the sodium/potassium/chloride co-transporter, or potassium channel in thick ascending limb of the loop of Henle. This leads to reduced reabsorption of sodium, potassium and chloride in the thick ascending limb of the loop of Henle. This in turn results in the delivery of these ions to the distal segments where only some sodium is reabsorbed and potassium is secreted[7].

Patients with Bartter syndrome exhibit a blunted pressor response to exogenous administration of angiotensin II. Recent reports suggest that overproduction of prostaglandins by the kidney plays a major role in the pathogenesis of this syndrome. Thus, administration of indomethacin, an inhibitor of prostaglandin synthesis, was followed by clinical and chemical improvement in the patients and recovery of their vascular sensitivity to angiotensin II as seen in our patient[8].

The classical pharmacological therapy includes potassium chloride supplementation, prostaglandin inhibitor (indomethacin), and aldosterone antagonist (spironolactone)[6]. Our patient improved with indomethacin. Indomethacin inhibits PGE2 which is overexpressed in Bartter syndrome. There are a few reports of Bartter syndrome in adults[7].

Conclusion

Though Bartter syndrome is diagnosed at a young age, an adulthood presentation is possible due to phenotypic variation as in our case.

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CASE REPORT

JIACM 2024; 25 (3): 144-47

Hyperpigmentation with Acute Delirium and Idiopathic Intracranial Hypertension: Suspect Addison's Disease

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Abstract

Addison's disease, presents with a wide variety of signs and symptoms making diagnosis challenging. The neuropsychiatric symptoms are well documented but not fully understood. Addison's disease (AD) associated with idiopathic intracranial hypertension (IIH) has been seen in children but there are very few cases reported in adults. We are presenting a case of 19-year-old lady of Addison's crisis admitted with neuropsychiatric symptoms and had IIH on investigations which improved on treatment.

Key words: Addison's disease (AD), Addison's crisis (AC), Idiopathic Intracranial Hypertension (IIH), neuropsychiatric symptoms, hyperpigmentation.

Introduction

Addison's disease (AD), also referred as primary adrenal insufficiency, is a rare autoimmune disorder affecting males and females equally, with a prevalence rate of 100 - 140 cases per million. AD is characterised by impairment of the adrenal glands, which prevents enough cortisol, aldosterone, and androgen production in human body[1]. The usual signs and symptoms of AD include persistent fatigue, nausea, vomiting, loss of weight, anorexia, hypotension, hyponatraemia, hyperkalaemia, hypoglycaemia, intra- and extra-oral skin pigmentation (bronzing of skin). Neuropsychiatric symptoms include psychosis and mood disturbances which are the unusual presentations during addison's crisis, hence making the diagnosis more challenging.

The clinical syndrome of idiopathic intracranial hypertension (IIH) without any evidence of vascular lesions or space-occupying lesions, without enlargment of the cerebral ventricles, and without a known cause is known as IIH. The syndrome is usually associated with obesity or a number of medications, such as the oral contraceptive pill, amiodarone, cyclosporin, systemic and topical steroids, and antibiotics (nitrofurantoin, and tetracyclines)[2]. However, underlying endocrine conditions such as Cushing's disease, hyperthyroidism, or the injection of thyroxine or growth hormone rarely cause IIH[3]. Though cases of IIH associated with AD in children have been reported, there are only few cases documented of this association in adults[4]. Here we are presenting a case of Addison's disease associated with IIH and neuropsychiatric symptoms.

Case history

A 19-year-old lady presented to the emergency department in a state of altered sensorium, complaining of severe headache. She had an episode of vomiting in the emergency room. On eliciting history, it was revealed that she had an episode of fever 5 days back, 2 episodes of vomiting and since then she was experiencing headache which became very severe last night. The patient was in a state of altered sensorium since last night in the form of extreme irritability and psychosis. No history of convulsions. On leading questions, her husband told that since the past 7 - 8 months they noticed darkening of her skin all over the body. (Fig. 1) which was fair 7 - 8 months back (Fig. 2) for which she visited many local doctors but it was not resolved. There was also a history of easy fatigability, loss of interest in surroundings, abnormal behaviour like agitation, salt craving, increased sensitivity to spicy food, loss of appetite, and weight loss since past 5 - 6 months.

She was married 3 years back (non-consanguineous marriage) and delivered a healthy boy via caesarean section 1 - 1/2 years back. Following this, she took 2 injections of depo medroxyprogesterone acetate as contraceptive 3 months apart with the last dose being administered 8 months back. She was not having any comorbidities, and was not taking any other medications. No history of tuberculosis in the past was found.

On vital examination, she was afebrile with a pulse rate of 62 bpm, Blood pressure of 84/60 mmHg, respiratory rate of 16/min with 97% oxygen saturation on room air. Random Blood sugar was 84 mg/dL.

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On general examination she was thin built, dark in complexion, had mild pallor, mucous membranes of mouth were also dark. Rest of the general examination was normal. She was delirious, irritable with no signs of neck rigidity, Bilateral pupils were normal in size and normally reacting to light. Bilateral plantars were mute. She was moving all four limbs equally and spontaneously. Fundus examination revealed signs of established papilloedema in both eyes (Fig. 3 and 4).

MRI brain was done which did not reveal any space occupying lesion or oedema.

In view of slowly progressive darkening of skin, altered behaviour, papilloedema, and hypotension, a probable diagnosis of Addison's disease with crisis was made.

Fig. 1: *Current photograph - dark skin.*

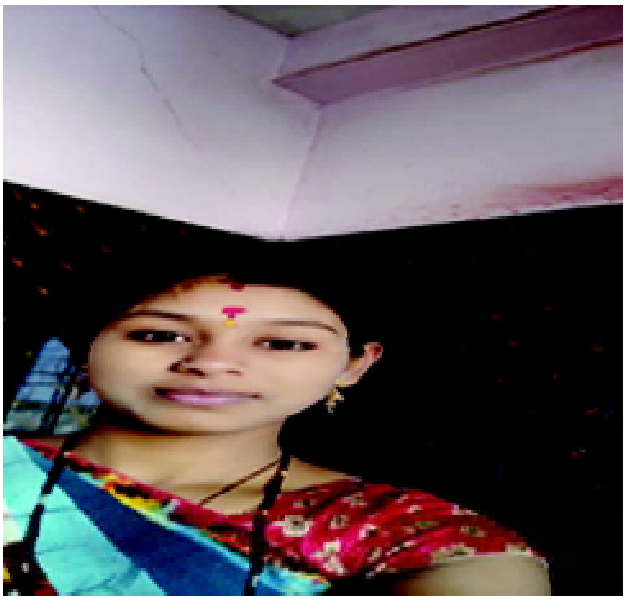

Fig. 2: *Easker photograph - fair skin.*

Routine labs, serum cortisol and serum ACTH levels were sent and injection hydrocortisone was given stat and 6 hourly to the patient. She was hydrated well. Injectable painkiller, antibiotic, and antiedema drug acetazolamide was started. Irritability of patient reduced within 6 hours. A lumbar puncture was done. Opening pressure of CSF was 30 mm of water.

