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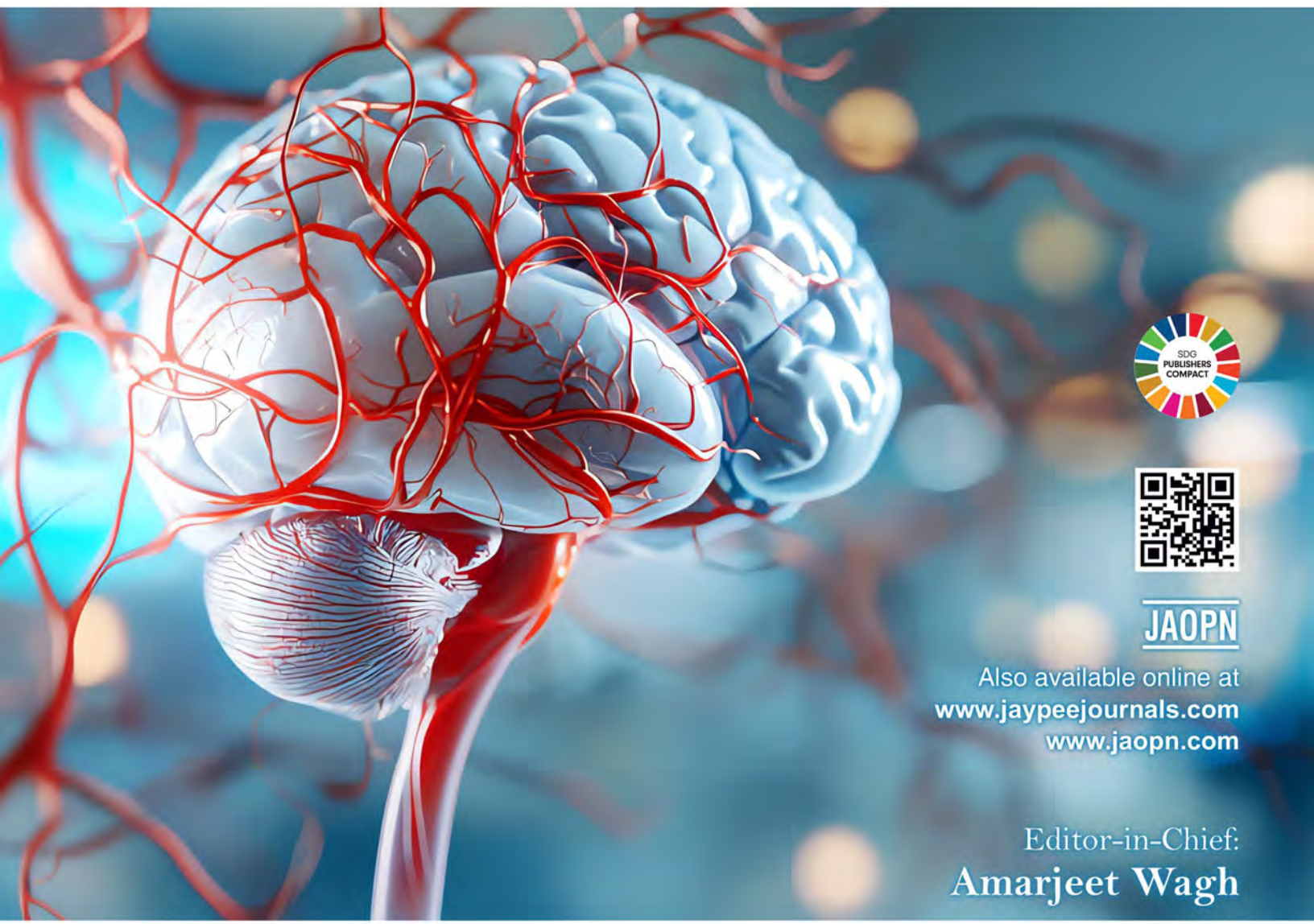

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Journal of Academy of Pediatric Neurology

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Journal of Academy of Pediatric Neurology (JAOPN) is the official Journal of the Academy of Pediatric Neurology, India (AOPN, India). The Journal publishes two issues in a year, i.e., January–June and July–December. It is a peer-reviewed open-access Journal that publishes manuscripts pertaining to clinical and translational investigations of pediatric neurological diseases that will allow clinicians and neurologists to enrich their knowledge of patient management and education, and clinical or experimental research. The aim of the Journal is to publish cutting-edge clinical research from around the world with more focus on the Indian subcontinent. JAOPN is directed at pediatricians, pediatric neurologists and all clinicians and academicians involved in children with neurological disorders.

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Contents

ORIGINAL RESEARCH

A Spectrum of Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Children and Outcome: A Treatable Neurological Disorder: Three Cases from Single Center

Vykuntaraju K Gowda[1], Vidya S Naik[2], Sharath Babu[3], Aqila B Abdullah[4]

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Abstract

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a treatable chronic disorder of the peripheral nervous system, with predominant motor involvement. The disease is characterized by insidious onset over several months or recurrent episodes. The pediatric population faces unique diagnostic challenges due to their rarity and therapeutic challenges due to lack of evidence, hence, we are reporting this series.

Objective: To describe the clinical and laboratory characteristics and treatment outcomes of Pediatric CIDP, aiming to improve the insights for future management approaches.

Results: This study presents three children diagnosed with CIDP based on their clinical presentation, nerve conduction studies (NCS), nerve biopsy findings, and criteria. Out of 3, two were male. The mean age of onset was 12.3 years (range 6–16 years). Two of the three cases exhibited gradual onset progressive weakness of limbs whereas one case had acute onset of quadriparesis mimicking Guillain-Barré syndrome. Two had cranial nerve involvement. All had abnormal NCS suggestive of demyelinating polyradiculoneuropathy. Nerve biopsy demonstrated evidence of inflammatory demyelination. All the cases were treated with pulse dosing of steroids and intravenous Immunoglobulin (IVIG) during the presentation, and subsequently managed with oral steroids. Steroid-sparing medications, rituximab and mycophenolate mofetil (MMF) were necessary for all of them for incomplete recovery and to prevent relapse, which led to a remarkably favorable response.

Conclusion: This case series highlights the variable nature of CIDP in its initial presentation, its course, and the requirement of steroid-sparing agents to prevent relapses.

Keywords: Abnormal reflexes, Chronic inflammatory demyelinating polyradiculoneuropathy, Intravenous immunoglobulin, Muscle hypotonia, Rituximab.

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Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare cause of acquired immune-mediated disorder in children. Most polyneuropathies occurring in children are hereditary 85%, and around 9% are immune-mediated causes like CIDP and Guillain-Barré syndrome.[1] The prevalence rate of CIDP is around 0.22 per 1,00,000 worldwide.[2] Chronic inflammatory demyelinating polyneuropathy is generally distinguished from GBS by duration of illness, with symptoms of CIDP progressive for at least 8 weeks. However, in children, disease onset may be acute, developing less than 4 weeks, or sub-acute in 4–8 weeks.[2] The course of CIDP may be polyphasic relapsing-remitting in 61% of patients, or monophasic, progressive in 39%.[3] Here we discuss and report three cases of CIDP in children with diagnostic difficulties and their outcome.

Materials and Methodology

This case series includes three children diagnosed with CIDP at our hospital from 2022–2023. Data on each patient's demographics, clinical presentations, diagnostic evaluation, treatment regimens, and clinical outcomes was collected.

Results

A summary of the cases is shown in Table 1.

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Case Series

Case 1

A 16-year-old girl presented with flaccid quadriparesis, ophthalmoplegia, bulbar palsy, and absent reflexes with intact sensorium.

Table 1: Shows clinical, and laboratory features, and outcomes of the study population of CIDP over 2 years

Parameter	*Case 1*	*Case 2*	*Case 3*
Age (year)	16	15	10
Age of onset (year)	14	14	6
Sex	F	M	M
Presenting complaints	Respiratory failure with ophthalmoplegia	Flaccid weakness	Flaccid weakness
Duration of symptoms	2 years	6 months	2 months
Weakness of all 4 limbs	Yes	Yes	Yes
Proximal more than distal	Yes	Yes	Yes
Cranial nerve involvement	Yes	No	Yes
Tone	Hypotonia	Hypotonia	Hypotonia
Reflexes	Absent	Absent	Absent
Cerebrospinal fluid			
Cells (Number/mm^3)	1	21	2
Protein mg/dL	82	416	38
Nerve conduction studies during acute episode			
Motor	Absent CMAP	Absent CMAP	Absent CMAP
Nerve conduction studies during follow-up			
Motor	Demyelination	Demyelination	Demyelination
Nerve biopsy	Inflammatory neuropathy with demyelination and axonopathy	Demyelinating neuropathy	Demyelinating axonal neuropathy with endoneural inflammation
Treatment			
Induction	Steroids, IVIG, rituximab	Steroids, IVIG, rituximab	Steroids, IVIG, rituximab
Maintenance	Steroids, MMF	Steroids, MMF	Steroids, MMF
Relapse	1	None	3

CMAP, compound muscle action potential; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil

History of similar weakness 2 months back but without any cranial nerve involvement, which was treated as GBS with Intravenous immunoglobulin (IVIG). On careful elicitation of history, there was slowly progressive weakness involving the upper limb followed by the lower limb over the past 2 years. Nerve conduction studies (NCS) revealed absent compound muscle action potential (CMAP) in all 4 limbs. She improved dramatically with IVIG and pulse dosing of steroids over 3 days, with some residual weakness. All Routine investigations were normal. Cerebrospinal fluid (CSF) analysis revealed albumino-cytological dissociation. A nerve biopsy revealed the following findings: Focal acute axonal breakdown with regenerating clusters is noted in the axons. There are moderate non-uniform multifocal pockets of myelinated nerve fiber loss, large more than small, with several thinly myelinated fibers. The onion bulb is not seen. There is moderately dense perivascular lymphocytic infiltration around small and medium sized arterioles in the epineurium. There are scattered endomysial histiocytes (CD68). Epineurium shows neovascularization with medial hypertrophy and sclerosis of small caliber arterioles. Repeat NCS showed demyelinating polyradiculopathy. Based on clinical and laboratory profiles, she was diagnosed with CIDP. As she had only partial recovery, 375 mg/m^2 of intravenous Rituximab was administered. She showed significant improvement following the maintenance dose of oral steroids 2 mg/kg/day for 2 weeks, 1.5 mg/kg/day for 2 weeks, 1 mg/kg/day for 1 month, and 0.5 mg/kg/day for 4 months and mycophenolate mofetil (MMF).

Case 2

A 15-year-old male child born of a non-consanguineous marriage, who had a normal birth and development history, presented to us with progressively worsening lower limb weakness followed by upper limb weakness during the previous five months, rendering him immobile for a month. He had no history of feeding and breathing difficulty or bowel and bladder involvement. Clinical examination showed hypotonia in all four 4 limbs, power of 2/5 (distal more than proximal), sluggish reflexes, and flexor plantar were noted. Cranial nerves were not affected. Investigations showed CSF protein of 413 mg/dL, sugar of 58 mg/dL, and cell count of 8/mm^3 all are lymphocytes. ANA profile, vasculitis profile, myositis profile, and anti-GM1 antibodies were negative. Nerve conduction studies showed both upper and lower limb nerves were not stimulatable. A nerve biopsy revealed features of inflammatory demyelination. Focal acute axonal breakdown with regenerating clusters is noted in the axons. There are moderate non-uniform multifocal pockets of myelinated nerve fibers and loss of thinly myelinated fibers. The onion bulb pattern is seen. There is moderately dense perivascular lymphocytic infiltration around small and medium sized arterioles in the epineurium. Epineurium shows neovascularization with medial hypertrophy. He was treated with a pulse dose of IV steroids, IVIG at 2 gm/kg initially followed by four doses of injection rituximab 375 mg/m^2 as there was an incomplete recovery. The child recovered after 1 month. He was put on a maintenance dose of oral steroids 2 mg/kg/day for 2 weeks, 1.5 mg/kg/day for 2 weeks, 1 mg/kg/day for 1 month, and 0.5 mg/kg/day for 4 months and maintenance of MMF. Nerve conduction studies showed features of demyelinating motor neuropathy of bilateral lower and upper limbs after 2 months of initiation of treatment.

Case 3

A 6-year-old male child with normal birth and developmental history, presented with slowly progressive weakness of the lower limb followed by upper limb (distal more than proximal) associated

with difficulty in swallowing food and reduced intensity of voice. The examination showed hypotonia of the upper and lower limbs. Power of 2/5 in ankle, knee, wrist, and elbow with shoulder and hip girdle muscles having power of 3/5. Nerve conduction studies showed absent CMAP in both the lower limb and upper limbs. A nerve biopsy from the sural nerve showed the following findings. Focal axonal breakdown with regenerating clusters is noted in the axons. There are moderate non-uniform multifocal pockets of myelinated nerve fibers and loss of thinly myelinated fibers. The onion bulb pattern is seen. There is moderately dense perivascular lymphocytic infiltration around small and medium sized arterioles in the epineurium. Epineurium shows neovascularization with medial hypertrophy. The child received IV methylprednisolone, followed by maintenance steroids and MMF. He relapses after 4 months of initial admission following abrupt self-discontinuation of medications. He was treated with IV methylprednisolone and was advised to taper the dose of steroids and MMF. Nerve conduction studies showed demyelinating motor neuropathy of bilateral lower and upper limbs after two months of initiation of treatment. He had a second relapse 4 years later at the age of 10 years with reduced fine motor activity in upper limbs, weak voice, and feeding problems for 10 days before admission and was noticed to have marked wasting of distal extremities with pes cavus. Nerve conduction studies showed demyelinating motor neuropathy of the bilateral lower and upper limbs. He was treated with IVIG, IV pulse dose steroids, and Rituximab with maintenance dose steroids tapered over 3 months and MMF a dose of 600 mg/m^2. The child recovered well, and he is ambulant with some residual disability.

