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Research Article

A Rare Case of Plus Minus Syndrome

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Abstract

Plus-minus syndrome is a rare neurological disorder marked by asymmetric eyelid dysfunction, typically linked to midbrain lesions. We present a case of a 32-year-old male who developed right-sided partial ptosis and left eyelid retraction following a febrile illness. Apart from these ocular findings, his neurological examination was unremarkable. Extensive investigations, including MRI brain, CE MRI brain, MRA, cerebrospinal fluid analysis, and nerve conduction studies, revealed no abnormalities. Given the recent infection and absence of structural lesions, a post-infectious demyelinating process was suspected. The patient was treated with a brief course of oral steroids, resulting in complete symptom resolution within four days. This case highlights a unique presentation of plus-minus syndrome without radiological evidence of midbrain involvement, suggesting an inflammatory or immune-mediated mechanism. It underscores the importance of considering non-structural causes in similar cases and supports the potential benefit of early corticosteroid therapy.

Keywords

Plus-minus Syndrome, Unilateral Ptosis, Ocular Myasthenia, Ocular Myositis

1. Background

Plus-minus syndrome is a rare neuro-ophthalmological disorder characterized by unilateral ptosis on one side and contralateral eyelid retraction. This occurs due to disruptions in the oculomotor nerve pathways and the nucleus of the posterior commissure, leading to an imbalance in levator palpebrae superioris muscle function. Initially described by Cahill and Biousse in 2008, this syndrome has been linked to midbrain pathology, particularly involving ischemic strokes, hemorrhages, tumors, inflammation, infections, and trauma [1].

2. Pathophysiology and Clinical Presentation

The oculomotor fascicle, which runs through the midbrain, is highly susceptible to damage from ischemia or compression. Lesions affecting this area impair levator muscle function on one side, leading to ptosis, while simultaneously removing inhibitory control over the opposite eyelid, causing contralateral lid retraction [2, 3]. This mechanism results in plus-minus lid syndrome, a variant of Collier's sign, which is typically associated with dorsal midbrain lesions. If the lesion extends further to the oculomotor nerve fascicle, the asymmetrical lid involvement becomes apparent [4, 5].

Several conditions have been associated with this syn-

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drome, including:

1) Midbrain infarcts and hemorrhages, particularly those affecting the paramedian midbrain.
2) Demyelinating disorders, such as multiple sclerosis, which may selectively involve the midbrain.
3) Ocular myasthenia gravis, which can cause fluctuating lid abnormalities mimicking this syndrome.
4) Ocular myositis and thyroid-related eye disease, both of which can impact eyelid function.
5) Paraneoplastic syndromes and inflammatory conditions affecting the brainstem.

A condition similar to plus-minus lid syndrome, referred to as pseudo plus-minus syndrome, presents with a comparable clinical picture but lacks any structural lesion on imaging. In such cases, neuromuscular disorders (such as ocular myasthenia gravis) or endocrine abnormalities (such as thyroid-associated orbitopathy) are potential culprits. One distinguishing feature of pseudo plus-minus syndrome is the positive curtain sign, where manually lifting the ptotic eyelid results in an improvement of the contralateral retraction, indicating a neuromuscular rather than a neurological cause [6].

3. Significance of This Case

What makes this case unique is the absence of an identifiable midbrain lesion on neuroimaging, despite the characteristic presentation of unilateral ptosis and contralateral eyelid retraction. Given the patient's recent febrile illness, a post-infectious immune-mediated mechanism was suspected. While demyelinating conditions like multiple sclerosis or neuromyelitis optica can involve the brainstem, the lack of imaging evidence suggests a clinico-radiological dissociation, where subtle inflammatory changes may not yet be detectable [7].

Similar cases have been observed in post-viral encephalomyelitis, where transient immune-mediated inflammatory responses in the central nervous system cause neurological deficits without overt radiological findings. The patient's rapid recovery following corticosteroid therapy supports the hypothesis of post-infectious immune involvement in plus-minus syndrome, an association that has not been extensively documented in existing literature.

This case expands the current understanding of plus-minus lid syndrome, emphasizing the importance of considering post-infectious immune-mediated mechanisms, particularly in patients with recent febrile illness. It also highlights the potential benefit of early corticosteroid therapy, even in cases where radiographic confirmation of a central lesion is lacking.

4. Case Report

A 32-year-old male with no known medical history presented with a sudden onset of partial drooping of the right upper eyelid (ptosis) and retraction of the left eyelid, persisting for one day. He did not report any associated headache, vomiting, diplopia, or other cranial nerve symptoms. Additionally, there were no complaints of limb weakness, sensory disturbances, or gait abnormalities. His medical history was largely unremarkable except for a febrile illness one week prior, characterized by high-grade fever lasting two days, which had resolved with the use of antipyretics.