She was re-evaluated the next morning. Now, she was conscious, oriented to time, place and person. Both pupils were normal sized reacting to light. She had normal vision with full bilateral eye movements. All limbs were moving equally.

Lab investigations revealed hyponatraemia – serum sodium 125 meq/L, with serum cortisol level 0.17 ug/dL and serum ACTH - 112 pg/mL. Lab investigations (Table I) combined with signs and symptoms edged towards a diagnosis of primary adrenal insufficiency. CECT (Abdomen + Pelvis) done which was within normal limits.

The relatives were counselled about the need for 21-alpha hydroxylase antibodies testing; the confirmatory test for autoimmune Addison (primary adrenal insufficiency) but could not be done due to non affordability.

She responded dramatically to steroids with symptomatic improvement seen within 24 hours of initiation of treatment. She regained normal sensorium, with no further complaints of headache, fever or nausea.

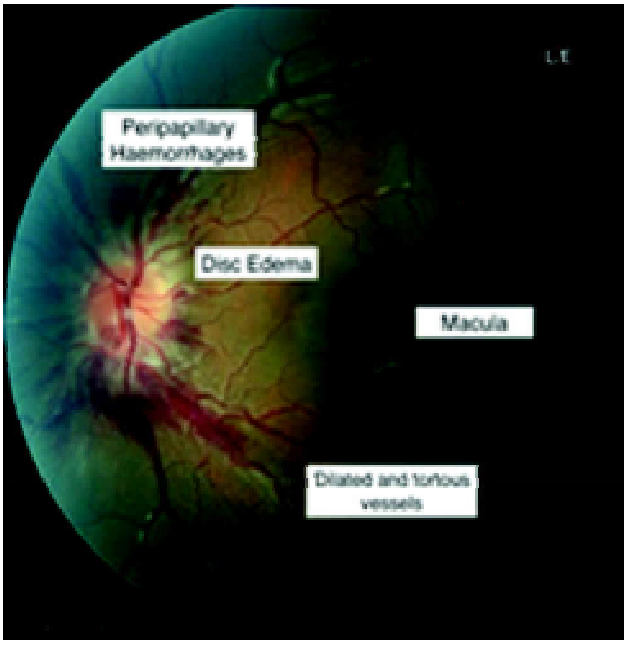

Fig. 3: *Papilloedema left eye.*

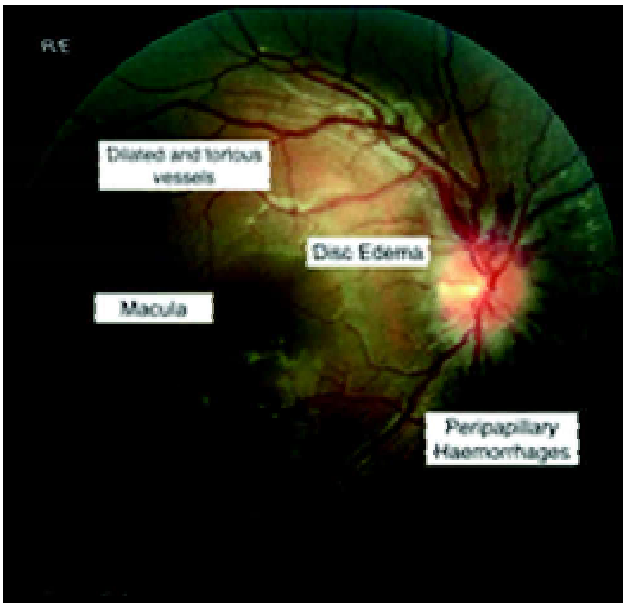

Fig. 4: *Papilloedema right eye.*

Table I:

Labs Parameter	Values
Haemoglobin	9.2 g/dL
Serum Sodium	125 meq/L (low)
Serum Potassium	3.2 meq/L
Serum Cortisol	0.17 μg/dL (low)
Serum ACTH	64.7 (Increased)
RFT/LFT/TFT	Within Normal Limits

Discussion

Addison's disease has an unusual presentation with a wide range of signs and symptoms, which can be confounding and often delay a definitive diagnosis.

Table II:

Symptoms	Incidence
Generalised weakness	>90%
Weight loss	>80%
Gastrointestinal symptoms	>80%
Body aches	18%
Salt craving Hyper pigmentation Syncope Disorientation	12 - 15%
Psychiatric symptoms	Rare

However, the common symptoms are mentioned (Table II) and psychiatric symptoms (sleep difficulties, mood and behaviour abnormalities) are rare. The specific cause of neuropsychiatric symptoms associated with AD is unknown; however, they may be due to abnormalities in electrophysiological, metabolic, and electrolyte imbalance[1]. The profound decrease in glucocorticoids that underlies many of the manifestations of Addison's disease is likely to contribute to the development of neuropsychiatric symptoms. Cortisol, the primary glucocorticoid in the body, is lipid soluble and therefore can diffuse through cell membranes and bind to intracellular glucocorticoid receptors in target cells. Once cortisol is bound to its receptor in the cytoplasm, the hormone-receptor complex translocates to the nucleus where it interacts with regulatory DNA sequences and modifies gene transcription. Glucocorticoid receptors are distributed throughout the brain, but are particularly abundant in the hippocampus. It has been demonstrated that adrenalectomy produces massive granule cell death in the dentate gyrus of the hippocampus. It is possible that granule cell death resulting from cortisol deficiency interrupts the hippocampal tri-synaptic circuit, producing memory impairment and cognitive changes[6,7].

Hyponatraemia occurs in the majority of patients and may contribute to cognitive changes and encephalopathy by causing brain swelling and increased intracranial pressure.

Hyperpigmentation occurs because melanocyte stimulating hormone (MSH) and ACTH share the same precursor molecule, Pro-opiomelanocortin (POMC). Then anterior pituitary POMC is cleaved into ACTH, MSH and beta lipoprotein. The subunit ACTH undergoes further cleavage for production of alpha-MSH, the most important MSH for skin pigmentation. One of the most important distinguishing feature of primary adrenal insufficiency is hyper-pigmentation. Conversely in secondary adrenal insufficiency, the skin has an alabaster like paleness due to lack of ACTH secretion.

The hallmark sign of Primary Addison's disease is hyperpigmentation of the skin due to excessive ACTH production, which in our case served as an important diagnostic clue (Fig. 1).

IIH is defined as the clinical syndrome of raised intracranial pressure, in the absence of space-occupying lesions or vascular lesions, without enlargement of the cerebral ventricles, for which no causative factor can be identified IIH is a diagnosis of exclusion. Persistent headaches, nausea, vomiting are the characteristic signs and symptoms of this condition. It is classically associated with obese females of reproductive age but is also known to occur in children Although IIH is often associated with papilloedema but it is not an absolute requirement to make the diagnosis.

Although the pathogenesis of IIH is unknown, proposed

theories include increased CSF production, decreased CSF absorption, or increased cerebral venous pressure creating resultant rise in CSF pressure. CSF arginine vasopressin (AVP) levels in IIH patients were shown to be higher than healthy controls. This appears to be in accordance with studies that patients with glucocorticoid insufficiency exhibit higher plasma AVP levels and prolonged hypersecretion of AVP despite plasma dilution. Thus, elevated serum and perhaps CSF AVP levels may facilitate IIH in Addison's illness[2,3].