Discussion

We present a case series of three children with CIDP from a single center, age of onset being 6 years and above (mean age of onset being 12 years and 6 months) and Male: Female ratio of 2:1. Out of three children, one child had an acute GBS like presentation with respiratory failure requiring ventilatory support for 3 weeks. Unlike adults, childhood CIDP can more frequently progress for less than 8 weeks.[2] A progression of symptoms in less than 4 weeks needs to be differentiated, especially from the GBS. However, if the patient exhibits deterioration after 8 weeks from onset, or when deterioration occurs three times or more, the diagnosis of CIDP is much more likely.[4]

All three children exhibited quadriparesis, with greater involvement of lower limbs than upper limbs. Notably, distal weakness was more pronounced than proximal weakness in each case, similar to previously published case reports and original articles.[5,6] Cranial nerve involvement in the form of ophthalmoplegia, ptosis, weak voice, and swallowing difficulty was found in 2 out of 3 cases, with all children having hypotonia and areflexia. Cranial nerve involvement as a significant characteristic of childhood CIDP has been highlighted in previous case reports by Silwal et al.[7] and Costello et al.[8] No laboratory tests can definitively confirm the diagnosis of CIDP; instead, the diagnosis relies on a combination of clinical and laboratory findings. This approach is supported by the diagnostic criteria established by the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force and modified by Mendell.[9] In our study, CSF examination was abnormal in 2/3 of children, with proteins being elevated disproportionately than cell counts. The nerve conduction study was abnormal in all 3 cases. Initially, two children showed absent CMAP, however, during follow-up studies, they showed a demyelinating pattern. A nerve biopsy showed evidence of inflammatory demyelination in all the patients.

Clinical presentation of CIDP may vary between children and adults, and the management strategies also differ as there are no standard guidelines and evidence of various immunotherapies. Steroids and IVIG are the first-line treatments for CIDP. Some authors recommend plasmapheresis as a reasonable first-line therapy.[10] However, socioeconomic and logistical factors, along with personal preference, are important elements that decide the most favorable treatment strategy for the individual patient. IVIG is the preferred initial treatment by many.[10] In our study, a combination of steroids and IVIG was used in all cases. All of them required rituximab and MMF for further disease control.

All three children showed improvement after steroids, and IVIG, and two children were mobile on the day of discharge, and all three children were mobile during their follow-up. Two children had relapsed after the first episode which responded to repeated courses of steroids and IVIG.

Conclusion

This case series highlights the variable nature of CIDP in its initial presentation, its course, and its response to treatment, particularly in children, as it can present acutely, with cranial nerve involvement and respiratory failure. Though rare, with timely diagnosis and treatment, CIDP in children has a better prognosis. Hence, careful evaluation, timely detection, and proper treatment are encouraged for better outcomes.

Declaration

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- Persons who have contributed partially have been acknowledged in the manuscript.
- As a corresponding author of this manuscript, I declare that there are no competing interests in the present study and there were no financial, personal or professional relationships that could influence the study.

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CASE SERIES

Unraveling the Mysteries of Childhood Stroke: Insights from a Comprehensive Case Series

Rajdeep Saha[1], Somjeet Jana[2], Samit Basu[3], Kalpana Datta[4]

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Abstract

A stroke is an acute neurologic emergency with the need for urgent diagnosis, central nervous system imaging, and prompt treatment, ideally in the set time window. A stroke in pediatric patients is associated with significant morbidity and mortality. This case series showing etiologies of childhood stroke are of a multifactorial nature, including both genetic predisposition and environmental triggers. Those five children mentioned in this series have a complete recovery following treatment and physical rehabilitation. None of our patients had a recurrence during the short duration of follow-up. To understand the natural history, larger cohorts, and longer follow-up would be needed. Establishing a disease-specific registry would be of importance for this.

Keywords: Childhood stroke, Focal cerebral arteriopathy, Mineralizing angiopathy.

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Background

"Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or resulting in death, with no apparent cause other than of vascular origin" is the definition of a stroke given by the World Health Organization (WHO).[1] Currently, however, the following revised definition of stroke is favored for the twenty-first century: "An acute-onset neurological sign or symptom attributable to focal brain infarction or hemorrhage".[2] As a serious neurologic emergency, stroke necessitates prompt diagnosis, imaging of the central nervous system, and prompt treatment ideally within a set window of time. In pediatric patients, stroke is linked to substantial morbidity and mortality.[3–5] The incidence of pediatric stroke is estimated to range from 1.3 to 13 cases per 100,000 children annually, with rates as high as 25–40 cases per 100,000 live births in neonates.[6–8]

The incidence of stroke in childhood is influenced by age, with the highest occurrence reported during the perinatal period, accounting for up to 25% of cases.[4,9,10] This is followed by a gradual decline in incidence with increasing age. During the perinatal period, arterial ischemic stroke (AIS) of arterial ischemic origin predominates, comprising up to 80% of cases.[5–18] In older children, the proportion of ischemic and hemorrhagic strokes is approximately equal, with a slight predominance of acute ischemic strokes.[18–20]

This case series highlights childhood stroke cases with uncommon multifactorial etiologies.

Case Description

Case 1

A 2-year-old boy admitted with acute-onset right-sided weakness with facial drooping of opposite side, 9 months after being diagnosed with Kawasaki disease. His parents stopped aspirin one week following discharge. Physical examination revealed right hemiparesis with left upper motor neuron type of facial nerve palsy. Both right upper and lower extremities had increased tone, power of grade 3/5, exaggerated deep tendon reflexes and up-going plantar reflex on right side. Routine blood investigation [include complete hemogram, liver function test (LFT), renal function test (RFT) and lipid profile] coagulation profile, antiphospholipid antibody (APLA) profile, prothrombotic and vasculitis workup were within the normal limit. 2D-echocardiography revealed decreased ejection fraction to 35% and aneurysms in left anterior descending artery (4 mm, *Z*-score 8.89), left main coronary artery (5.5 mm, *Z*-score 6.71) and left circumflex artery (3.5 mm, *Z*-score 5.00) (Fig. 1). Diffusion-weighted magnetic resonance imaging (MRI) (Fig. 1A) shows acute infarct seen involving the left parietofrontal and adjacent temporal regions in the left middle cerebral artery (MCA) territory, and magnetic resonance angiography (MRA) (Fig. 1B) reveals narrowing of left internal carotid artery with complete blockage of the left MCA. With a provisional diagnosis of right-sided hemiparesis due to underlying cardioembolic stroke, low-molecular-weight heparin and aspirin (5 mg/kg/day) were added. There was no further neurological deterioration following the start of treatment. Remarkable improvement of the clinical condition was seen over the next 2 weeks, along with intensive rehabilitation. However, the child still walked with a slight hemiplegic gait at the 6-month follow-up, and the right digits still lacked dexterity.[21–28]

Case 2

A 6-year-old boy presented with acute-onset respiratory distress with pain in the abdomen. He had a history of facial puffiness

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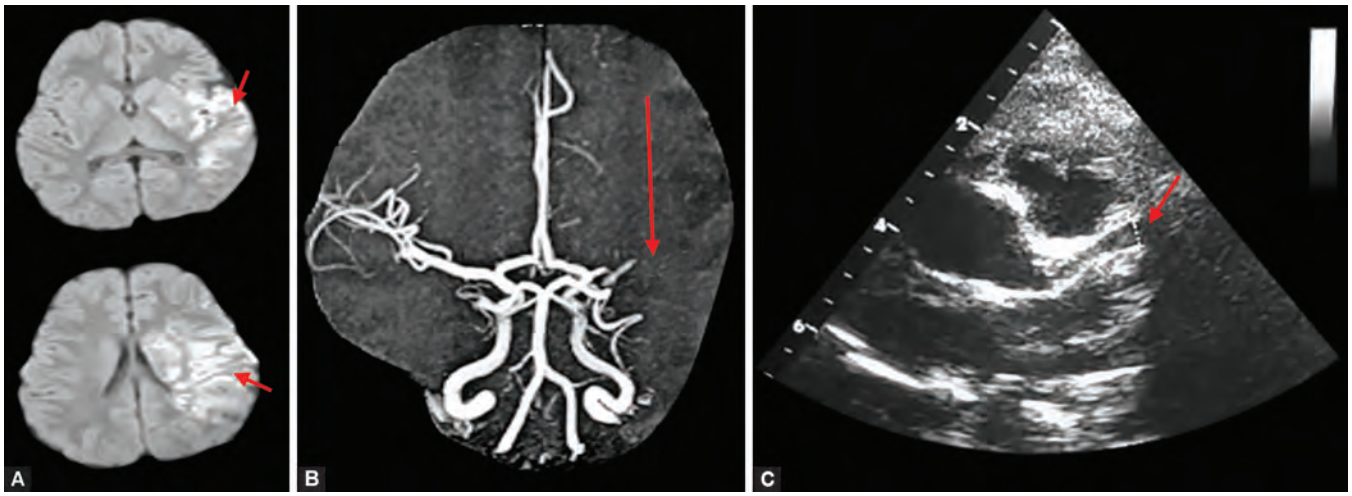
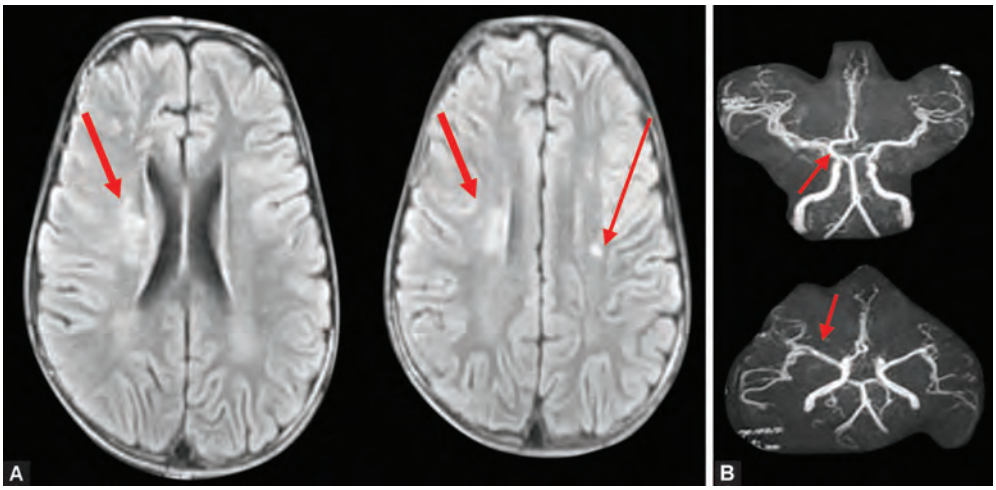


Figs 1A to C: (A) Diffusion-weighted magnetic resonance imaging shows acute infarct seen involving left parietofrontal and adjacent temporal region in left MCA territory; (B) Magnetic resonance angiography reveals blockage of left middle cerebral artery with complete block of left middle cerebral artery; (C) 2D-echo showing coronary aneurysm (LAD)

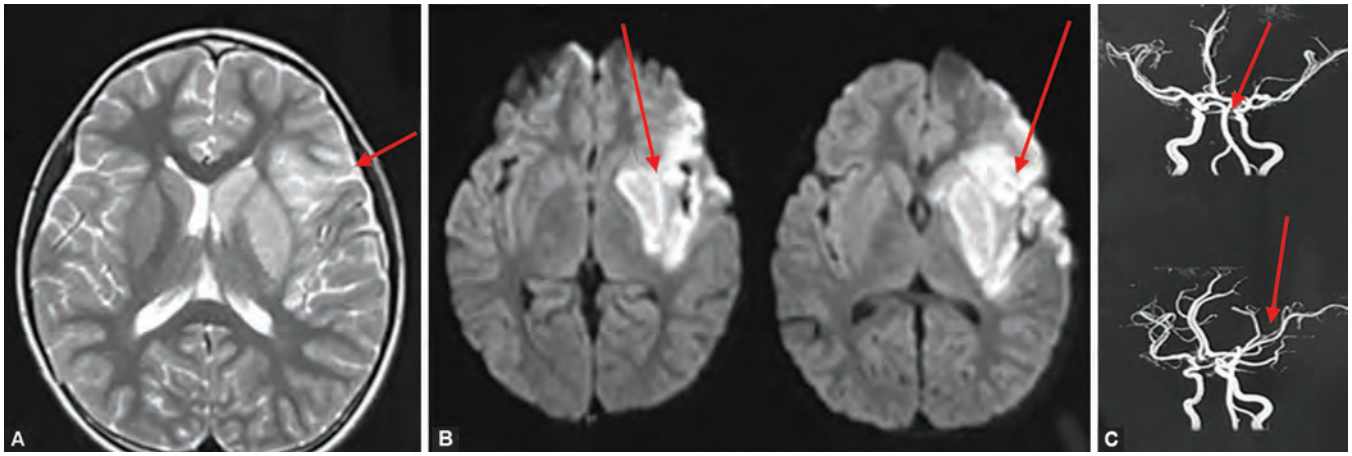


Figs 2A and B: (A) Magnetic resonance imaging brain (FLAIR) showing areas of acute infarct in right parietofrontal and perisylvian region in right middle cerebral artery territory. Small such lesion is seen in left parietofrontal and periventricular region; (B) Mild narrowing of distal part of right ICA middle cerebral artery

