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Case Report

Paediatrics Section

Idiopathic Intracranial Hypertension Secondary to Methotrexate in a Young Child with Juvenile Idiopathic Arthritis: A Rare Case Report

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ABSTRACT

Idiopathic Intracranial Hypertension (IIH) is characterised by the signs and symptoms of increased intracranial pressure, but where a causative mass or hydrocephalus is not identified. It is also known as pseudotumor cerebri, a rare neurological disorder in children, which, if not treated properly, may lead to severe visual dysfunction. A 6-year-old male child presented with a 2-month history of progressively increasing joint pain and intermittent low-grade fever. After comprehensive evaluation and ruling out infectious, malignant, and systemic autoimmune disorders, the diagnosis of Juvenile Idiopathic Arthritis (JIA) was established and the Disease-Modifying Anti-Rheumatic Drug (DMARDs) for management drug Methotrexate was initiated. On follow-up, the child was diagnosed to have IIH for which, after detailed investigation, no cause was found and then it was ascribed to be caused by methotrexate and hence the drug was withheld. He was started on Acetazolamide subsequent to which there was resolution of symptoms. Clinicians should be aware of a potential, although rare, side effect of DMARDs like methotrexate and advise caregivers of children with chronic disorders like JIA to be on regular follow-up for early recognition of serious side effects, which would thereby halt any potential fatal or life-altering condition.

Keywords: Intracranial pressure, Joint pain, Optic nerve, Papilloedema, Pseudotumour cerebri

CASE REPORT

A 6-year-old male child presented to the paediatric outpatient department with chief complaints of joint pain and fever for 2 months. The fever was low grade, continuous, and not associated with chills and rigor. The joint pain, which involved both knee joints, had been progressively increasing, gradually limiting his daily activities. He was developmentally normal, first in birth order, born out of a non-consanguineous marriage. There was no prior history of blood transfusions, bleeding from any site, rash over the body, nasal discharge, ear discharge, neck swelling, drug intake, swelling over the body or any swelling, haematuria, loose stools, tingling or numbness, facial deviation, neck stiffness, abnormal body movements, hyper/hypopigmentation, or difficulty breathing. He had no prior history of hospital admissions and no family history of arthritis or any rheumatological disorder.

On examination, pulse rate was 78/min, regular and good volume with No radio-radial or radio-femoral delay, respiratory rate was 22/min, saturation on room air was 99%, and blood pressure was 90/62 mmHg (less than 90th percentile for age). There was no pallor, icterus, clubbing, cyanosis and lymphadenopathy or oedema. Body mass index for the child was 10.5 kg/m^2. Central nervous system examination revealed no sensory or motor system involvement and no involvement of cranial nerves, no cerebellar involvement and the gait was normal. Locomotor system examination revealed a local rise of temperature over the bilateral knee joint with decreased range of motion in both flexion and extension and reduced range of motion over the bilateral wrist joint. There was no organomegaly on abdominal examination. The cardiovascular, respiratory systems suggested no abnormality.