It has also been postulated that IIH arises from an increase in CSF volume secondary to delayed CSF absorption, without ventricular dilatation due to increased resistance of flow across absorptive channels following acute corticosteroid withdrawal. The putative effects of acute withdrawal of steroids implicate the enzyme 11 beta-hydroxysteroid dehydrogenase type1, an enzyme highly expressed in choroid plexus epithelium that converts inactive cortisone to active cortisol. Cortisol can activate mineralocorticoid receptors in the choroid plexus with similar affinity to aldosterone, leading to active sodium secretion by the Na^+/K^+ ATPase at the choroid plexus membrane, movement of sodium ions into the cerebral ventricle, and an osmotic gradient to drive CSF secretion[4].

Similarly there have been case reports showing that after surgical treatment of Cushing's disease, IIH develops as a rare complication. A sudden lowering of supraphysiological levels of glucocorticoids can lead to IIH[4,5].

Zainordin *et al* reported a case of partial adrenal suppression with prolonged use of depomedroxy progesterone acetate (DMPA) for 16 years[8]. DMPA has been identified to have a notable cortisol-like glucocorticoid activity on the hypothalmic-pituitary-adrenal (HPA) axis since the 1970s when patients on DMPA presented with Cushingoid symptoms, such as weight gain, facial swelling and generalised oedema .This cortisol-like effect is believed to exert a negative feedback action on the hypothalamus or the pituitary leading to low plasma ACTH, suppression of adrenal function and decreased cortisol secretion and manifesting as secondary adrenal insufficiency. In our case the patient had received only 2 doses of DMPA and manifested as primary adrenal insufficiency so we can conclude that medroxyprogesterone acetate was not responsible for adrenal insufficiency.

In this case, hyperpigmentation increasing over a period of 7 months served an important initial clue and further lab investigations that revealed hyponatraemia, hypoglycaemia and hypotension consolidated the diagnosis. A dramatic response to steroids with rapid symptomatic improvement within 24 hours justified the diagnosis.

Conclusion

Addison's disease should be considered when hyperpigmentation, hyponatraemia and IIH co-exist. Though acetazolamide is the treatment for IIH, early steroid replacement helps in alleviating symptoms and preventing vision loss, which can be catastrophic for the patient.

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CASE REPORT

JIACM 2024; 25 (3): 148-50

A Case of Sickle Cell Disease First Diagnosed at the Age of 62 Years Following Acute Pancreatitis

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Abstract

Sickle cell disease (SCD) is a haemoglobinopathy characterised by haemolytic anaemia and vasoocclusion. There can be varied clinical manifestations of SCD. It usually manifests in childhood. During the first five to six months, infants are protected by elevated levels of haemoglobin F (Hb F); once the levels of Hb F start to reduce, the disease starts manifesting. Thus, most cases of SCD are detected in childhood or adulthood. Here we report a case of an Indian man diagnosed with sickle cell disease for the first time at the age of 62 years while being treated for acute pancreatitis. This case was an atypical manifestation of SCD, and points towards the fact that the course of sickle cell disease in an individual depends on genetic and environmental factors and their interaction. This also emphasises that elderly age group should not be used as an exclusion criterion for the diagnosis of SCD. The timely identification by screening can allow timely treatment and thus better quality-of-life for such patients.

Key words: Sickle cell disease, elderly population, acute pancreatitis.

Introduction

Sickle cell disease (SCD) is an inherited autosomal recessive haemoglobinopathy with disastrous multi-organ complications when sub-optimally managed. It is characterised by production of abnormal haemoglobin, which, when deprived of oxygen, changes its shape to sickle shape, and then has a propensity to cause occlusion and progressive vascular injury causing multiorgan damage[1]. The clinical manifestations of SCD are quite variable and reflects interactions with other genetic and environmental factors. There is a pervading heterogeneity in the clinical features between different communities, but sometimes also in the same family. Despite the fact that SCD is present since birth, most infants do not develop any problems until 5th or 6th months of age[2,3]. Here we report a case of an Indian man who was diagnosed with sickle cell disease for the first time at the age of 62 years. This atypical presentation of SCD at the age of 62 years is the centre of discussion in this report.

Case report

A 62-year-old man presented to us with complaints of exertional dyspnoea for two weeks and pain abdomen for 3 days. There was history of three to four episodes of jaundice in the past, which resolved without any treatment but episodes were not evaluated. Apart from this, he gave no history of prior hospitalisation or other co-morbidities. He was a non-smoker and non-alcoholic. On examination, his vitals were stable. He had severe pallor and icterus. The abdomen examination revealed diffuse tenderness and splenomegaly without hepatomegaly.

The routine laboratory investigations showed complete blood count with haemoglobin - 4.1 g/dL, total leukocyte count - 13800 cells/mm^3, platelet count - 2.05 lakhs/mm^3, MCV - 77.5 fL, MCH - 24 pg, MCHC - 31 g/dL and PCV - 24.5%. Reticulocyte count was 15.6%. Liver function test revealed total bilirubin - 5.6 mg/dL, direct bilirubin - 3.1 mg/dL with normal SGOT and SGPT. Renal function test was within normal limits. Serum amylase was 1,285 U/L, lipase 1759.1 U/L. Serological investigations were negative for commonly known causes of hepatitis. A fasting lipid profile was unremarkable. Serum Calcium was 9.2 mg/dL. Serum Folic acid and Vitamin B12 levels were unremarkable. LDH was elevated significantly. Abdominal ultrasound showed splenomegaly, (spleen size was 13.5cm) with normal liver size and texture. No obstruction was noted in the hepatobiliary system. This was an unexpected finding as in most patients with sickle cell disease, the spleen shrinks by adolescence due to numerous episodes of splenic infarction. Abdominal CT was done which showed features of acute pancreatitis and no features of obstruction in the hepatobiliary system (Fig. 1).

To evaluate the aetiology of anaemia, peripheral smear was done which showed RBCs which were microcytic hypochromic with a few normocytic normochromic cells and a severe anisopoikilocytosis in the form of sickle cells

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and tear drop cells, (Fig. 2) WBCs were increased with neutrophila and no atypical cells and platelets were normal. On further evaluation, Sickling test was positive. High performance liquid chromatography (HPLC) test was done and it showed Hb Sickle 76.20%, Hb A2 6.00%, Hb Adult 12.30% and HbF 5.5%. Direct and indirect coombs tests were negative (Fig. 3).