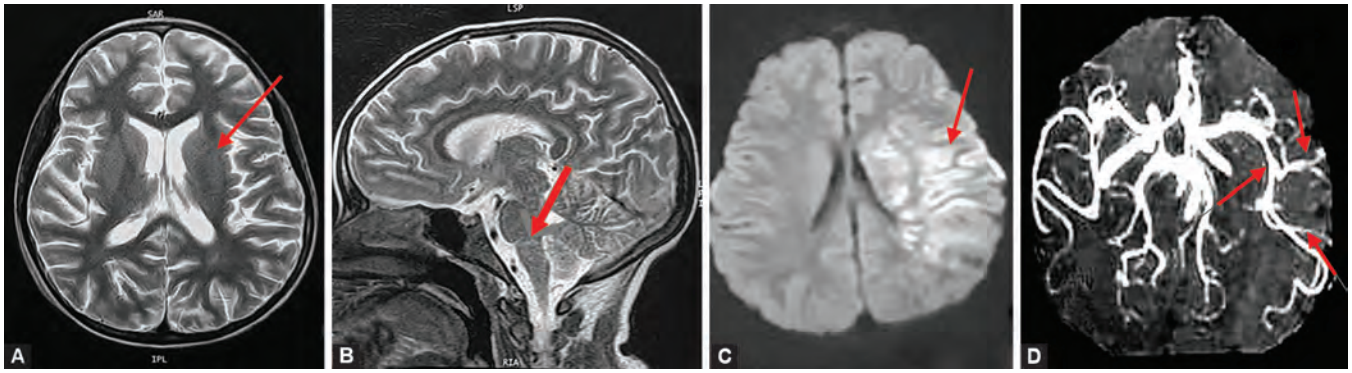
followed by swelling of limbs and trunk after an episode of undocumented fever for 2 days. He was transferred to the pediatric intensive care unit (PICU) due to underlying hypertensive encephalopathy. Subsequently, only right-sided limb movement and facial deviation towards the left side were noted. Physical examination revealed power of grade 0/5 and up-going plantar on left side and right-sided upper motor neuron type facial nerve palsy and elevated blood pressure (>95th percentile). His initial routine investigation reports (complete hemogram, lipid profile, LFT, RFT) C3, C4, ANA, anti ds-DNA (serum autoimmune panel), prothrombotic workup were normal except for microscopic hematuria and raised ASO-titer. Diffusion-weighted imaging (DWI) shows areas of acute infarct in the right parietofrontal and perisylvian regions in right MCA territory. A small-such lesion was seen in the left parietofrontal and periventricular regions. Narrowing of the distal part of the right internal carotid artery and middle cerebral artery were noted in MR angiography. It was diagnosed as left-sided hemiparesis due to thromboembolic stroke with hypertensive encephalopathy in a case of post-infectious glomerulonephritis (PIGN). In view of underlying thromboembolism, low-molecular-weight heparin (LMWH) for 5 days and aspirin (5 mg/kg/day) daily dose along with multiple antihypertensives were started, and no further neurological deterioration followed that. Significant recovery was seen following intensive rehabilitation and discharge after 1 month of pediatric intensive care unit (PICU) staying (Fig. 2).[29–34]

Case 3

A 9-year-old boy admitted a complaint of sudden-onset drowsiness while playing, followed by right-sided weakness and deviation of the lower part of the face towards left-side sparing the forehead. He had three episodes of tonic focal seizures involving the right upper limb and shoulder and developed aphasia and agnosia. There was no history of febrile illness or significant trauma. On admission, the boy was disoriented to time, place and person, glassgow coma scale (GCS) was 10/15; increased tone in right upper and lower limbs, power of 3/5, exaggerated deep tendon reflex with



Figs 3A to C: (A) Noncontrast computed tomography scan revealed perilesional edema in left side of brain; (B) Diffusion-weighted imaging showing area of acute infarct involving frontoparietal and adjacent temporal region of left middle cerebral artery territory; (C) Magnetic resonance angiography left internal carotid artery and middle cerebral artery are showing narrowing

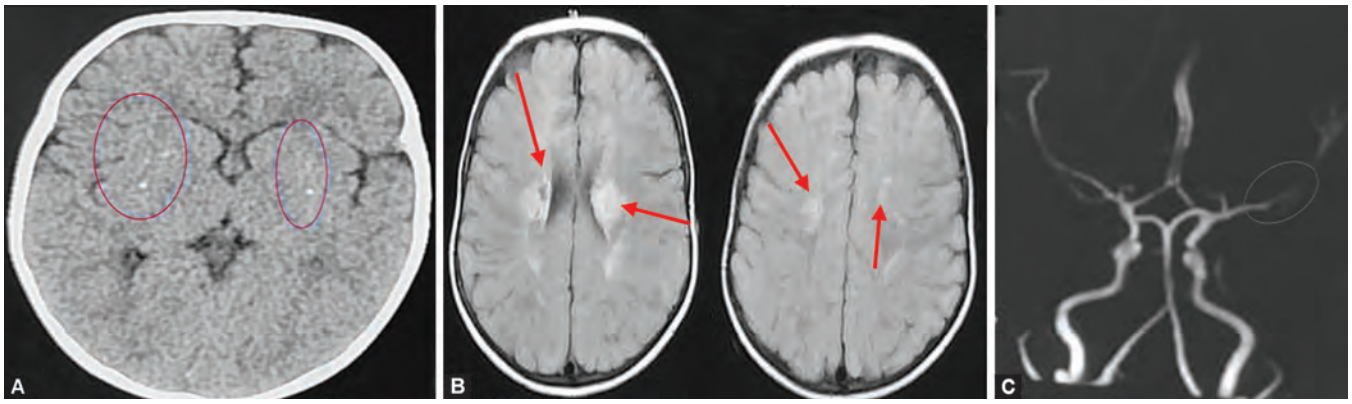


Figs 4A to D: (A) Magnetic resonance imaging of brain (T2 weighted) shows hyperintensities of left basal ganglia; (B) Ischemic foci in brainstem; (C) Diffusion-weighted imaging showing area of acute infarct in the left MCA territory; (D) Magnetic resonance angiography showing narrowing in left MCA of brain

extensor right plantar. Noncontrast computed tomography scan (NCCT) brain (Fig. 3A) revealed perilesional edema in the left side of the brain. Diffusion-weighted MRI (Fig. 3B) shows an area of acute infarct involving frontoparietal and adjacent temporal regions of the left MCA territory. In MRA (Fig. 3C), the left internal carotid artery and MCA are showing narrow lumens. Relevant reports, including complete blood count, LFT, RFT, vasculitis workup (ANA, anti-ds DNA, APLA profile), prothrombotic workup parameters (protein C, protein S, factor V mutation, antithrombin III), were within normal limit negative. 2D-echocardiography has no abnormality. As there was a family history of stroke among 1st-degree relatives, including his parents, whole exome sequencing was done that revealed a heterozygous variant of uncertain significance in exon 2 of the F5 gene. After adding oral aspirin (3–5 mg/kg/day) limb weakness, facial palsy and aphasia completely resolved by next week. After the acute event, the boy received intensive physiotherapy and showed good recovery of function without any residual weakness. It was diagnosed as a case of focal cerebral arteriopathy of an undetermined variant.

Case 4

A 10-year-old girl presented with a history of non-remitting fever for the last 3 months, followed by the acute-onset of right-sided hemiparesis involving upper and lower limbs with drowsiness on the day before admission. Seven days following admission, the girl developed facial weakness in the left lower part and difficulty in deglutition with dysphagia. At emergency, the child was irritable, not oriented to time, place, and person, GCS-11/15. There was neck rigidity, Kernig's sign and Brudzinski's sign were positive; increased tone and power of grade 3/5 in the right upper and lower extremities, right ankle clonus present (>5 jerks) right plantar extensor, right-sided deep tendon reflexes were exaggerated. Cerebrospinal fluid (CSF) study showed mild lymphocytic pleocytosis with normal protein and glucose levels. There was DCT-negative anemia (Hb 7.8 gm%), raised erythrocyte sedimentation rate, normal C-reactive protein and presence of microscopic hematuria (15–20/HPF), non-reactive serological markers, 24 hours urinary protein excretion of 0.84 gm. The serum autoimmune vasculitis panel has ANA hep-2 (3+, mixed pattern), anti-ds-DNA >800 IU/mL, serum C3 and C4 decreased. Cardiolipin antibody (IgG) is positive but <40 in APLA profile. Chest X-ray PA view showed mild bilateral pleural effusion. 2D-echocardiography showed mild pericardial fluid collection. Magnetic resonance imaging of the brain (T2 weighted) (Fig. 4A) shows hyperintensities in the left basal ganglia and ischemic foci in brainstem (Fig. 4B). Diffusion-weighted image (Fig. 4C) showing area of acute infarct in the left MCA territory.



Figs 5A to C: (A) Noncontrast computed tomography scan shows bilateral linear calcification; (B) An old infarct at the right basal ganglia region and a new infarct in the left basal ganglia region was noted in magnetic resonance imaging (MRI FLAIR cut section) of brain; (C) Magnetic resonance angiography showing mild narrowing of the left MCA and calcification suggestive of mineralizing angiopathy of lenticulostriate vessel

The MCA is showing narrowing on the left side of the brain on MRA (Fig. 4D). With a diagnosis of neuropsychiatric juvenile onset systemic lupus erythematosus, treatment was started with a pulse dose of IV methylprednisolone (30 mg/kg/day) for 5 days, followed by a maintenance dose of oral prednisolone at 1 mg/kg/day for the next 4 weeks initially. Oral aspirin was added along with. Symptoms of bulbar palsy including difficulty swallowing and facial deviation, were resolved gradually on day 18 onwards. Renal biopsy showed class III lupus nephritis, and cyclophosphamide was added at the monthly dose for the next 6 months, along with hydroxychloroquine and maintenance of prednisolone for the next 6 months.

Case 5

An 11-month-old girl presented with a history of trauma to the left side of the head following a fall from bed. The patient had three episodes of vomiting followed by loss of consciousness following this episode, and she regained consciousness after 15 minutes. Then she developed decreased movement of the right upper limb after the fall, which was insidious in onset and eventually involved the right lower limb within 24 hours. This was followed by a deviation of the angle of the mouth towards the left side two days following the head trauma without any restriction to eye closure. The child has a history of a previous fall 3 months back from the mother's lap causing trauma to the right side of the head followed by a focal clonic seizure involving the left upper and lower limbs, lasting <2 minutes and self-resolving along with reduced movement of the left upper and lower limbs with a right-sided deviation of the angle of the mouth. There was no significant birth history or any developmental delay. Physical examination revealed spasticity of both right upper and lower extremities, power of grade II/V, exaggerated deep tendon reflexes, and an extensor right plantar reflex. The angle of the mouth seems to deviate towards the left side while the baby was crying. On close examination, the right-sided nasolabial fold is less prominent as compared to the left. Antiphospholipid antibody profile, serum homocysteine level, antithrombin III factor and protein C, S levels were within the normal limit. Linear bilateral calcification is seen in a non-contrast enhanced computed tomography scan (Fig. 5A). An old infarct in the right basal ganglia region and a new infarct in the left basal ganglia region were noted in MRI of the brain (T2 FLAIR) (Fig. 5B). Magnetic resonance angiography (Fig. 5C) shows mild narrowing of the left MCA and calcification suggestive of mineralizing angiopathy of lenticulostriate vessel. Gradual improvement of clinical condition was observed over the next 2 months.

Discussion

Ischemic stroke is characterized by underlying processes such as thrombosis and embolism. A predisposing factor can be identified in 70% of cases, with congenital heart disease being the most frequent cause.[34–38] The clinical presentation of ischemic stroke is determined by the vascular territory involved and the resulting brain damage. Hemiplegia is the most commonly reported symptom in childhood ischemic stroke, observed in 91% of cases according to a study by Dusser et al.[39]

In children, detecting symptoms can be challenging, as hemiparesis may present subtly, such as through a limp or uneven hand usage. Seizures, which are uncommon in adult stroke, are more frequently seen in pediatric cases and often occur soon after the onset of hemiparesis. In this case series, focal seizures were observed in cases 1 and 5.

Following stroke confirmation via imaging, thorough investigations are crucial to identify the underlying cause.[32–40] In pediatric patients, diagnostic tools such as echocardiography and MRA play a significant role. In this series, MRA was performed on most patients and was instrumental in confirming the diagnosis.

The use of anticoagulation in children remains a topic of debate due to limited research in this area. Nevertheless, heparin or LMWH may be considered in cases of cardiac embolism, arterial dissection, coagulation disorders, or recurrent stroke.[38,40] Anticoagulation might also be appropriate for children showing progressive neurological deterioration or during the early evaluation of a new cerebral infarction.[38] When anticoagulation is not administered, low-dose aspirin (3–5 mg/kg) is recommended. In this series, all cases received low-dose aspirin, resulting in significant improvement.