On neurological examination, the patient exhibited partial right-sided ptosis and left-sided eyelid retraction, raising suspicion of an oculomotor dysfunction. Pupillary responses were symmetrical and reactive to light, and extraocular movements were full and unrestricted. Fundoscopic examination was unremarkable, with no signs of optic disc edema or retinal abnormalities. There was no involvement of other cranial nerves, and motor and sensory assessments of all four limbs were normal. Deep tendon reflexes were preserved, and plantar reflexes were flexor bilaterally. There were no signs of meningeal irritation, such as neck stiffness or Kernig's and Brudzinski's signs.

Further evaluation revealed a negative curtain sign, ruling out myasthenia gravis. The patient showed no fatigability, diurnal variation of symptoms, or worsening with prolonged use. His gait was normal, and he did not exhibit any cerebellar signs, such as dysmetria or intention tremor.

Figure 1. *Before treatment – right eye partial ptosis and left eye retraction.*

Figure 2. *After treatment – complete resolution of ptosis and restoration of palpebral symmetry.*

5. Investigations

A comprehensive set of laboratory tests was conducted to identify potential metabolic, infectious, or autoimmune caus-

es. His haematological and biochemical parameters were within normal limits, and thyroid function tests were unremarkable, ruling out thyroid-associated orbitopathy.

To assess possible structural brainstem involvement, an MRI of the brain with post contrast administration and MRA was performed. The imaging showed no evidence of ischemia, haemorrhage, demyelination, or mass lesions in the midbrain or brainstem. Cervical vascular imaging did not reveal any signs of arterial dissection.

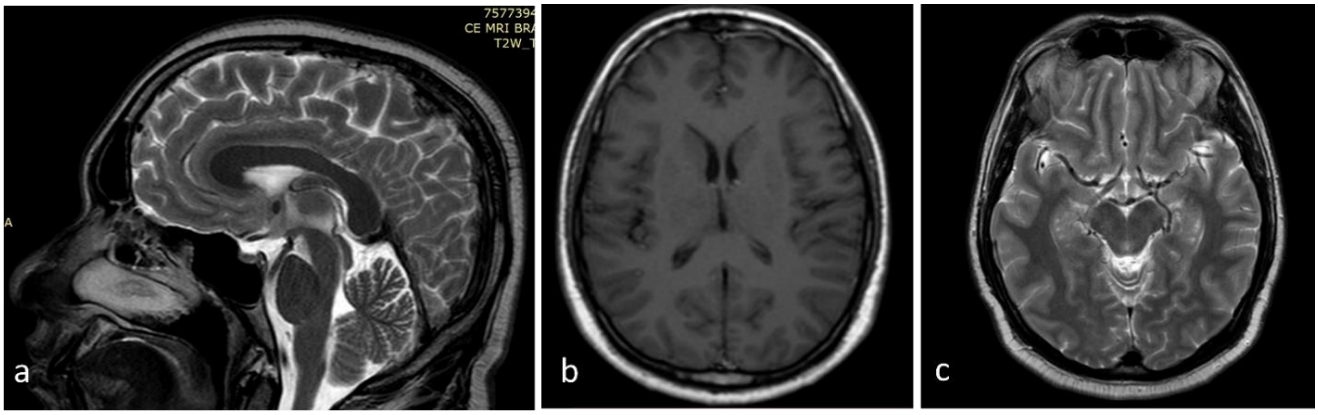

Figure 3. *T2 sagittal (a), T2 axial (b), and T1 axial (c) sections of brain with normal morphology.*