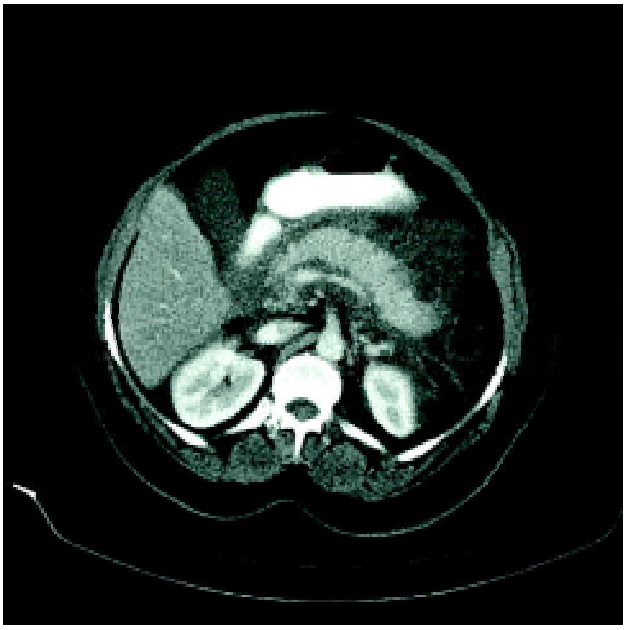

Fig. 1: *Abdominal CT showing features of acute pancreatitis.*

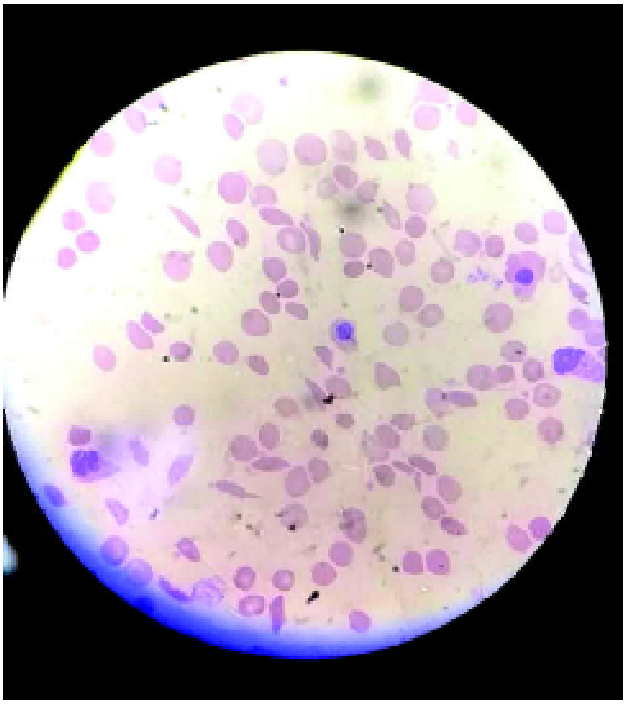

Fig. 2: *Peripheral smear showing microcytic hypochromic cells and sickle shaped RBCs.*

During his hospitalisation, patient was treated for both acute pancreatitis and sickle cell disease. His treatment included adequate IV fluids, four units of matched packed red blood cells transfusion and other adjuvant treatment. Patient was closely monitored for complications. His condition ameliorated substantially, and dyspnoea and abdominal pain resolved. He was discharged with advice to have plenty of fluids and folic acid. At a subsequent visit after three months, he had developed easy fatigability and blood investigations showed that his haemoglobin had dropped to 7 g/dL. Per patient preference, he was started on chronic transfusions (over hydroxyurea therapy) to keep haemoglobin levels around 10 g/dl. He is currently maintained on chronic transfusions for long-term management and continues to do well.

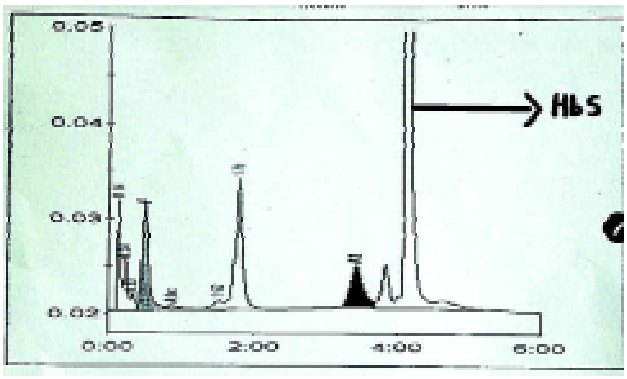

Fig. 3: *Haemoglobin HPLC (High performance liquid chromatography) showing elevated levels of HbS, HbF and reduced levels of Hb Adult.*

Discussion

SCD is one of the most common aetiologies of haemolytic anaemia. It is a monogenic disease with an autosomal recessive inheritance. Its intricate manifestations are due to the elevated levels of haemoglobin S (HbS), which results from the substitution of the glutamic acid with valine in 6th position of the beta-globin chain. HbS, under low oxygen tension, polymerizes and leads to sickling of the red blood cells[2]. Repeated episodes of sickling lead to vaso-occlusive pain crises. It is also known to cause a myriad of complications like acute chest syndrome, pulmonary hypertension, priapism, retinopathy, hepatosplenic sequestration and stroke. Patients are usually asymptomatic for the first five to six months of life due to the presence of fetal haemoglobin (HbF). As HbF eventually reduces and HbS starts to predominate, they become symptomatic. Most cases are diagnosed in childhood. There are several subtypes of sickle cell disease. Few subtypes have gradual clinical progression, and may be misdiagnosed or remain undiagnosed for years, as in this case[2,4].

SCD can widely vary in clinical features and age of presentation with some presenting in childhood and the rest may remain asymptomatic into adulthood. In patients presenting with vague, mild symptoms such as intermittent pain or easy fatigability, SCD is often missed owing to mild anaemia and indeterminate smears. In these cases, microcytosis with normal iron levels might be the only aberration[5]. Yaranal *et al* reported a case of SCD diagnosed for the first time in a patient with paraplegia at the age of 55 years[6]. Sood *et al* reported a case of fat embolism in a 46-year-old, in previously unrecognised SCD[5]. Padrick *et al* reported 19 cases of SCD which were diagnosed in adulthood and suggested that diagnosis may be missed in the absence of screening programmes[7]. Claeys *et al* have discussed factors which influence age at presentation in SCD in children[8]. They reported that factors like lack of clinical suspicion, lack of laboratory resources and difficulty in accessing healthcare settings in locations where SCD prevalence are high contribute to delayed diagnosis of SCD. They also reported that SCD genotype like HbSC or Hb$S\alpha^+$, Arab/Indian haplotype and co-inheritance of alpha-thalassaemia may affect the age of presentation[8].

In our case, given a history of multiple episodes of jaundice and presence of sickle cells in the smear, we ordered for sickling test. The test was positive. Consequently, additional evaluation with haemoglobin high performance liquid chromatography (HPLC) showed elevated levels of HbS; a feature suggestive of SCD haemoglobinopathy. Despite having multiple episodes of jaundice, he was never evaluated. In addition to this, he never had any considerable sickling episodes nor any situation which required blood transfusion, which explains the undiagnosed SCD. This case highlights that acute pancreatitis can also result from painful vasoocclusive crises. Acute pancreatitis due to SCD is a diagnosis of exclusion. Very few cases in the literature have been reported. It may occur as a result of microvascular occlusion[2]. Laboratory parameters and clinical manifestations are similar to pancreatitis due to other aetiologies[9]. This case also underscores the need for a good peripheral smear examination while evaluating patients with anaemia. Meanwhile, as there was an increase in HbA2 and splemomegaly, suspecting co-inheritance of beta-thalassaemia and to delineate SCD genotype, patient was advised for family study and DNA analysis to assess α-globin gene mutation. But could not be done due to financial constraints. Despite the fact that most SCD are recognised in childhood or early adulthood, our approach based on the clinical features and initial laboratory investigations helped us clinch the diagnosis.