Antithrombotic therapy (ATT) is advised for both the primary and secondary prevention of AIS in children. For initial treatment, aspirin or LMWH is commonly recommended, as it has been shown to be safe and effective in reducing the risk of AIS recurrence.[22–25] In cases of AIS caused by cardiac conditions, arteriopathy, extra cranial dissection, or prothrombotic disorders like thrombophilia, LMWH or warfarin may be preferred for 3–6 months or longer, depending

on hematology recommendations.[5,22] For idiopathic AIS and other cases, aspirin (3–5 mg/kg/day) is recommended for prevention.[5]

According to the published data, ATT is used in the majority of childhood AIS cases (60%) but is less frequently applied in perinatal AIS (13%), likely due to the lower risk of recurrence in neonates.[18] The risks of anticoagulation therapy, including a 4% chance of symptomatic and 7% chance of asymptomatic intracranial hemorrhage, must be weighed against the risk of AIS recurrence, which is estimated to increase by 1.5–2 times over the following two years without ATT.[17,18,23,26]

In the acute phase of AIS, ATT (e.g., heparin) is contraindicated in cases of hemorrhagic diathesis, bleeding disorders, or large infarction with a high risk of hemorrhagic transformation, such as complete MCA occlusion.[21,27] Given the potential risks associated with administering ATT, its use should be carefully tailored to each patient and guided by consultation with a pediatric hematologist.

Neurointensive care primarily involves supportive therapy aimed at maintaining stable physiological parameters, including normoxemia, normocapnia, normotension (50–95th percentile for age and height), normothermia, normoglycemia, and euvolemia. Aggressive seizure management, potentially with continuous electroencephalogram (EEG) monitoring when necessary, and early initiation of rehabilitation are also essential components of care.[6,21,22,28] For patients with intracranial hypertension or those at risk of herniation, osmotic therapy using mannitol and/or hypertonic saline, as well as decompressive craniectomy, may be considered.[5,28–30] However, the utility of intracranial pressure monitoring in pediatric AIS remains uncertain due to inconsistent evidence.[30,31]

Rehabilitation should begin as soon as the acute phase is managed. Children recovering from stroke have unique rehabilitation needs, which may include the use of specialized disability assessment tools such as the pediatric stroke outcome measure (PSOM) or the modified rankin scale (mRS).[41] Beyond physical disabilities, rehabilitation programs should address overall functional, cognitive, and behavioral impairments, with clear goals that adapt as the child grows. Collaboration among a multidisciplinary team including a pediatric neurologist, physiotherapist, occupational therapist, speech therapist, psychologist, teacher, social worker, and family is critical to developing an effective rehabilitation plan.[42]

Children generally have better stroke recovery outcomes compared to adults, likely due to the plasticity of the developing brain. This positive prognosis was reflected in all the patients described in this case series.

Conclusion

Pediatric stroke is a complex condition with a multifactorial etiology involving a combination of genetic, environmental and physiological factors. Unlike adult strokes, pediatric strokes often have unique underlying causes, like infections, trauma, and autoimmune disorders. The multifactorial nature emphasizes the importance of thorough diagnostic evaluations to identifying all contributing factors, as those often interact in complex ways. Early recognition, multidisciplinary management and proper rehabilitation are crucial to minimizing long-term neurological and developmental outcomes.

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CASE SERIES

Clinical Presentation and Genetic Insights of Mowat–Wilson Syndrome: A Case Series from India

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Abstract

This case series focuses on two female infants presented with developmental delay associated with multiple congenital anomalies who were eventually found to have Mowat–Wilson syndrome. To begin with, the first case discusses an 8-month infant with notable dysmorphic facial features, congenital heart defect, and developmental milestones delays. Genetic panel tests showed both exome sequencing and a new mutation of the genes including Zinc finger E-box binding homeobox 2 (ZEB2). Another case presented included a 12-month-old who had global developmental delay and hypotonic with an unusual shape craniofacial head. Consistent genetic testing also strong evidence sequenced Mowat–Wilson syndrome with ZEB2 mutation. All of them were evaluated and concluded the diagnosis using comprehensive physical rehabilitation, metabolic nutrition, and even genetic counseling in order to try and fix as much as possible their developmental problems. So, this case series has highlighted various features and the need for syndromology and genetic assessment in congenital disorders with non-specific measures.

Keywords: Congenital heart defect, Esotropia, Hirschsprung's, Mowat–Wilson syndrome, Zinc finger E-box binding homeobox 2 mutation.

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Introduction

The Mowat–Wilson syndrome (MWS) was first identified as a hereditary illness by Mowat et al.[1] There is a hereditary disorder caused by mutations in the Zinc finger E-box binding homeobox 2 (ZEB2) gene that results in facial dysmorphism, intellectual impairment, and in some cases, Hirschsprung disease.[1]

In addition to these usual signs, it can cause multiple system involvement scenarios in relation to growth failure, epilepsy, or congenital heart disease.[2–4] More recently, studies have started to focus on the range of neurology associated with MWS.[5,6] Immunodeficiency has been seen in some of the patients which has increased the variety of the symptoms that develop in the illness.[7] Compared with previous investigations that only concerned gross somatic symptomatology, more recent investigations are starting to uncover behavioral and psychological profiles of patients with this disease.[6]

Mowat–Wilson syndrome can be diagnosed using genetic testing of ZEB2 mutations.[4,8] A good number of symptoms are seen in a distinct manner in people with MWS. Due to the symptoms and the variability in the severity of the disease, it is very important to study the disease before one provides a diagnosis or even embarks on treating the disease.[9]

Globally, the incidence of Mowat–Wilson syndrome is not well established due to the rarity and relatively recent identification of the disorder. The exact prevalence varies by region and is likely underdiagnosed due to a lack of awareness and availability of genetic testing.

As for India, specific epidemiological data on the incidence of Mowat–Wilson syndrome is limited. There are no extensive studies or centralized databases that provide a precise incidence rate within the Indian population. The rarity of the condition, combined with varying levels of access to genetic testing and healthcare resources across the country, contributes to the challenge of obtaining accurate data.

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Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

Case Series

Case 1

An 8-month-old infant was brought to our child neurology clinic with developmental delays. She was delivered through a cesarean section at 38 weeks, hence gave birth prematurely. Her head circumference measured 32 cm (5th percentile), her length was 45 cm (10th percentile) and weight stood at 2.8 kg (around the 25th percentile). However, there were no other complications despite these problems and there was no family history of genetic diseases. We noticed some medical abnormalities such as a wide mouth with the prominent jaw, deep-set eyes, peculiar earlobes where there is a central dent in them, and broad nasal bridge (Fig. 1). It was also during her birth that doctors discovered that she had congenital heart disease (Patent Ductus Arteriosus). Her parents subsequently observed low muscle tone, delayed motor skills, and the inability to control her head or sit up alone.

A chromosomal microarray and karyotype test were done because of a variety of symptoms she had but found no abnormalities (Fig. 2). We opted for a whole exome sequencing (WES) due to the complexity of her condition. This confirmed Mowat–Wilson syndrome as there was a novel mutation in the ZEB2 gene on the intron 6 location with heterozygous zygosity).

Fig. 1: Showing a wide mouth with a prominent jaw, deep-set eyes, peculiar earlobes where there is a central dent in them, and a broad nasal bridge

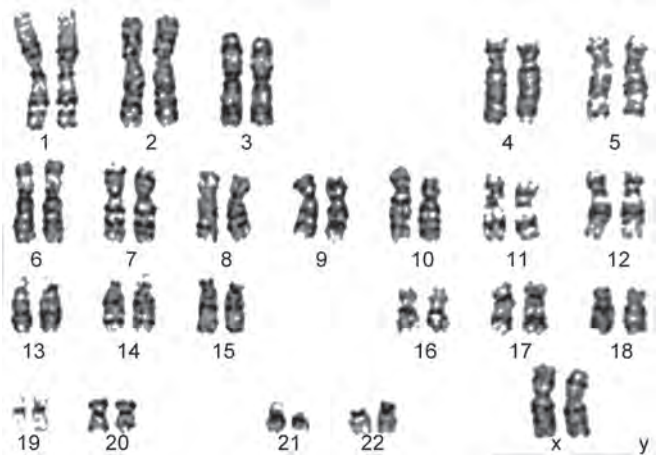

Fig. 2: Showing normal female karyotyping 46 XX

She began receiving physical and occupational therapy as part of early intervention services to aid in her development. For purposes of monitoring vision and hearing, she was attended by professionals in ophthalmology and audiology departments.

Because she was not gaining weight, we saw a pediatric dietitian and they had her on an extremely high-calorie diet. We also scheduled her to see a gastroenterologist, merely as needed for follow-up care/testing should she develop any symptoms consistent with Hirschsprung's (which is not something we can diagnose at this young age without specific testing) since the bowels and intestines are one giant long muscle; it all works together.

Finally, we offered genetic counseling to her family as a result of her disease and the implications for herself or any future pregnancies.

Case 2

We present the 2nd case of a 12-month-old female infant who is the first child of a non-consanguineous marriage. Her clinical presentation involves complex symptoms that prompt an exploration of several potential congenital and metabolic disorders. The infant was brought to our clinic with concerns regarding global developmental delay. Her parents noticed that she had not yet reached developmental milestones typical for her age. Additionally, they observed persistent hypotonia, and she exhibited behaviors such as babbling and frequently mouthing her hands and feet.

On physical examination, we noted several distinguishing features: intermittent esotropia characterized by cross fixation, a generally happy demeanor suggestive of a "happy puppet" appearance, a high-arched palate, and a broad philtrum. Remarkably, her ears were positioned posteriorly (Fig. 3), and she had smaller-than-average feet adorned with excessive skin folds. Additional examinations included an ultrasound (USG), which revealed right hydronephrosis. Her echocardiogram (2D ECHO) showed the presence of a small patent ductus arteriosus.

Given the complexity of the symptoms, differential diagnoses include a spectrum of congenital disorders. These range from congenital disorders of glycosylation and congenital or metabolic myopathies to mitochondrial disorders. There is also a suspicion of Mowat–Wilson syndrome, as several phenotypic features match this condition, known for its distinctive facial features and potential developmental challenges. Neurometabolic disorders also remain a possibility that warrants investigation.

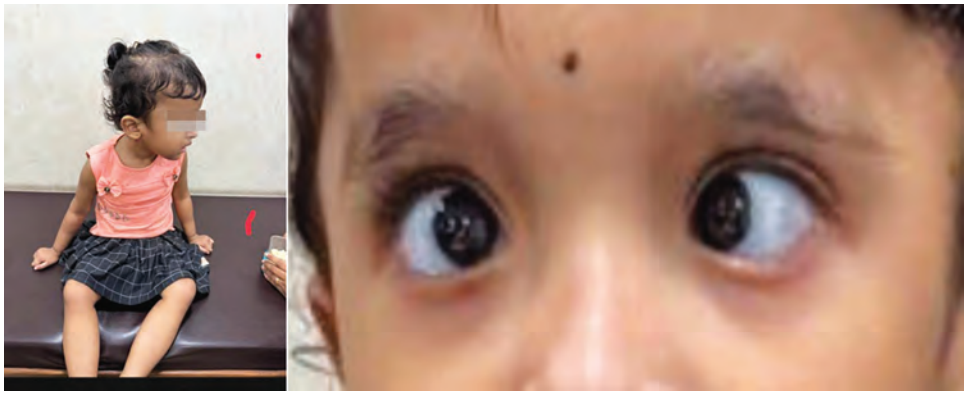

Fig. 3: Showing ear posteriorly placed and esotropia

The infant is undergoing genetic testing to identify any pathogenic variations that could confirm the underlying disorder. This confirmed Mowat–Wilson syndrome as there was a novel mutation in the ZEB2 gene on the intron 6 location with heterozygous zygosity.

The course of action includes not only genetic counseling for the family but also an individualized therapeutic approach to address the developmental delays and associated complications.

Discussion

Our study adds important knowledge to the growing literature on MWS focusing in particular on prevalent and rare phenotypic features of this syndrome. As in previous studies we found prominent intellectual disability and characteristic facial features. These reflect the developmental delays and craniofacial anomalies reported in previous reports of patients with rare duplications.[2,4,6,10]

We therefore also confirm the large variability in neurological symptoms found by Cordelli et al.,[5] as characteristic for patients with MWS. Adam et al.[4] reported that their behavioral traits are consistent with our observations, demonstrating some of the behavior patterns prevalent in this group. This underscores the importance of targeted behavioral therapies for individuals with MWS. In addition, our investigation documented additional immunodeficiency cases which confirmed Liang.[7] This indicates that to lower the threat of severe infections and additional intensification pre-existent comorbidity, MWS clients need regular evaluation of their immune function.[7] The wide range of symptoms we observed in our cohort underlines the need for comprehensive phenotypic descriptions for patients with MWS.[8] Because the syndrome presents with a combination of common and rare clinical features, clinicians require broad-based diagnostic testing to confirm the diagnosis as well as genetic testing for mutational status if they choose to treat patients.[1,12]

As noted by Kammoun[9] a further research to clarify the relationship among different genotypes and phenotypes is essential for future new biomarkers to successfully facilitate earlier diagnosis with dedicated medication. Management should be multidisciplinary with combined medical, developmental, and psychological inputs as MWS has multi-systemic involvement. This project intends to improve standards in diagnosis and treatment by increasing our knowledge of the numerous symptoms associated with MWS, improving outcomes and quality of life.