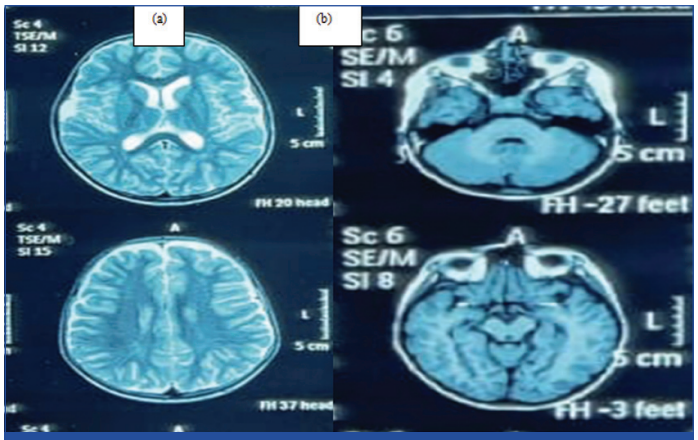
Laboratory investigation [Table/Fig-1] revealed, counts were normal, liver function and renal function tests were within normal range, Erythrocyte Sedimentation Rate (ESR) was raised, C-Reactive Protein (CRP) was positive, and Anti-Nuclear Antibody (ANA) and Anti-streptolysin O (ASO) were negative. Urine analysis was normal and had no bacterial growth. The tuberculin test was negative after 48 and 72 hours. Workup for tropical infections like Brucella, scrub typhus, and Leptospira was negative. Blood cultures were sterile. Fundus examination was normal. Prothrombin and partial thromboplastin time were also within normal limits. Bone marrow examination was normal. After ruling out possible infectious causes, malignancies, and systemic autoimmune diseases, the patient was diagnosed with oligoarticular Juvenile Idiopathic Arthritis (JIA) based on the International League of Associations for Rheumatology (ILAR) classification criteria [1]. He was started on weekly injection methotrexate (15 mg/m^2 once a week, subcutaneously) and was discharged on haemodynamically stable conditions.

Laboratory parameter	Value	Normal range
Hb (g/dL)	9	13-15
WBC (cells/cumm)	8800	5000-14500
DLC (P/L/M/B)	32/61/6/1	51/42/5/3
Platelets (lacs/cumm)	5	1.5-4.5
AST/ALT (U/L)	21/16	40/40
Albumin (gm/dL)	3.3	3.5-5.5
ALP (U/L)	239	<400
Serum creatinine (mg/dL)	0.5	0.7-1.3
Blood urea (mg/dL)	20	10-50
Uric acid (mg/dL)	3.3	3-7
INR	1.2	<1.5
ESR (mm)	54	<20
Na/K (mEq/L)	142/3.8	135-145/3.5-5.5
Ca/P (mg/dL)	8.8/4.5	8.3-10.5/
CRP	Positive	N/A
Hepatitis B antigen	Non-reactive	Non-reactive
Anti hepatitis C IgG	Non-reactive	Non-reactive
HIV	Non-reactive	Non-reactive

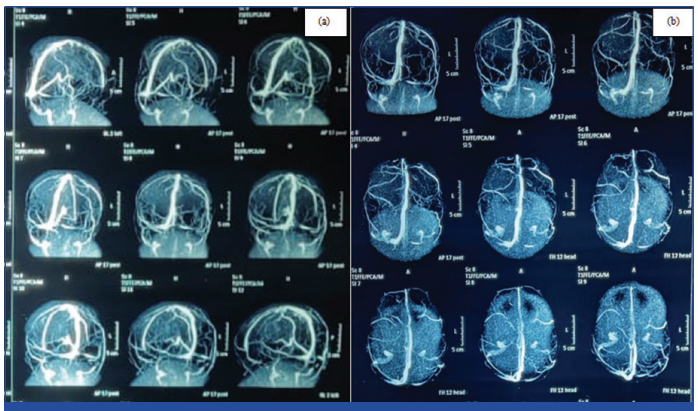
ANA	Negative	N/A
ASO	Negative	<200 TODD Units
Ferritin	72	7-142

[Table/Fig-1]: The following Investigations were performed.
Hb: Haemoglobin; WBC: White blood cell; DLC: Differential leukocyte count; AST: Aspartate transaminase; ALT: Alkaline transaminase; INR: International Normalised Ratio; ESR: Erythrocyte sedimentation rate CRP: C-reactive protein; HIV: Human immunodeficiency virus; ANA: Anti-nuclear antibody; ASO: Anti-streptolysin O