Conclusion

SCD is an entity that is widely present but not a thoroughly apprised entity. When newborn screening is not mandatory some cases can be missed and SCD can remain unrecognised for years. It can manifest for the first time in disparate ways and at unusual ages. This report presents the case of a male with SCD whose condition was not diagnosed until he developed acute pancreatitis at the age of 62 years. After gleaning information from his clinical history, examination and appropriate investigations, we arrived at the diagnosis of SCD. The diagnosis helped us to short appropriate long-term management with chronic transfusion. Ergo through this report we want to emphasize the possibility of undiagnosed SCD in adults. Elderly age group should not be used an elimination criterion for the diagnosis of SCD; if done can lead to a missed diagnosis. It also emphasizes the low threshold for additional tests like peripheral smear and haemoglobin electrophoresis while suspecting thalassaemia and SCE, which can clinch the diagnosis earlier.

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CASE REPORT

JIACM 2024; 25 (3): 151-54

A Rare Case of Tracheobronchopathia Osteochondroplastica in Inflammatory Bowel Disease

Ankit Pandey, Prateek Gupta*, Desh Deepak**, Amit Suri****

Abstract

Tracheobronchopathia osteochondroplastica (TO) is a rare, benign disorder characterised by cartilaginous/osseous nodules in the airways. Its aetiology is not known but various associations have been reported. We report an association of Inflammatory Bowel Disease with TO for the first time. The patient also had organising pneumonia and bronchiectasis with bronchocoele that are known associations with IBD and suggest an autoimmune link between IBD and the pulmonary findings.

Introduction

Tracheobronchopathia osteochondroplastica (TO) is a rare, benign disorder characterised by cartilaginous/osseous nodules in the lower trachea and upper bronchi with occasional involvement of larynx and subglottis, detected in approximately 1 in 2,000 bronchoscopies[1]. TO was historically found incidentally in autopsies but has been increasingly diagnosed with the evolution of flexible bronchoscopy and CT[2]. Its differential diagnoses include infectious deposits, sarcoidosis, chondromas, endobronchial hamartomas, squamous cell papillomas, and rarely malignant conditions like squamous cell carcinoma and adenoid cystic carcinoma. Tracheobronchial nodules are also associated with inflammatory bowel disease (IBD); however, an association of TO with IBD has not been reported[3].We report a case of a young adult male with active IBD exhibiting multiple pulmonary involvements, including TO.

Case report

A 38-year-old male presented with 18 months of progressively worsening rectal bleeding, accompanied by recurrent episodes of high-grade fever and cough. The patient was admitted to the gastroenterology department for evaluation. His familial, personal, occupational and drug history were not contributory. Colonoscopy revealed proctosigmoiditis. Biopsy indicated colonic mucosal erosion, ulceration, irregular crypt spacing, and cryptitis, with chronic inflammation in the Lamina Propria without any evidence of granulomas or malignant cells, confirming the diagnosis of Ulcerative Colitis.

The patient was referred to pulmonary medicine for evaluation of fever and cough. A detailed history revealed that he had been having cough for around 5 years which had become productive for a year. His chest X-ray showed a patchy opacity in the left mid and lower zone. CT thorax revealed calcified nodules in the trachea (Fig. 1A), a patch of consolidation suggestive of organising pneumonia in left lower lobe (Fig. 1B) along with bronchiectasis and a bronchocoele in the right lower lobe (Fig. 1C).

The patient underwent Flexible Fibreoptic Bronchoscopy (FOB) under conscious sedation. In the trachea, nodules were present anterolaterally, starting below the subglottic space, extending from the trachea into the right main bronchus (RMB) and the left main bronchus (LMB), sparing the posterior wall suggesting a possible cartilaginous origin (Fig. 1D). The size of nodules decreased supero-inferiorly (Fig. 1E-F). Further, multiple nodules were identified anteriorly in the RMB up to 1 cm from the carina, alongside a solitary nodule in the Right Middle Lobe (RML). Similarly, multiple nodules along anterolateral walls were observed in the LMB up to 2.5 cm from the carina. Additionally, purulent secretions were noted in both the Left Upper Lobe (LUL) and Left Lower Lobe (LLL) bronchi. Bronchial washings were taken from the LUL and LLL. Forceps biopsy was attempted from the tracheobronchial nodules but was hindered by the nodules' hardness; only small pieces were obtained. Cryobiopsy of the tracheal nodules also yielded only mucosa in alignment with the possible osteocartilagenous nature of the nodules. Transbronchial Lung Biopsy (TBLB) was taken from the LLL in view of the organising pneumonia pattern on HRCT.

Cytological scrutiny of the bronchial wash specimen, showed the presence of respiratory epithelial cells amid a proteinaceous milieu, accompanied by moderate mixed inflammation and absence of any atypical cells. Pyogenic

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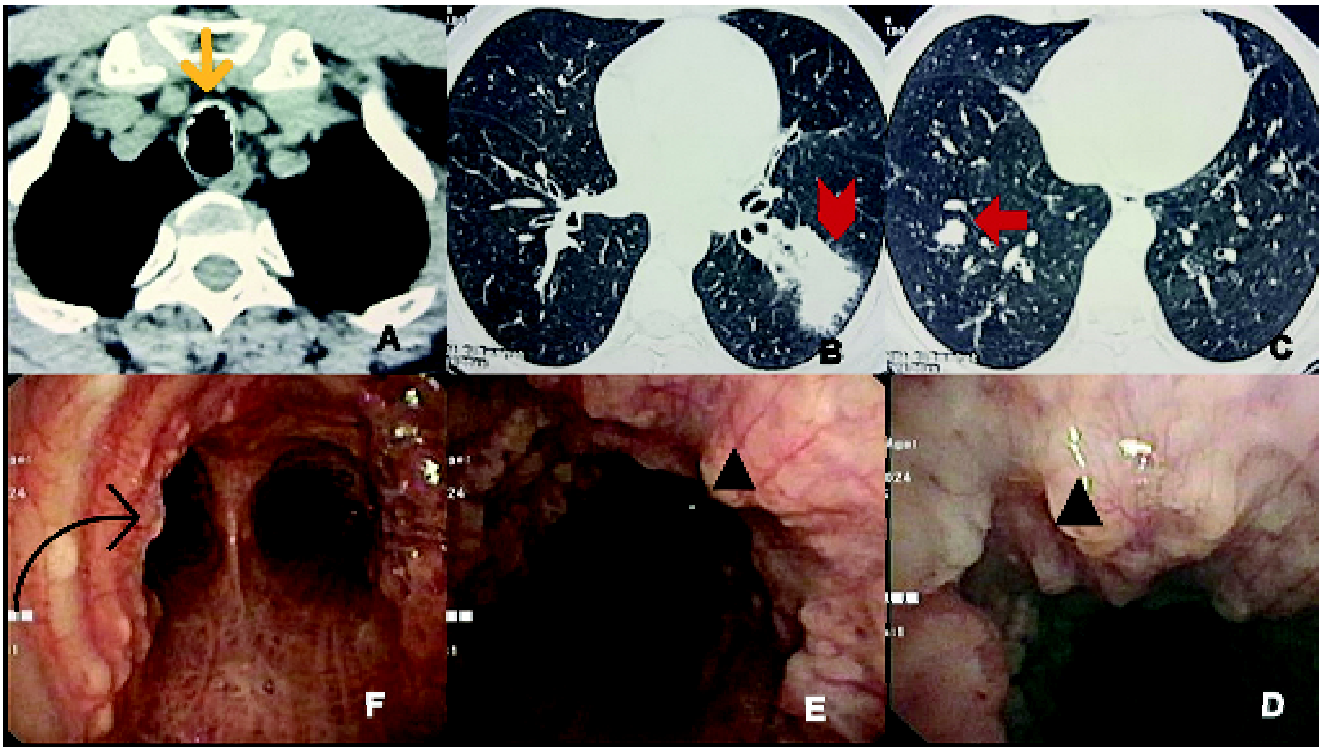