Conclusion

These cases illustrate the variability and complexity of the presentation of Mowat–Wilson syndrome, thus emphasizing the importance of considering genetic tests in the diagnostic approach for infants with atypical developmental tracks and distinguishable morphological features. Early identification and individualized therapeutic approaches help maximize outcomes for these affected individuals. Thus, these observations support the need for an interdisciplinary approach to offer comprehensive care and support for patients and their families so that better management of the current challenges and future implications of the syndrome may be undertaken. Further research and awareness will increase the understanding and propagate improved intervention strategies among clinicians across the world.

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CASE REPORT

A Rare Case of *KCTD7* Gene Mutation Masquerading as Opsoclonus-myoclonus Ataxia Syndrome – A Case Report

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Abstract

Introduction: The *KCTD7* gene is a potassium channel-related gene. Mutations in this gene, either homozygous or compound heterozygous, typically result in early-onset, intractable myoclonic seizures before the age of 2 years, often accompanied by developmental regression. In this case, a homozygous missense variant in exon 3 of the *KCTD7* gene (chr7:g.66638272C>T; depth: 97x) was identified, causing an amino acid change from arginine to cysteine at codon 112 (p.Arg112Cys; ENST00000639828.2). Due to limited evidence in the literature, this variant has been classified as one of uncertain significance, necessitating careful correlation with clinical findings.

Clinical description: We present a rare case of a 1-year-old male patient presenting with acute onset of myoclonus, opsoclonus, and ataxia with developmental delay. Patient was given intravenous and oral steroids, but showed little improvement; so, intravenous rituximab treatment was also tried. He also had abnormal epileptic discharges from right hemisphere with background abnormality. Previous high-resolution computed tomography scan of the thorax, computed tomography scan of the abdomen, and magnetic resonance imaging of brain were reported as normal. Therefore, whole exome sequencing was sent, which reported as homozygous, autosomal recessive, *KCTD7*(+) mutation, which is mainly reported as a cause for progressive myoclonic epilepsy-3.

Conclusion: An evaluation for *KCTD7* gene mutation should be done if a patient presents with an atypical course of opsoclonus-myoclonus with ataxia.

Keywords: Case report, *KCTD7*(+) mutation, Myoclonus, Opsoclonus-myoclonus/ataxia syndrome.

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Introduction

Opsoclonus myoclonus syndrome (OMS), also called dancing eyes-dancing feet syndrome and Kinsbourne syndrome, is a rare neurological condition. In young children, the immune system mistakenly attacks the nervous system, most often triggered by a tumor.[1] It can also be idiopathic or following a viral or bacterial infection. The primary symptoms of OMS include rapid and erratic eye movements (opsoclonus), sudden shock-like muscle jerks (myoclonus) in the arms or legs, difficulty in walking and balance (ataxia), hand tremor, behavioral changes, challenges with speech, trouble eating or sleeping, poor coordination, and hypotonia. The key objective in managing OMS is early, intensive immunotherapy aimed at sustained neurological remission. Surgical resection is standard if a tumor is present. In children, tumors such as low-stage neuroblastomas or ganglioneuroblastomas (stages I or II) are frequently observed. These cases typically do not require chemotherapy or radiation therapy. However, tumor resection alone may not sufficiently alleviate OMS symptoms.[2] For moderate to severe cases, the most effective treatment protocol documented in North America involves single use or a combination of high-dose corticosteroids (administered intravenously or orally) or adrenocorticotropic hormone, intravenous (IV) immunoglobulin, and rituximab. This three-agent approach has been shown to result in significant improvement for most patients (80–90%). However, maintaining long-term neurological stability often requires ongoing management and a gradual reduction of therapy.[2]

Progressive myoclonic epilepsies (PME) are a group of over 10 rare forms of epilepsy characterized by their "progressive" nature. Individuals with PME experience a gradual decline in motor skills, cognitive abilities, and balance as the condition advances. These epilepsies are typically marked by a combination of myoclonic seizures (sudden, rapid muscle jerks affecting different parts of the body) and tonic-clonic seizures. As the condition progresses, additional symptoms often emerge, including unsteadiness, muscle rigidity, difficulties with balance, and cognitive deterioration. Over time, individuals with PME require significant assistance with daily activities and often become dependent on a wheelchair. The condition also leads to a shortened life expectancy.[3] Progressive myoclonic epilepsies are inherited in an autosomal recessive manner and affect males and females equally.

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Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

Table 1: OMS rating scale

	Score			
OMS rating scale	*On 2nd admission*	*On 2nd discharge*	*On 3rd admission*	*On 3rd discharge*
Stance	2	2	3	2
Gait	3	2	3	2
Arm/hand function	2	2	1	1
Opsoclonus	1	1	1	0
Mood/behavior	1	1	1	0
Speech	3	3	3	3
Total	12/18	11/18	12/18	08/18

Clinical Description

The patient is a 1-year-old male born of consanguineous marriage. He was delivered full term without any complication at birth.

He was apparently alright till 1 year of age; then parents noticed abnormal movements of body, which were generalized mild tremulous movements, along with multiple episodes of sudden jerks while awake without any change in consciousness state. He was admitted for these jerks, where intermittent abnormal eye movements were noticed. His neurological examination was done, which showed multifocal myoclonus, opsoclonus, and generalized decreased muscle tone but preserved power and brisk deep tendon reflexes. He was able to stand with support with wide base momentarily and was able to sit unsteadily. He was only able to vocalize at this age, but his comprehension appeared to be normal. He had mild increase in irritability but consolable. Upon questioning, it was noted that he had mild developmental delay. Magnetic resonance imaging (MRI) of brain was reported normal. A clinical diagnosis of OMS was considered and IV methylprednisolone was given for 3 days and discharged on oral prednisolone. His symptoms were reduced but persistent. Then he had two episodes of generalized tonic-clonic seizures at 1 year and 6 months of age, one of which lasted for 30 minutes; he was admitted. Mitchell and Pike OMS scoring on admission was 12/18 (Table 1), and sleep electroencephalogram (EEG) depicted right hemispheric epileptiform discharge with background abnormality suggestive of symptomatic epilepsy with underlying cerebral dysfunction. During this time, high-resolution computed tomography of chest and computed tomography of abdomen were also done to look for neuroblastomas, but they turned out to be normal. Whole exome sequencing was discussed with parents to rule out genetic epilepsy. He was given rituximab injection along with another course of IV methylprednisolone and on discharge oral prednisolone, levetiracetam, and clobazam were continued (OMS rating; Table 2). After a month from discharge, his symptoms worsened and he was admitted and given another dose of rituximab injection, and his sample for whole exome sequencing was also collected and reported as homozygous missense variant in exon 3 of the *KCTD7* gene (chr7:g.66638272C>T; depth: 97x), causing an amino acid change from arginine to cysteine at codon 112 (p.Arg112Cys; ENST00000639828.2). His OMS rating of this admission and discharge are mentioned in Table 1.

Discussion

We present a case involving a mutation in the *KCTD7* gene, a potassium channel-related gene, associated with a unique clinical phenotype. The patient exhibited acute-onset ataxia and myoclonus accompanied by abnormal eye movements resembling opsoclonus. Clinical improvement was observed following steroid and immunotherapy treatment. Additionally, the patient experienced episodic generalized tonic-clonic seizures alongside a background of mild developmental delay. A clinical diagnosis of OMS is typically made when at least three of the following four features are present: behavioral changes and/or sleep disturbances, myoclonus/ataxia, opsoclonus, and neuroblastoma.[4] In this case, the presence of epilepsy raised suspicion of an underlying genetic cause. Whole exome sequencing revealed a mutation in exon 3 of the *KCTD7* gene, previously linked to PME-3 with or without intracellular inclusions.

There are significant clinical overlaps between PME and OMS. In PME, myoclonus is often multifocal, fragmentary, and triggered by external stimuli, such as light, sound, touch, posture, or movement.[5] It primarily affects facial and distal extremity muscles, but may also include massive bilateral jerks involving proximal limb muscles. In contrast, the myoclonus seen in OMS patients is typically multifocal, including the face, head, neck, limbs, and trunk. It may sometimes manifest as isolated movements in the fingers, described as minipolymyoclonus. The myoclonus in OMS can occur spontaneously or be stimulus-sensitive, with exacerbations triggered by crying, excitement, or stress. It may persist during sleep, and severe myoclonus mimicking convulsive status epilepticus has also been reported.[6,7] The onset of PME varies from childhood to adulthood. For infantile or early childhood cases, neuronal ceroid lipofuscinoses are a common cause. Pediatric OMS, on the other hand, typically begins between 18 and 20 months of age, with the youngest reported case occurring at 4 months.

There are notable clinical distinctions between PME and OMS. Opsoclonus, which is a hallmark of OMS, has not been reported in patients with PME. Additionally, seizures and abnormal EEG findings, which are common in PME, are generally not observed in OMS. The differential diagnosis between these two conditions can be challenging, especially since EEG abnormalities may develop later in PME. While opsoclonus is a key feature of OMS, it can, in rare cases, be absent.[8] Myoclonus, a symptom present in both conditions, shares similar characteristics. The epileptic origin of myoclonus in either disorder may require ictal video EEG to diagnose.

As *KCTD7* gene-related disorders are actually a type of neuronal ceroid lipofuscinosis, MRI of brain is expected to show changes such as cerebral and cerebellar atrophy. The patient's MRI of brain is reported to be normal, which correlates with other previous similar case reports, patient 3 of Van Bogaert et al. and Blumkin et al.[9,10]

An interesting aspect of our case was the patient's limited response to steroid and immunotherapy, in contrast to patients

Table 2: Comparison of five patients of *KCTD7* gene mutation

Characteristics	*Van Bogaert et al.*[9] *Patient 1*	*Van Bogaert et al.*[9] *Patient 2*	*Van Bogaert et al.*[9] *Patient 3*	*Blumkin et al.*[10]	*This case*
Age of onset	18 months	24 months	16 months	10 months	12 months
Perinatal history	Normal	Normal	Normal	Normal	Normal
Sex	Female	Female	Female	Male	Male
Early psychomotor development	Normal until 18 months	Normal until 24 months	Normal until 16 months	Normal until 10 months	Mild developmental delay
Presenting sign	Multifocal myoclonic seizure	Seizure	Head shaking, episodes of sudden loss of tone, brief absences	Ataxia, recurrent nonepileptic myoclonic status	Myoclonus, opsoclonus, and ataxia
Myoclonus	+	+	+	+	+
Ataxia	Severe	No	Severe	Moderate truncal and mild limb	Moderate
Speech	Anarthria	Severe dysarthria	–	Severe dysarthria	Only vocalizes
DTR	Brisk	–	–	Normal	Brisk
EEG	Diffuse slow dysrhythmia, multifocal spike-waves and polyspike-waves. No correlation with action myoclonus	Multifocal epileptiform discharges. Frequent posture-evoked negative myoclonus but inconstantly related in time with epileptiform discharges	Slow dysrhythmia and bilateral multifocal asynchronous spike-waves	Bilateral epileptic activity with spike and wave pattern. No correlation between the epileptic discharges and minipolymyoclonus and gross myoclonus	Right hemispheric epileptiform discharge with background abnormality suggests symptomatic epilepsy with underlying cerebral dysfunction
MRI of brain	–	–	Normal	Normal	Normal
Antiepileptic drugs	Dramatic, but transient response to levetiracetam	Seizure-free on lamotrigine and clonazepam	Transient response to topiramate, lamotrigine, and felbamate	No response to valproic acid, levetiracetam, topiramate, carbamazepine, and clonazepam	Responded to Levetiracetam and clobazam
Steroids	Significant but transient improvement	–	Significant but transient improvement	Significant improvement of myoclonus	Limited improvement

in the studies by Van Bogaert et al. and in Blumkin et al. who after failing antiepileptic drug treatment, subsequently responded to steroids.[9,10]

Prior to the onset of epilepsy, the clinical presentation may resemble that of OMS. As a result, patients with an atypical progression of OMS should be assessed for *KCTD7* mutations.

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CASE REPORT

Scrub Typhus: An Uncommon Cause for Pediatric Acute Cerebellitis in India – A Case Report

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Abstract

Scrub typhus is a clinical condition, which is endemic to our country. It is an acute to sub-acute form of febrile illness, causing range of milder symptoms from fever, body pain to more severe complications such as acute kidney failure, scrub meningitis and sometimes even death. Recently, since last few years, the cases of scrub typhus are on a rise and the total number of documented cases are quite less than the actual prevalence. Many cases go unreported, or gets diagnosed only in the 2nd week of illness because of its undifferentiated symptoms from other common diseases. This clinical condition can literally affect any organ, and has become one of the commonest causes of pyrexia of unknown origin (PUO). But once the diagnosis is done, the specific treatment is available and in majority of cases, the cure is complete specially if started early, therefore, it is important to have an awareness among doctors regarding the nature, symptoms, and treatment of scrub typhus.

In this article, we present a case report of a 8 years old boy with atypical presentation of fever followed by ataxia.

Keywords: Ataxia, Case report, *Orientia tsutsugamushi*, Pyrexia of unknown origin, Scrub typhus.