Four months later, the child started developing a headache, blurring of vision and repeated episodes of vomiting, with palsy of the left abducens, following which repeated fundus examination suggested bilateral grade 4 papilloedema. The child was admitted, injection methotrexate was withheld and the child was started on carbonic anhydrase inhibitor, acetazolamide at 50 mg/kg/day. Magnetic resonance imaging brain [Table/Fig-2a,b] was done, which had features suggestive of raised intracranial pressure, showed mild optic nerve tortuosity, and posterior globe flattening, while Magnetic Resonance Venography (MRV) [Table/Fig-3a,b] was normal. Lumbar puncture was performed, which revealed an opening pressure of 60 mmHg. The child was diagnosed with Idiopathic Intracranial Hypertension (IIH). Injection methotrexate was withheld and the child was started on carbonic anhydrase inhibitor, acetazolamide at 50 mg/kg/day. The child was discharged on haemodynamically stable conditions. Four weeks later, he had resolution of symptoms and acetazolamide was continued for a total of 10 weeks and eventually stopped. On follow-up, he had no recurrence of symptoms.



[Table/Fig-2a,b]: MRI brain: raised intracranial pressure, showed mild optic nerve tortuosity and posterior globe flattening.



[Table/Fig-3a,b]: Magnetic Resonance Venography: Normal.

DISCUSSION

Idiopathic Intracranial Hypertension (IIH) is a condition characterised by signs and symptoms of raised intracranial pressure, requiring early intervention to prevent any neurological sequelae [2].

It is a rare condition, predominantly affecting obese reproductive-aged females, with an even smaller percentage occurring in children with IIH, affecting 1 in 100,000-150,000 children [3]. It commonly presents with headache, transient visual obscurations, or pulsatile tinnitus, and the most frequent signs on examination are papilloedema, visual field defects, or abducens palsy. It is associated with many systemic illnesses such as Addison's disease, hypoparathyroidism, and anaemia, as well as, common medications like steroids, vitamin A overuse, and tetracyclines, strong correlation with a positive family history [4].

Methotrexate is an antimetabolite that can be given intravenously, orally, and intrathecally for various malignant, rheumatological or autoimmune conditions [5]. However, methotrexate is not commonly known to cause raised intracranial pressure. IIH may be primary or occur secondary to certain conditions. Upon reviewing the literature, the association between IIH with uveitis has been reported in only four children so far [6-8].

In the paediatric population, there is a paucity of evidence to suggest that methotrexate causes IIH. Zhang Y et al., reported a case of a 7-month-old girl with Acute Lymphoblastic Leukaemia (ALL) who presented with a bulging anterior fontanelle after completing the first and second courses of High-Dose Methotrexate (HD-MTX) chemotherapy, which turned out to be IIH [9]. She was administered infusions of dexamethasone, which prevented recurrence of neurological side effects observed after the first and second courses of HD-MTX. The prophylactic use of dexamethasone prevented acute intracranial hypertension following HD-MTX infusion [9]. According to the World Health Organisation-Uppasala Monitoring Centre (WHO-UMC) Casuality scale, a 'probable' association between the drug and the adverse event was assigned [10]. To the best of our knowledge, ours is the second paediatric case in literature to suggest methotrexate as a cause of IIH.

Juvenile Idiopathic Arthritis (JIA) has been reported to lead to uveitis with incidences ranging from 8.3% to 25% [11]. However, the incidence of the process leading to raised intracranial pressure has rarely been reported. In the present case, the child experienced symptoms of raised intracranial tension a few weeks after initiation of methotrexate, which, after a thorough workup to rule out other systemic conditions, was found to be the offending agent. Since methotrexate is the most commonly used drug for JIA, clinicians should be aware of a potential, although rare, side effect of DMARDs like methotrexate and advise caregivers of children with chronic disorders like JIA to be on regular follow-up for early recognition of serious side effects.

CONCLUSION

Clinicians should be aware of a potential, although rare, side effect of DMARDs like methotrexate and advise caregivers of children with chronic disorders like JIA to be on regular follow-up for early recognition of serious side effects, which would thereby halt any potential fatal or life-altering condition.

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