Fig. 1: *Computed Tomography of Chest,* ***A:*** *Mediastinal cut showing multiple calcified tracheal nodules along the anterior surface sparing the posterior surface (Yellow arrow);* ***B:*** *Demonstrates patchy consolidation in the left lower lobe, indicative of organising pneumonia (Red Pointer);* ***C:*** *Shows areas indicating bronchiectasis and Bronchocoele (Red arrow);* ***D:*** *Flexible Fibreoptic Bronchoscopy (FOB) shows large tracheal nodules with cobblestone appearance antero-laterally starting below the subglottic space (Black Triangle);* ***E,F:*** *The nodules were seen to be decreasing in size supero-inferiorly clearly demonstrating their origin along the Tracheal rings (curved Black arrow).*

Table I: Shows the findings from three major case series of Tracheobronchopathia osteochondroplastica.

Author	No of cases	Year	Mean age (years)	M: F Ratio	Location	Chief complaints	Radiological and Spirometry findings	Outcome
Härmä *et al*[5]	30 (over 12 years)	1977	46.5	1:3.6	Finland	long-term recurrent cough, hoarseness, and periodic expectoration	Not studied	Ten cases were incidentally identified via bronchoscopy, 2 through autopsy, and 18 through systemic examination. Among the latter, 10 received preliminary diagnoses via indirect laryngoscopy.
Vivian Leske *et al*[8]	41	2001	63 ± 15	1:1	France	29% had atrophic rhinitis, sinusitis, or pharyngitis and 51% had chronic or recurrent lower respiratory tract disease	74% of Chest CT scans showed submucosal nodulesPFT in 39% of cases was Obstructive, 18% a restrictive defect, and normal spirometry in 43%.	Atypical Posterior tracheal wall involvement occurred in 15% of patients. Initial diagnosis revealed airway stenosis in 10% of patients. Subsequent endoscopic follow-up showed stability in 55%, minimal progression in 28%, and significant progression in 17% of patients.
Ying Zhu *et al*[14]	22	2014	47.45 ± 10.91	1:1	China	chronic cough (n = 14) and increased sputum production (n = 10).	In 18 out of 22 patients, CT revealed findings consistent with TO, including beaded intraluminal calcifications and/or increased luminal thickness Spirometry not studied	Patients were categorised by bronchoscopic severity: Stage I (n = 2), Stage II (n = 6), and Stage III (n = 14). Two patients, treated with inhaled corticosteroids, showed bronchoscopic improvement, indicating potential disease resolution.

culture of the BAL fluid revealed *Pseudomonas* growth. A Ziehl-Neelsen stain for acid-fast Bacilli (AFB) yielded a negative result, Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) for *Mycobacterium tuberculosis* and Potassium Hydroxide (KOH) stain and fungal culture of the BAL fluid were subsequently negative.

Histological examination of the tracheal biopsy specimen showed squamous metaplasia of the respiratory epithelium,

presence of chronic inflammatory cells, fragments of cartilage, and presence of calcified material. No evidence of malignancy was seen. Considering the pattern of tracheobronchial nodules, their consistency, biopsy findings and radiological appearance a diagnosis of Tracheobronchopathiaosteochondroplastica (TO) in association with Ulcerative colitis was made. Transbronchial lung biopsy showed presence of granulation tissue within alveoli with lymphocytic and plasma cell infiltrates with scanty fibrosis, confirming the presence of organising pneumonia. The patient was given antipseudomonal antibiotics as per the culture sensitivity reports of Broncho-alveolar lavage fluid and became afebrile in a week.

Discussion

In 1910, Aschoff[4] coined "Tracheopathiaosteoplastica" suggesting a connective tissue disorder affecting the internal elastic membrane of the trachea and major bronchi. Infective associations with Atrophic Rhinitis, *Mycobacterium avium, Mycobacterium tuberculosis*, and *Klebsiella* are reported[5]. Occupational silica exposure, tissue degeneration, calcium and phosphorous metabolic disturbances, congenital anomaly, chemical or mechanical irritation, primary amyloidosis, familial occurrence, and cold climate conditions in regions like Finland and Northern Sweden are linked to TO[6]. Table I shows the findings of 3 major case series of TO. The harsh climate or irritation contributing to chronic infections, and thereby leading to increased sensitivity of the airway epithelium has been postulated as a possible pathogenetic mechanism[5]. Regardless of the trigger, histopathologic evidence suggests a significant role of bone morphogenetic protein-2, in synergy with transforming growth factor-β1, in nodule formation in the tracheal submucosa[7].

Chronic cough, attributed to mucociliary escalator dysfunction, often lasting 4 - 6 years before diagnosis, is the primary presentation of TO. Other symptoms may include acute pneumonia, hemoptysis, dysphonia, and breathing difficulties[8].

CT is the recommended imaging for TO diagnosis and monitoring, while bronchoscopy is the gold standard, revealing characteristic appearances like cobblestone or stalactitic cave formations[6,9] (Fig. 1A). Forceps biopsy may be challenging due to the nodules' hardness, but histopathologic examination is crucial for confirmation in atypical cases. Cryobiopsy is not suitable as the nodules are osteocartilagenous in nature[10].

The most frequent histopathologic findings are the characteristic presence of bone in bronchial submucosa and squamous metaplasia of the tracheal epithelium.

Our patient had a co-existing biopsy proven IBD. IBD can have pulmonary complications, including bronchiectasis, bronchiolitis, organising pneumonia, necrobiotic nodules, interstitial lung disease and treatment-related complications[3]. Tracheal nodules, in TO are usually calcified nodules in the cartilaginous trachea sparing posterior membrane, while in IBD, there is diffuse or focal tracheal narrowing[11]. This is the first reported case of concurrent TO and IBD, suggesting a possible autoimmune link. Routine bronchoscopy for cough in IBD patients and IBD evaluation for incidentally found TOs during bronchoscopy may elucidate their association. IBD rarely involves the lungs with various pathologies, implying a potential connection between TO and IBD-related pulmonary manifestations such as organising pneumonia and bronchocoele[12].