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Introduction

Scrub typhus is caused by the rickettsial organism *Orientia tsutsugamushi*. The organism is endemic in South Asia and South-east Asia countries. In India, it is found in the rural areas, especially in the hilly and forest regions. Its larval form which is also the pathogenic form—the "chiggers" are transmitted to humans via the vector Trombiculide mite.[1] Humans are accidental host. Transovarian transmission is the main mode for the natural propagation.[1]

Scrub typhus can present with fever, eschar rash (7–69%) and multi- system involvement affecting liver, brain, heart , kidney etc, with lymphadenopathy. It has varied neurological manifestations seen in 20% of cases affecting both central and peripheral nervous system. It can result in acute aseptic meningitis, acute meningo-encephalitis, Gullaine barre syndrome (GBS), acute cerebellitis, acute demyelinating encephalomyelitis (ADEM), longitudinally extensive transverse myelitis (LETM) and opsoclonus myoclonus ataxia syndrome (OMAS). The mechanisms include direct invasion of the organism, a vasculitis-like process, or an immune-mediated injury.[2–5] Diagnosis of scrub typhus is confirmed by the detection of *O. tsutsugamushi* IgM antibody in serum. Acute encephalitis syndrome and aseptic meningitis have been reported but acute infective cerebellitis is uncommon and only few cases have been described previously. [1–3]

Case Description

Here, we describe a 8 years old boy, hailing from a remote area of Western India, was referred by the pediatrician with 4 days history of fever, 3 days history of vomiting with morning headache followed by difficulty in walking and maintaining balance. There was no history of seizures, focal neurological deficit, loss of consciousness, recent travel, immunization, any animal or insect bite. On examination, he had normal sensorium, he was febrile with positive cerebellar signs, such as ataxia, nystagmus and past pointing. The power was 4/5 with decreased tone, with intact deep tendon reflexes. There was no eschar. The rest of the systemic examination was normal.

Laboratory investigations revealed hemoglobin of 10.4, total leucocyte count of 7580 cells/mm^3, C-reactive protein – 80 mg/L, SGPT-23 mg/dL, Dengue NS1 and IgM was negative, malaria card test – negative, serum sodium-132 mg/dL, serum potassium 4.05 mg/dL, ionized calcium – 1.19 mg/dL.

Cerebral spinal fluid (CSF) analysis revealed a total of 60 cells/mm^3 with lymphocytic predominance – 70%, neutrophil – 30% with protein of 71.3 mg/dL, glucose – 64.2 mg/dL. MRI brain plain and contrast was done in the referring institute (on day 3 of illness) which was normal.

Being in an endemic region, his tropical panel was sent which revealed negative for leptospirosis and brucellosis. His scrub typhus IgM w came positive. So he was started on IV methylprednisolone 30 mg/kg/day single dose for 3 days and IV doxycycline 5 mg/kg/day for 5 days.[5] His fever disappeared on day 2 of admission and his gait

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Table 1: Scrub typhus antibody IgM by ELISA

Test	*Result*	*Biological ref. interval*
Sample O.D	1.821	
Cut off absorbance	0.500	
Scrub typhus IgM antibody	Positive	Negative: OD of patient <cut off Positive: OD of patient >cut off

ataxia and nystagmus started to improve as well. He was discharged after 5 days with improved cerebellar signs (Table 1).

Summary

Scrub typhus is not an uncommon cause for an acute infectious encephalitis , especially in endemic regions. Awareness among health care providers regarding the different presentations of this disease is very crucial in order to reduce morbidity and mortality. Co-infection with dengue and/or chikungunya viruses may occur in endemic regions. The history of an acute febrile illness preceding the neurological illness is the clue. Presence of an eschar rash is pathognomonic for the disease – which is usually found in conspicuous sites like nape of the neck, behind the ears, axilla and around the groin region. So, careful search for the eschar is essential; however, the absence of the eschar, cannot exclude the diagnosis of scrub typhus.

Acute infective cerebellitis due to scrub typhus is uncommon, and has been reported in the literature in only few cases so far. It is worth noting that neuro imaging can sometimes be normal as well, as in our case, though all the previously reported cases had T2 and FLAIR hyper intensities in the cerebellar cortex. The neurological symptoms respond dramatically to doxycycline. Other options include azithromycin of 10 mg/kg/day for 5 days. Studies show efficacy of doxycycline and azithromycin are comparable.[5] Second line agents include rifampicin and chloramphenicol.[6]

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CASE REPORT

Atypical Presentation of Pompe Disease: Overlapping Features of Infantile-onset Pompe Disease and Late-onset Pompe Disease – A Case Report

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Abstract

Background: Pompe disease, a lysosomal storage disorder characterized by the deficiency of the enzyme acid alpha-glucosidase (GAA), leads to harmful glycogen accumulation within cells, resulting in muscle weakness and organ dysfunction.

Clinical description: This case report discusses an atypical manifestation of Pompe disease in a 6-year-old male, who initially presented with dilated cardiomyopathy at 2.5 months and later exhibited overlapping features of both infantile and late-onset Pompe disease. Despite the typical prognosis of infantile-onset Pompe disease, which often results in early mortality, this patient survived due to timely interventions. His clinical history revealed developmental delays, hypotonia, and recurrent heart issues, ultimately leading to a diagnosis confirmed by low GAA enzyme activity. Genetic testing showed no deletions or duplications, highlighting the rarity of this presentation.

Conclusion: The results highlight the significance of identifying unusual presentations of Pompe disease, which may deviate from typical timelines or symptomatology, stressing the necessity for increased vigilance in clinical environments. Enzyme replacement therapy (ERT) is crucial for effective management, and this case demonstrates the possibility of prolonged survival through early intervention and continuous treatment.

Keywords: Atypical Pompe disease, Acid alpha-glucosidase enzyme level, Case report, Enzyme replacement therapy.

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Introduction

Pompe disease, also known as the "lysosomal storage disorders" (LSDs). For the lysosomal degradation of glycogen-acid alpha-glucosidase (GAA) is the key enzyme responsible. Low blood levels of GAA cause it to accumulate within cells, which leads to cellular malfunction, tissue damage and organ dysfunction. This will be clinically manifested by muscle weakness and muscle wasting.[1,2]

The classic infantile type of Pompe disease is the most severely impacted subtype. It presents with rapidly progressive muscle weakness, hypotonia, respiratory deficiency and hypertrophic cardiomyopathy within the first three months of life. About 98% of all patients died before 1.5 years. None of the patients grew older than 2.9 years.[3] While "atypical pompe" presents with milder myopathy with respiratory failure between 12 and 18 months of age but can live longer with respiratory and nutritional support.[2]

Many infants have a large, protruding tongue and a moderate hepatomegaly. Absence of deep tendon reflex (DTR) was the most common neurologic examination. Cognition is usually normal. The majority of all infants experience hearing loss. Levels of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and lactate dehydrogenase (LDH) rise considerably with age and may serve as more reliable indicators of disease progression compared to CK.

Case Description

A 6-year-old male came with complaint of gait abnormality and proximal weakness with associated pain over both legs since 1 week. On examination, "time taken to rise" was 1.9 sec with both feet inverted with a waddling gait. There was hypotonia in all four limbs with hyperextensibility of joints and DTR +1. Creatine phosphokinase (CPK) MM was 50 within normal limit. On asking birth history-child was preterm with a birth weight of 1.5 kg and had a NICU stay for 9 days for low birth weight. The child had delayed gross motor development with some sensory and autistic traits with stereotypes and poor eye contact at the time of presentation.

At age of 2.5 months of age, in view of feeding difficulty, after failure of improvement in symptoms by local doctor child was referred to paediatric cardiologist, where dilated cardiomyopathy with left ventricular ejection fraction (LVEF) of 15–20% was detected

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and the child was started on anti-cardiac failure medication. Creatine phosphokinase-MB level –38.31 was high (0–24 U/L). Repeat 2D-ECHO after 3 months shows improvement in LVEF to 40–45%, so cardiac medication was modified. And as repeat 2D-ECHO after 6 months of starting treatment was normal, so all cardiac medication was stopped.

Again at 10 months of age, the child presented with WALRI with CCF with 2D-ECHO suggestive of mild TR with mild LV dysfunction. So cardiac medication restarted and continued for 6 months. After that, at the age of 2.5-year a repeat 2D-ECHO was done, which was normal.

After an asymptomatic phase of 3 years, as child had developed again reappearance of symptoms and presented to us for first time, we have clinically diagnosed as mixed overlapping feature of early as well as late features of Pompe disease and sent enzyme level of GAA, and it comes to be positive with enzyme activity level <0.26 (normal >0.29). Genetic analysis on sequencing was normal, which we generally do for 5–13% deletion and duplication. 2D-ECHO was normal.

After confirming diagnose of Pompe disease, MR-angiography of aorta and internal carotid was done to look for any missing anomaly of vessels as aneurysm and arterial dolichoectasia of vessels, likely caused by glycogen accumulation in arterial walls, are more common in atypical case of pompe.[3] The child was referred to higher center for further management for enzyme replacement therapy (ERT).

Summary

Atypical presentation of Pompe disease, which starts with an early onset of 2.5 months with dilated cardiomyopathy and again represents a late-onset childhood type, has not been mentioned in literature till now. As infantile-onset Pompe disease generally died within 1 year of life, that was not seen in this case, which might somewhat contributed to early intervention in the form of anti-congestive cardiac failure measure for this child just soon after detection of dilated cardiomyopathy. But after 3 years of asymptomatic phase, again the appearance of myopathy-like features with normal cardiac function was unusual, which might point towards late-onset childhood Pompe disease in the same child.

Enzyme replacement therapy, along with supportive therapies, is fundamental in the management of Pompe disease. Numerous patients may require respiratory assistance as a result of differing degrees of respiratory dysfunction.

Enzyme replacement therapy is an established treatment option for all individuals diagnosed with Pompe disease. This therapy is referred to as "MYOZYME" (alglucosidase alfa), which is a lysosomal glycogen-specific enzyme. It comprises the human enzyme GAA, derived from the most common of the nine identified haplotypes of this gene, and received food and drug administration (FDA) approval in 2006. The annual cost of treatment varies based on the patient's weight, ranging from 3.5 million to 7.5 million rupees for those weighing up to 20 kg.[4]

In 2021, the FDA granted approval for avalglucosidase alfa-NGPT (Nexviazyme) as a treatment for patients aged one year and older diagnosed with late-onset Pompe disease. This ERT is administered intravenously and aids in decreasing glycogen buildup in the body.

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CASE REPORT

MOGADs Presenting as Cortical Cerebral Encephalitis in Adolescent: A Case Report

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Abstract

Myelin oligodendrocyte glycoprotein antibody associated diseases (MOGADs) is an inflammatory demyelinating condition of the central nervous system (CNS) characterized by a monophasic or relapsing course of neurological dysfunction. We hereby discuss the case of an 11-year-old girl with frequent relapses of MOGADs and complications related to her therapy. Each episode was characterized by visual deficits associated with severe headaches, giddiness and altered sensorium. Magnetic resonance imaging (MRI) brain suggestive of heterogeneous abnormal signal lesions in posterior parietal area involving the cerebellar peduncles. Cerebrospinal fluid (CSF) for myelin oligodendrocyte glycoprotein (MOG) antibody was positive. She had three relapses in a span of 5 months while on maintenance treatment on steroid with mycophenolate mofetil and treated with intravenous immunoglobulin (IVIG) and oral steroids during relapse. Myelin oligodendrocyte glycoprotein antibody positivity with bilateral optic neuritis (ON) and absence of Dawson's fingers appearance/periventricular lesion on MRI brain ruled out multiple sclerosis (MS) in this patient, while adolescent age, female gender and ON are overlapping features.

Keywords: Acute demyelinating encephalomyelitis, Autoimmune encephalitis, Case report, Optic neuritis, Multiple sclerosis, Myelin Oligodendrocyte glycoprotein antibody associated diseases.

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Introduction

Myelin oligodendrocyte glycoprotein antibody-associated diseases (MOGADs) are an inflammatory demyelinating condition of the central nervous system (CNS) characterized by a monophasic or relapsing course causing neurological dysfunction. We are here to discuss case of 11-year-old girl with frequent relapses of MOGADs and complications related to her therapy.

Case Decsription

An 11-year-old girl with third degree consanguinity, presented with visual deficits associated with severe headache, giddiness, convulsions and altered sensorium Magnetic resonance imaging (MRI) brain suggestive of confluent asymmetric areas of abnormal signal intensities, right more than left (Fig. 1). Discrete small lesions in both frontal lobes, right thalamocapsular region, right superior and both middle cerebellar peduncles suggestive of demyelination. Cerebrospinal fluid (CSF) showed pleocytosis and CSF Myelin oligodendrocyte glycoprotein (MOG) antibody was positive, while NMO, *p*-ANCA, *c*-ANCA were negative. Electroencephalogram (EEG) was suggestive of generalized epileptiform activity. The child was treated with Methylprednisolone and discharged on oral steroids and anticonvulsants. Clinically, the child improved but had relapses within 3 weeks' time, as soon as the steroids were stopped. During this episode, she was treated with intravenous immunoglobulin (IVIG) and sent home on oral steroids. She developed a third relapse after 4 months, soon after the steroids were tapered. In view of frequent relapses, she was started on monthly IVIG and daily azathioprine. She had 5 relapses in a span of 8 months while on maintenance doses of immune-modulators as per standard guidelines. Each episode characterized by altered sensorium, visual deficit, and convulsions. Subsequent MRI brain scan done during next episodes is suggestive of persistent lesions seen at the onset with an increase in peri temporal lesions and some new lesions like hyperintensities in bilateral periventricular regions, and acute demyelination in the left uncus, hippocampus, atrophic optic nerve and chiasma respectively. Plasmapheresis was done in the last 2 episodes as there was no symptomatic improvement in the child with IVIG. Azathioprine along with monthly IVIG therapy, replaced the steroids as she developed steroid toxicity (Fig. 2). She developed progressive optic atrophy and complete visual deficit during subsequent episodes. After 4 months of starting azathioprine and monthly IVIG the child brought in status epilepticus and unfortunately succumbed to pancytopenia and septic shock.