Treatment for TO ranges from providing symptomatic relief to more invasive bronchoscopic interventions for severe airway obstruction. While inhaled corticosteroids, such as Budesonide, have shown efficacy in managing inflammation associated with TO, their effectiveness is limited when it comes to addressing osseous lesions. Further research is imperative to establish optimal dosage and treatment duration, especially in cases involving bony lesions. Options such as laser ablation, mechanical debulking, and surgical resection of the affected airway exist, but there remains a lack of specific guidelines for the management of this condition[13].

Conclusion

IBD is known to have various pulmonary complications including tracheobronchial nodules. We report a case of TO occurring in IBD for the first time. In patients of IBD presenting with chronic cough, TO should be suspected. Also, patients with TO should be evaluated for IBD. This report highlights a potential association between TO and IBD and mandates further studies.

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CASE REPORT

JIACM 2024; 25 (3): 155-57

Diabetic Striatopathy: Case Report and Review

Ajinkya Deshmukh, SH Talib**, Abdulla Ibji***, Pankaj Patil****

Abstract

Background: Diabetic striatopathy (DS) also known as hyperglycaemic non-ketotic hemichorea-hemiballismus syndrome presenting with uncontrollable involuntary jerky motions with ballism, typically more proximal, with large amplitude and choreic movements as distal, largely associated with poorly controlled diabetes mellitus. The entity is a rare disorder with an estimated prevalence of 1 in 1,00,000. Screening of patients, young or elderly who present with involuntary movements and hyperglycaemia or presenting without prior history of diabetes mellitus is essential[1]. Unfortunately it's prevalence in the literature is low owing to unfamiliarity of this entity amongst physicians.

Case presentation: 63-year-old male patient having 10 years history of uncontrolled Type 2 diabetes mellitus and essential hypertension presented to our hospital with acute onset of involuntary movements as hemiballismus-hemichorea (HB-HC) of left upper and lower extremities, and involving face and neck. These movements were not noted in sleep. The patient discontinued the diabetes medications a month prior to the onset of the present problem. MRI brain done revealed altered signal intensities in the right lentiform nucleus consistent with a clinical diagnosis of non-ketotic hyperglycaemic HB-HC. This clinical entity is described as diabetic striatopathy. He received insulin injections, tetrabenazine as anti-choreic drug with vitamins and minerals as supportive therapy. The patient had a complete remission of symptoms within just 2 weeks of control of blood sugar.

Conclusion: Diabetic striatopathy (DS) is an uncommon neurological condition of uncontrolled hyperglycaemia induced hemichorea/hemiballismus syndrome. The clinical presentation and brain MRI findings highlight its recognition while stringent glycaemic control with use of anti-choreic drugs revert the manifestations of DS.

Keywords: Hemichorea-Hemiballismus, uncontrolled diabetes mellitus, brain MRI; anti-choreic drug; basal ganglia.

Introduction

Diabetic striatopathy (DS) which is variously known as hyperglycaemic non-ketotic hemichorea-hemiballismus or chorea hyperglycaemic basal ganglion syndrome[1]. Both chorea and ballismus refer to random, uncontrollable, involuntary jerky motions associated with poorly controlled diabetes mellitus, either type 1 or 2. The development of HB-HC is associated with hyperintensity on T1-weighted magnetic resonance imaging of putamen, caudate nucleus and globus pallidus either in isolation or combined. These findings of MRI in presence of non-ketotic hyperglycaemia is considered a *sine qua non* of this entity[2,3].

Case presentation

A 63-year-old male, non-smoker, hypertensive and with uncontrolled diabetes mellitus type 2 presented with continuous involuntary movements of left upper and lower extremities and also involving face and neck. Movement disorders were observed 2 days before presenting to this hospital. He was diabetic for 10 years, on metformin and glimepiride but with poor adherence. He discontinued his diabetes medications 6 weeks prior to hospitalisation without any justification. History of viral febrile illness, COVID-19 and intake of any drugs/alternative medicines was denied. History of movement disorders in the family was also denied. His speech was unaffected. The gait was unsteady and interrupted by violent motions, but suppressed during sleep.

On examination, patient was conscious, oriented and had normal vital features. His height was 172 cms, weight of 60 kgs, and BMI of 20.3 kg/m^2. He had violent high amplitude choreoathetotic movements of the left side of the body including the face, neck and trunk. High amplitude movements were observed at the shoulder, hip, elbow, and ankle (video on *www.jiacm.in*), pupils were reactive to light with normal accomodation reflex. Eye movements were normal in all directions. No nystagmus was seen. The motor and sensory systems were unremarkable. Co-ordination could not be tested on the left side due to irregular movements. Deep tendon and plantar reflexes were normal. Routine investigations were within normal limits with random blood sugar levels of 440 mg/dL and HbA1c of 14% (Normal range - 3.8 - 5.6%). Urine ketones were negative, serum ketones were not tested. MRI T1-weighted images of the brain revealed

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hyperintense signal in the right lentiform nucleus. Diffusion weighted imaging (DWI) revealed subtle restricted diffusion in right lentiform nucleus. No evidence of blooming seen on GRE sequences. Mild age-related atrophic changes were also noted. Based upon the characteristic presence of HB-HC movements, poorly controlled diabetes mellitus, negative family history of chorea and characteristic MRI findings; a strong presumptive possibility of diabetic striatopathy was entertained. Insulin injections for better blood glucose management and tetrabenazine 12.5 mg twice daily for control of abnormal movements were initiated with supportive nutritional supplements. The patient demonstrated substantial improvement in movement disorder in next 2 weeks of time. A follow-up visit after 3 months showed no residual movement abnormalities. The blood glucose levels were well controlled, with HbA1c improvement from 14% to 7.4%.

Discussion

India is the capital of the diabetic world. Involuntary movements of varied nature are described in association with diabetes mellitus. The myriad aetiopathological concepts of this entity include neurogenetic, autoimmune, infectious, inflammatory. metabolic and neurodegenerative entities as potent aetiologies of this clinical syndrome. The clinical, radiological and laboratory correlation, as observed in the case, narrows down the differential diagnoses of this potential condition. The common presentation of DS is with HB-HC movement disorder, occurring in a subject with poorly controlled diabetes mellitus. Reversibility in clinical, imaging and neurological deficits is invariably observed on achieving adequate blood sugar control.