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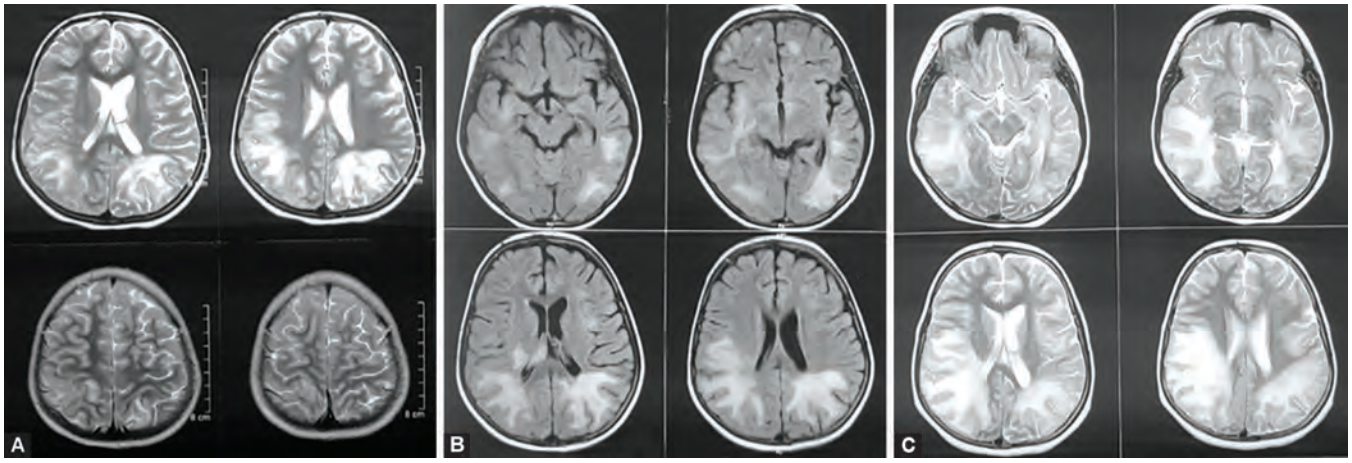

Figs 1A to C: (A) Confluent asymmetric areas of abnormal signal intensities, right > left. Discrete small lesions in both frontal lobes, right thalamocapsular region, right superior and both middle cerebellar peduncles; (B) Bilaterally fairly symmetrical areas of signal abnormality in the posterior parietal periventricular and subcortical white matter. Small FLAIR hyper intensities in bilateral frontal deep white matter, medial third thalamus and middle cerebellar peduncle; (C) Multiple heterogeneous enhancing lesions in the bilateral parietotemporal and frontal lobes with moderate perilesional edema. Peritemporal lesions appear to be enlarged compared to MRI of 28/10/2021

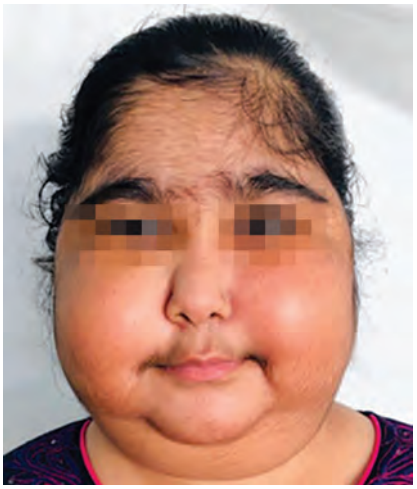

Fig. 2: Moon facies of steroid toxicity

Discussion

Myelin oligodendrocyte glycoprotein-associated disease is a rare; antibody-mediated inflammatory demyelinating disorder of the CNS, with various clinical features including optic neuritis (ON), transverse myelitis, acute demyelinating encephalomyelitis (ADEM) and cortical encephalitis. The exact incidence of MOGADs is not known, but according to studies in Europe, incidence of MOGAD is 1.6–3.4 per 1,000,000 person years.[1,2] Myelin oligodendrocyte glycoprotein antibody-associated diseases can present in all age groups, with a mean/median age at onset of approximately 28–30 years while children account for up to half of the reported cases.[2]

Initial presentation and each relapse in our patient had ON as the predominant symptom. Optic neuritis is the most common symptom of MOGAD occurring in 54–61% of the patients.[3] Bilateral ON is common, but unilateral ON is seen in few patients. Rempe's study showed that, as compared with neuromyelitis optica spectrum disorder (NMOSD) patients, MOGAD patients with ON were more prone to bilateral ON.[4] Ramanathan et al. compared the differences (Table 1) among multiple sclerosis (MS), NMOSD and MOGAD patients in manifestation of ON, and results showed that MOGAD patient had severe visual impairment in the acute phase.[5] In MOGAD data suggest ON is bilateral in up to 50% of cases with simultaneous vision loss of both the eyes.[5] Our patient, during each relapse, presented with features of ON and eventually developed optic atrophy and blindness. Optic coherence tomography (OCT) was done, suggestive of damage to retinal nerve fibers.

At onset as well as during subsequent episodes apart from ON the patient had features of cerebral cortical encephalitis and status epilepticus in the terminal stage. Acute demyelinating encephalomyelitis like syndrome (ADEM with ON, multiphasic disseminated encephalomyelitis) is the most common initial presentation of MOGAD in children, noted in 68% of all MOG-positive pediatric cases.[1–8] Cerebral cortical encephalitis is now recognized as a novel feature of MOGAD.[8–10] Its clinical manifestations include seizures, aphasia, stroke-like episodes, headaches and fever. Seizures may be the presenting feature in MOGAD, most commonly, it is a focal motor seizure, bilateral tonic-clonic seizures. Infrequent seizures may lead to status epilepticus requiring mechanical ventilation.[7,8]

Diagnostic Criteria for MOGAD is,[10]

- Serum positivity for MOGAD-Ig G
- A clinical presentation consistent with any of the following CNS syndrome-ADEM, ON, transverse myelitis, or brain or brainstem demyelinating syndrome.

In our case, a diagnosis of MOGAD was made based on clinical features and the presence of MOG positive antibody.

International Recommendations for MOG Antibody Testing Include[11]

- Monophasic or relapsing acute ON, myelitis, brain stem encephalitis.
- Radiologic ON or, only in-patient with a history of ON.
- Electrophysiological findings compatible with CNS demyelination.

Table 1: Clinical differentiation between ADEM with or without MOG-antibody MS, and neuromyelitis optica spectrum disorder

	ADEM with or without MOG-antibody	*Multiple sclerosis*	*Neuromyelitis optica*
Age gender	<10 years Boys and girls equal	>10 years Female preponderance	Around 40 years of age
Seizures	+	–	–
Encephalopathy	+	–	–
Fever/vomiting	+	–	+
Family history	No	20%	No
Optic neuritis	Bilateral	Unilateral	–
Manifestations	Polysymptomatic	Monosymptomatic	Polysymptomatic
CSF	Pleocytosis (lymphocytosis) OCBs negative	Acellular OCBs positive	Commonly >50 white cell count/mm^3, glial fibrillary acidic protein at relapse. OCBSs in 10–25% patients

- Magnetic resonance imaging changes suggestive of longitudinally extensive spinal cord lesions, conus medullaris lesions, lesions suggestive of ADEM, no lesions adjacent to lateral ventricle.
- Papilledema on fundoscopic examination.
- Cerebrospinal fluid study suggestive of pleocytosis.

Myelin oligodendrocyte glycoprotein-IgG1 is a specific biomarker for MOGAD, it has a low positive predictive value (72%), and hence MOG antibody testing is not advised in patients with atypical phenotypes because of the increased probability of a false positive result.[10,11]

Patients with MOGADs can have a monophasic course, while in some patient's relapses are seen. Relapses are commonly seen in young adults (<18 years of age) with higher MOG antibody titers and patients with ON. Relapses were uncommon in patients who presented with transverse myelitis. Our patient had frequent relapses, probable risk factors being young age and ON at presentation and persistence of MOG antibody.

First line therapy with steroids for acute attacks was associated with a more monophasic course of MOGAD than untreated patients. More than 50% of patients who presented with ON and were treated with IV methylprednisolone recovered. A decrease in the dose of steroid or discontinuation of steroids has been reported with worsening of the disease. Our patient had relapse when steroids were tapered. Studies have shown that persistent positivity of MOG antibodies is associated with relapsing disease course and increased disability.

Patients with acute presentation of MOGAD are treated with IV Methylprednisolone (20–30 mg/kg/day) for 3–5 days or IVIG (2 gm/kg) over 2–5 days. In case, there is no response to steroids, IVIG and plasmapheresis are considered.[12,13] Maintenance therapy/treatment for relapse includes acute treatment of relapse with methylprednisolone or IVIG and maintenance therapy with steroid sparing agents like azathioprine.[12] In cases of steroid toxicity, azathioprine, rituximab, and mycophenolate mofetil can be used.

Our patient had multiple relapses, with the presenting features being convulsions, behavioral issues, and decreased vision. The child had severe vision loss and behavioral issues on maintenance therapy. The child developed steroid toxicity in the form of weight gain, buffalo hump, and truncal obesity, he was started on azathioprine. On monthly IVIG, azathioprine there was no improvement in vision. Plasmapheresis was done in further relapses. Within a few months, child presented in the Emergency Department with status epilepticus, altered sensorium, signs of raised intracranial pressure. The child developed pancytopenia, associated with azathioprine. Patient required IPCU and was intubated for poor sensorium. A child succumbed to septic shock.

Risk of relapse is less with a monthly IVIG treated group. Therapeutic options for relapsing disease include azathioprine, mycophenolate mofetil, IVIG, rituximab, and tocilizumab. Azathioprine and mycophenolate mofetil are the most commonly used steroid sparing agents. Plasma exchange is administered every alternate day for 5–7 cycles. Plasma exchange leads to functional neurological recovery in patients with severe disability with acute attacks of inflammatory demyelinating disease.

Conclusion

Acute demyelinating encephalomyelitis is the most common presentation of MOGADs in Pediatric patients. Frequent relapses are common in patients who present with ON, young patients, and untreated patients. Myelin oligodendrocyte glycoprotein antibody is specific for MOGADs. It has a low positive predictive value it should not be used in patients who present with an atypical phenotype. Judicious use of alternative treatments with mycophenolate mofetil, azathioprine is necessary. Early treatment decreases the risk of future relapses.

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CASE REPORT

A Challenging Case of Neuropsychiatric Juvenile-onset Systemic Lupus Erythematosus: Case Report

Rajdeep Saha[1], Pamela Pattanayak[2], Kalpana Datta[3], Moumita Samanta[4]

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Abstract

The involvement of the nervous system in systemic lupus erythematosus (SLE) patients leads to a nonspecific and heterogeneous group of neuropsychiatric (NP) manifestations. No laboratory or radiological biomarker nor other formal system exists for setting up a diagnosis and guiding therapy decisions in neuropsychiatric SLE (NPSLE). In clinical practice, an individual multidisciplinary diagnostic and therapeutic approach based on the suspected cause and severity of symptoms is recommended. We are reporting a case of NP juvenile-onset systemic lupus erythematosus which presented like a case of meningoencephalitis with unilateral hemiplegia.

Keywords: Case report, Childhood stroke, Neuropsychiatric systemic lupus erythematosus, Vasculitis.