Choon-bing Chao and coworkers in 2020[4] identified 72 articles comprising of a total of 176 patients of which 96.6% were diabetic subjects, and of these 17% were newly diagnosed diabetics. The average blood glucose level described was 414 mg/dL and HbA1c of 13.1%. The present case manifested as violent unilateral HB-HC movements and had a blood glucose level of 440 mg/dL and HbA1c of 14%. These findings of the case raised the possibility of diabetic striatopathy. These movements disappeared during sleep. However, in literature a few cases are reported with partial or no suppression of DS abnormal movements during sleep[5]. Among patients with poorly controlled diabetes mellitus (HbA1c 10%) hospitalised for any cause, 0.58% had DS, while incidence rose to 1.2% among these who were hospitalised for neurological disorders[6]. The disease prevalence is higher in females than males with male: female ratio of 1:1.77[4]. The hemichoreas are also seen in diabetes type 1[7]. The reported low prevalence of the disease could be because of unfamiliarity of this entity amongst physicians, leading to an erroneous diagnosis of intracerebral haemorrhage. This confusion of diagnosis is noticeable chiefly with findings of hyperdensities on CT[8]. High prevalence of this entity in females is attributed to estrogenic changes that are observed in post-menopausal women (representing elderly age group) affecting GABA and dopamine receptors.

There are several considerations for MRI sequence findings of hyperintensities. These imaging abnormalities could be induced by a) presence of calcifications (should show HU value of 80) b) microhaemorrhages which are often transient, acute in onset and match with tissue density for hyperdensity of 40-50 HU[9]. c) T1 shortening and hyperintensities are found with a reduction in velocity of blood flow, presence of fat, high protein contents in the cell and presence of paramagnetic metals, viz., iron, zinc, copper and manganese[10]. In absence of mass effect or oedema, the presence of MRI findings is congruous with the concept of microbleed in tissue. Mestre and colleagues in 2009 demonstrated deposits of hemosiderin in putamen and suggested that hyperglycaemic status may transiantly induce blood-brain barrier dysfunction, resulting in RBCs and hemosiderin extravasation in putamen[11]. Protein hydration may cause swollen gemistocytes inside the cytoplasm as seen in sclerosing panencephalitis or epilepsy with resultant hyperdensities. Prolonged period of hypoperfusion and ischaemia often result in dysfunction of neurons. The hypoperfusion does not explain the presence of bilateral chorea with observed unilateral pathology on MRI. A few cases are reported with presence of focal microhaemorrhages based upon this vascular theory. Applications with gradient echo-weighted (T2-GRE) and susceptibility weighted imaging (SWI) MRI sequences help further to narrow the wide differential diagnoses. Presence of paramagnetic materials in basal ganglion like copper, iron or manganese simply can be excluded as the cause of hyperdensities with judicious clinical assessment of patient. Copper and iron disorders may have a chronic course as seen with Wilson's and other degenerative disorders. Manganese deposition is usually related to parkinsonism while fat separation images can rule-out the possibility of presence of fat as the cause of MRI hyperintensities. The resolution of involuntary movement disorder is highly variable from few days to about 10 months after correction of hyperglycaemic status. Few cases are described with partial improvement between 3 months and 5.6 years[12]. Most patients also need anti-choreic drugs to achieve symptom control. Tetrabenazine (TBZ) exerts anti-choreic effects by decreasing the amount of dopamine in the brain. Further, this drug has the highest binding in caudate nucleus and putamen. These are the pathological locations in most diabetic striatopathies. Resistant cases not

responding to conventional therapies may require deep brain stimulation of putamen, caudate nucleus, and subthalamic nucleus for control of movement disorder.

Conclusion

The recognition of the entity of DS is important in cases of uncontrolled diabetes mellitus. The clinical scenario and brain MRI findings that are consistent with entity, support this diagnosis. Stringent glycaemic control and use of anti-choreic medications help the to achieve faster recovery.

Patient video available at *www.jiacm.in*

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JIACM 2021; 22(3): 158

Infective Endocarditis Presenting as Deep Vein Thrombosis and Symmetric Peripheral Gangrene

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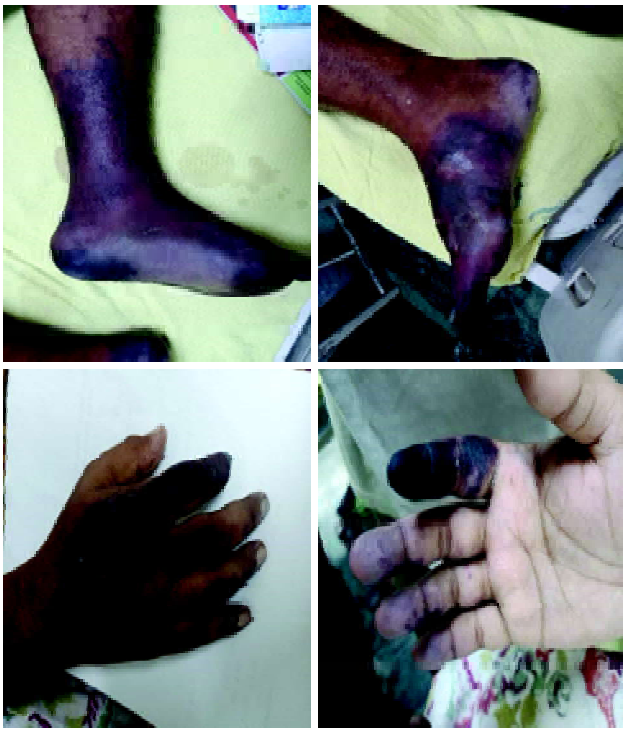

Fig. 1: *Acral gangrene in all 4 limbs.*

A 34 year-old man presented with fever, dyspnoea, heart failure, severe sepsis, septic shock and blackish discolouration of all 4 limbs suggestive of symmetric peripheral gangrene (SPG). Arterial doppler confirmed thrombosed vessels (both arteries and veins) of lower limbs. 2D ECHO showed rheumatic heart disease with moderate mitral stenosis and mitral regurgitation with vegetation over anterior mitral leaflet. Two blood cultures grew *Acinetobacter baumannii*. Patient went into sudden cardiac arrest on day 3 of admission and died despite antibiotics and anticoagulation.

SPG presents as symmetrical gangrene of two or more extremities due to microcirculatory thrombosis, without large vessel-obstruction or vasculitis. Fingers, and toes (rarely nose, ear lobes or genitalia) are affected. It manifests unpredictably in conditions associated with sepsis, low output states, vasospastic conditions, myeloproliferative disorders or in hyperviscosity syndrome. Disseminated intravascular coagulation has been implicated as the final common pathway in the pathogenesis and it carries a mortality rate upto 35 - 40%. There is failure of the natural anticoagulant systems, both the proteinC system (crucial for down-regulating thrombin generation in the microvasculature) and the antithrombin system due to hepatic dysfunction or failure (shock liver), since the liver synthesizes protein C (a vitamin K-dependent anticoagulant) and antithrombin. This produces a procoagulant state which causes small vessel occlusion and SPG. Owing to this severe procoagulant state, large vessel obstruction may also ensue. Deep vein thrombosis (DVT) predisposes to micro-thrombosis in limbs due to decreased blood flow and/or direct contiguous extension of thrombosis. Thus, our patient appears to have developed SPG (sepsis, hypotension resulting in shock liver, hypercoagulable state) together with presence of DVT in lower limbs with ischaemic necrosis. He developed a greater degree of ischaemic injury in the limbs affected by DVT, indicating that concomitant DVT can modulate the clinical course of SPG.

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