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-system inflammation, a fluctuating course, and a wide variety of clinical manifestations.[1] Involvement of the nervous system in SLE patients results in a diverse and nonspecific range of neuropsychiatric (NP) manifestations.[2] There are no specific laboratory or radiological biomarkers available to confirm its diagnosis, and a standardized universal protocol is lacking. In clinical practice, a tailored multidisciplinary approach to diagnosis and treatment, based on the suspected cause and severity of symptoms, is strongly advised.[3] Many studies on NPSLE have reported minor, nonspecific symptoms, such as mild depression or anxiety, which are often influenced by the investigator's assessment.[4]

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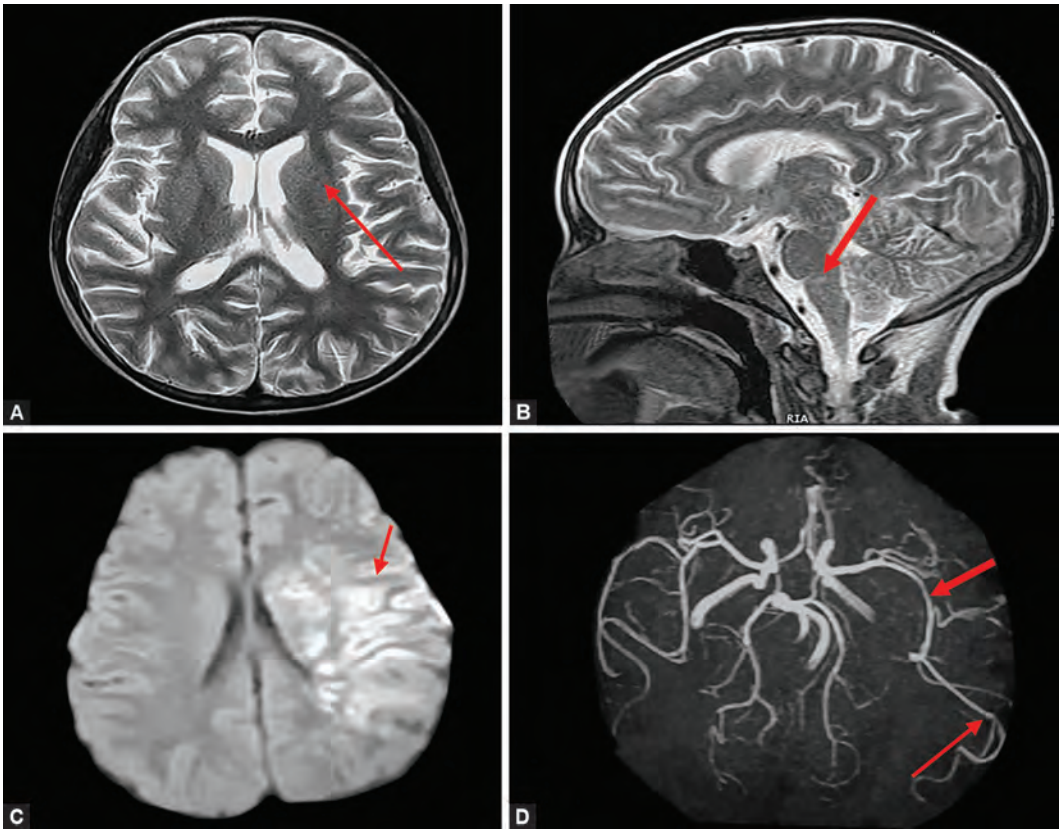
Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

Case Description

A 10-year-old girl presented with a history of non-remitting fever for the last 3 months, anxiety disorder and persistent headache for 1 month. She developed acute onset right-sided weakness involving both upper and lower limbs with drowsiness on the day before admission. At presentation, the child was irritable and confused, bilateral pupils were constricted and reactive to light but no papilledema on ophthalmological examination. Further thorough neurological examination revealed Glasgow coma scale (GCS) 11/15 [E2 V4 M5], the presence of neck rigidity, positive Kernig's sign, and Brudzinski's neck and leg sign. Right upper and lower limb showed increased tone and power of grade III/V, the presence of right ankle clonus, upgoing right plantar and exaggerated right-sided deep tendon reflexes.

Seven days following admission, the girl developed left-sided facial deviation and difficulty in deglutition. During the course of her hospital stay, she had painless multiple oral ulcers and complained of pain in bilateral knee and hip joints. Initial investigation revealed Hb 7.5 gm% (DCT negative), [PBS showing hypo-chromic anisocytosis, poikilocytosis], total leukocyte count (TLC) 7,230/cmm, platelet 3,03,000/cmm and corrected reticulocyte count was 1.16, raised ESR 62 mm in 1 hour but normal other parameters including coagulation profile, liver function test, serum urea, creatinine, and C-reactive protein (CRP). Non-contrast CT (NCCT) brain revealed no abnormality. Initially, after considering meningoencephalitis due to tubercular origin, we did a lumbar puncture, and a cerebrospinal fluid study showed 7 cells/cmm (mononuclear 43% and PMN 57%) with normal protein and sugar, no growth on culture and negative CSF CB-NAAT. There was microscopic hematuria [15–20/HPF] and nonreactive serology. As the girl developed new onset difficulty in deglutition and left-sided lower motor neuron type of facial nerve palsy, we performed magnetic resonance imaging (MRI) of the brain which showed widening of cortical sulci with prominent lateral ventricles (T2 weighted) hyper-intensities in basal ganglia region (Fig. 1A) and ischemic foci in the brainstem (Fig. 1B). Diffusion weighted imaging (DWI) shows infarction in the left middle cerebral artery (MCA) territory (Fig. 1C), and magnetic resonance angiography (MRA) shows mild narrowing in the left MCA (Fig. 1D). By that time, we got reports of vasculitis panel that showed positive anti-nuclear antibody (3+, homogenous, mixed pattern) in 1:640 dilution, positive anti-ds-DNA >800 IU/mL (1:10 dilution), decreased serum C3 (60 mg/dL), and C4 (8.8 mg/dL). Cardiolipin antibody (IgG) positive. Chest X-ray PA view showed pleural effusion. Two-dimensional echocardiography revealed mild



Figs 1A to D: (A) Magnetic resonance imaging of brain (T2 weighted) shows hyper intensities of left basal ganglia; (B) Ischemic foci in brainstem; (C) Diffusion weighted imaging showing area of acute infarct in the left MCA territory; (D) Magnetic resonance angiography showing narrowing in left MCA of brain

pericardial effusion. A renal biopsy was done and revealed class III immune complex-mediated glomerulonephritis.

With a diagnosis of SLE by SLICC criteria, pulse dose of IV methylprednisolone was continued for 5 days followed by a maintenance dose of oral prednisolone at 1 mg/kg/day for the next 4 weeks along with low-dose aspirin (5 mg/kg/day). Symptoms of bulbar palsy and facial deviation were completely resolved by the next 2 weeks. The patient has been discharged after getting 1st dose of cyclophosphamide with a plan of continuation for a monthly dose for the next 6 months along with oral hydroxychloroquine and prednisolone maintenance dose. After 3 months of follow-up, the girl is doing well without further neurological deterioration and aspirin is ongoing at a low dose as cardiolipin antibody titer (IgG) after 3 months is still high.

Discussion

Seven of the 19 NP disorders that the American College of Rheumatology (ACR) panel suggested in 1999 involve the peripheral nervous system, while the remaining 12 involve the central nervous system. Damage to the neurological system caused by SLE will be responsible for less than 40% of NP symptoms.

In the remaining cases, symptoms are often better explained by other causes, such as therapy-related effects or primary neuropsychiatric disorders. Due to the lack of a definitive diagnostic gold standard, NPSLE is typically diagnosed by exclusion and relies on expert consensus. It is essential to rule out alternative explanations, including infections, coincidental diseases, metabolic abnormalities, or adverse drug reactions. For SLE patients presenting with unexplained neuropsychiatric symptoms or signs indicative of NP involvement, the initial step is to evaluate and characterize these symptoms, following the same principles applied to patients without SLE.

While psychiatric exams ought to examine behavior, cognition, perception, thought processes, mood, and affect, neurological assessments should concentrate on headaches, seizure activity, alertness levels, and motor or sensory deficiencies. Formal neuropsychological testing should be conducted when cognitive impairment is suspected. The diagnostic approach for such patients should incorporate all relevant investigations typically performed for non-SLE individuals with similar symptoms.

In clinical settings, NPSLE diagnosis is individualized, using a combination of clinical, laboratory, electrophysiological, and neuroimaging findings based on the specific clinical presentation. Among circulating autoantibodies, antiphospholipid antibodies (aPL), including anticardiolipin (aCL), lupus anticoagulant (LAC), and beta-2 glycoprotein antibodies are particularly valuable for diagnosing NPSLE, especially in cases involving focal neuropsychiatric events like cerebrovascular disease and seizures. Additionally, anti-ribosomal P antibodies have been suggested to have a specific association with lupus psychosis. Though we have not done this in our case due to scarcity of its availability in our institution.

Magnetic resonance imaging is the preferred neuroimaging modality for NPSLE and remains widely utilized in clinical practice. It enables the localization of brain and spinal abnormalities,

facilitating the detection of lesions associated with NPSLE, such as infarcts or myelopathy, as well as differentiating conditions like tumors or infections. However, MRI findings are often nonspecific, with many patients showing no abnormalities or only nonspecific white matter hyper-intensities, irrespective of the type or severity of the NPSLE syndrome.

In cases of NPSLE, corticosteroids are frequently used when an inflammatory process is suspected, though this approach is primarily supported by clinical experience.[5] Despite the limited evidence base, the common practice for severe NPSLE involves administering 1 gm of intravenous methylprednisolone daily for three consecutive days, followed by oral prednisolone (initial dose of 1 mg/kg/day) with a tapering regimen over 3–12 months. For milder manifestations, the typical starting dose ranges from 0.5 to 1 mg/kg/day, with tapering protocols varying widely.

About 13 patients with lupus psychosis who had oral cyclophosphamide (1–2 mg/kg/day) and oral prednisone (1 mg/kg/day) for 6 months, with a gradual dose reduction and azathioprine (1–2 mg/kg/day) afterward, showed good results, according to Mok et al.[6] The combination of monthly intravenous cyclophosphamide (250–1000 mg/m^2) and glucocorticoids was found to offer therapeutic improvements in a retrospective trial that included 31 NPSLE patients.[7] Similarly, 25 NPSLE patients with central nervous system involvement who were all given weekly low-dose cyclophosphamide pulses (500 mg/m^2) were retrospectively reviewed by Ramos et al. With the exception of one patient, almost all patients experienced no serious side effects and demonstrated notable recovery after an average of 11 days.[8]

In another study by Stojanovich et al., outcomes of 60 NPSLE patients were compared between two groups: One treated with monthly low-dose intravenous cyclophosphamide (200–400 mg/m^2) alongside prednisone, and the other receiving prednisone alone. The findings revealed that patients in the cyclophosphamide group demonstrated greater clinical and electrophysiological improvements in cerebral function.[9]

Conclusion

Our findings emphasize the importance of early detection and timely intervention in NP-SLE to improve outcomes and prevent further progression of the disease. In clinical practice, a tailored, multidisciplinary diagnostic and therapeutic strategy is advised, taking into account the suspected cause and severity of symptoms. In conclusion, clinicians should maintain a high level of suspicion for neuropathy in pediatric SLE patients, even in the absence of other SLE manifestations. Treatment should be promptly initiated with steroids in combination with immunosuppressive agents. Uncommon manifestations of common diseases would be thought of first before rare diseases.

Ethical Clearance

Ethical clearance has been taken [Memo no- MC/KOL/IEC/NON-SPON/2022/05/2024] and patient's parents have given the consent for publication of her case.

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LETTER TO EDITOR

An Unusual Cause of Extreme Irritability in a Toddler

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Keywords: Anti-seizure medications, Epstein–Barr virus, Neuroblastoma, Opsoclonus myoclonus ataxia syndrome.
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Sir,

Irritability in childhood is a major concern for both pediatricians and parents. There are numerous causes for irritability in early childhood which include common conditions like infections in the ear and throat, foreign body partial impaction in the respiratory tract, constipation, and abdominal pain as seen in appendicitis or intussusception. Once these causes are ruled out, the next important etiology can be meningitis which is ruled out by examination and lumbar puncture. However, in the absence of an apparent cause for irritability, counseling of parents and further work-up becomes extremely difficult. Opsoclonus myoclonus ataxia syndrome (OMAS) is one of the causes of extreme irritability in young children. When a child with OMAS has myoclonus and opsoclonus along with irritability, diagnosis is very easy. However, frank clinical signs of opsoclonus, myoclonus and ataxia may take few days time to become apparent in a given case.[1] In early stage of the disease, irritability and agitation may be the only symptoms. Apart from neuroblastoma, a variety of infections can cause OMAS, including *Mycoplasma*, *Streptococcus*, Epstein–Barr virus, adenovirus, HIV, and dengue virus. Opsoclonus myoclonus ataxia syndrome responds well to immunotherapy and supportive anti-seizure medications.[2] Hence, early diagnosis and appropriate treatment can help in relieving distress to the parents and the child.

Here, we report a case of 14-month-old boy who presented with a history of excessive irritability for the last 8 days along with difficulty in walking unsupported noted since the last 8 days. The child was admitted to a local hospital and was evaluated for meningitis. CSF analysis was normal and CT brain was normal. In view of persistent irritability, the child was treated for viral meningitis. However, irritability did not subside and the child was added to multiple anti-seizure medications and sedatives without any relief. The child was referred to us for further management. Parents were very anxious. On examination, vitals were stable. BP was normal. Neurological examination revealed subtle ataxia while walking with left-hand myoclonus intermittently. Sensorium was normal. The child was provisionally diagnosed with OMAS forme fruste (Mitchell Pike score 4/18). Electroencephalography and magnetic resonance imaging of the brain were normal. Neuroblastoma was ruled out by performing contrast computed tomography of the chest, abdomen, and pelvis. The child was managed with a pulse dose of steroids (inj. Methylprednisolone) and immunotherapy in the form of rituximab. The child was noted to have a significant reduction in irritability in 3 days and the gait improved. The child was discharged after a week and follow-up after 3 months showed that the child was normal.

To conclude, OMA forme fruste should always be considered in the differentials of extreme irritability in a toddler and should be worked up for the same. Other signs of OMAS like myoclonus, opsoclonus, and ataxia can be subtle and may appear after a few days. Early treatment with immunomodulation is helpful in the control of symptoms. Careful work-up and annual screening for underlying neuroblastoma for at least 3 years is necessary in these cases.[2]

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