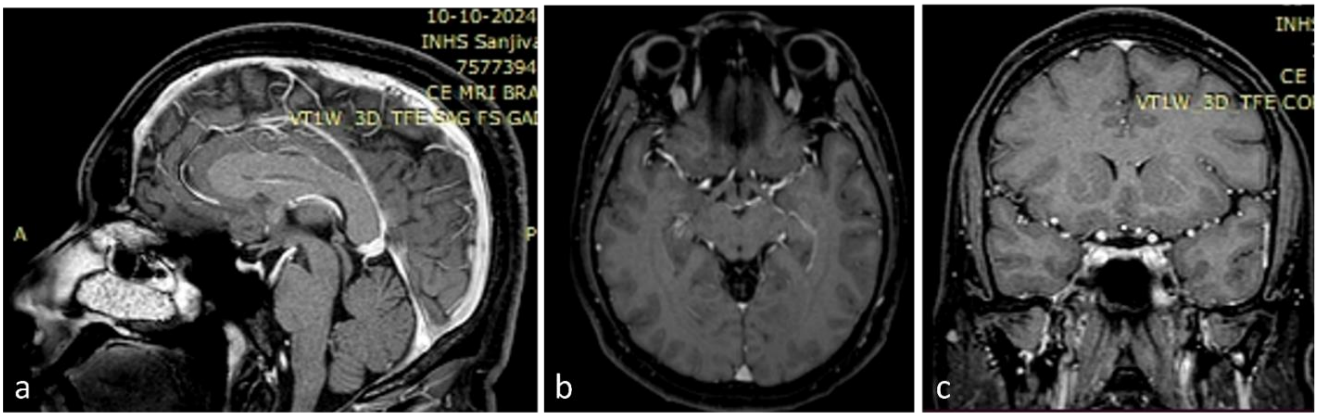

Figure 4. *T1FS post contrast sagittal (a), axial (b), and coronal (c) section with normal enhancement pattern and vascular anatomy.*

Table 1. *CSF analysis report.*

CSF Analysis			
Cytology		**Biochemistry**	
Appearance	Clear	Glucose	70mg/dl
Total Cells	01/cumm	CSF protein	40mg/dl
WBC	01/cumm	LDH	-
RBC	Nil		
Predominant	Lymphocyte		
Impression – Lymphocyte predominant moderately cellular CSF smear – Normal study			

Considering an autoimmune or neuromuscular aetiology, cerebrospinal fluid (CSF) analysis was performed, which was normal (Table 1), with no indications of infection, inflammation, or demyelination. Atropine neostigmine testing and repetitive nerve stimulation (RNS) studies were conducted to evaluate for ocular myasthenia gravis, both of which were negative. Given the atypical presentation and absence of an identifiable midbrain lesion, an ophthalmology consultation was sought to exclude local mechanical causes of ptosis, such as levator aponeurosis dehiscence or orbital pathology. No local abnormalities were detected.

6. Diagnosis and Management

With the clinical presentation of unilateral ptosis with contralateral eyelid retraction, coupled with the absence of structural pathology on imaging, a diagnosis of plus-minus lid

syndrome was considered. Given the history of a preceding febrile illness, an immune-mediated post-infectious demyelination was suspected as the underlying cause.

The patient was started on an empirical course of oral corticosteroids (prednisolone 60 mg daily for five days) to reduce potential inflammatory or autoimmune-mediated dysfunction. He exhibited significant clinical improvement within four days, with complete resolution of ptosis and eyelid retraction.

After one week of hospital observation, he was discharged with advice for regular follow-up to monitor for any recurrence or delayed neurological sequelae. The rapid response to short-term corticosteroid therapy further supported the likelihood of post-infectious inflammatory involvement in the pathogenesis of plus-minus syndrome.

7. Discussion

Plus-minus lid syndrome is a rare, acquired neurological disorder characterized by the simultaneous presence of unilateral ptosis and contralateral eyelid retraction. This distinctive ocular presentation has been linked to dysfunction in the midbrain, specifically involving the nucleus of the posterior commissure, which plays a crucial role in eyelid movement regulation. Lesions affecting this region can lead to bilateral supranuclear lid retraction, commonly referred to as Collier's sign. However, if the lesion extends to involve the oculomotor fascicle, the lid retraction on one side may be masked by ptosis due to concurrent oculomotor nerve palsy, resulting in the characteristic plus-minus appearance [8-10].

Neuroimaging in previously documented cases often reveals unilateral midbrain involvement, particularly affecting the posterior commissure with ventral extension to the oculomotor fascicle on the ptotic side. The underlying causes of plus-minus syndrome are diverse and may include vascular insults such as ischemic or hemorrhagic stroke, demyelinating diseases like multiple sclerosis, infections, trauma, or compressive brainstem lesions [11].

Accurate diagnosis is essential, given the clinical overlap with ocular myasthenia gravis, thyroid eye disease, dorsal midbrain syndrome, and facial nerve palsy with unopposed action of the levator palpebrae superioris. A related condition, pseudo plus-minus syndrome, presents with similar clinical features but is distinguished by a positive curtain sign and the absence of radiological abnormalities [12]. Differential diagnoses commonly considered in such cases include thyroid eye disease and ocular myasthenia gravis [13].

In our patient, MRI brain with contrast administration and MR angiography did not reveal any structural midbrain pathology, yet the clinical features strongly suggested plus-minus syndrome. Importantly, the curtain sign was negative, and no laboratory markers supported a diagnosis of thyroid eye disease or ocular myasthenia gravis. Given the acute onset of ptosis, an underlying vascular event was initially considered; however, imaging findings ruled out ischemic or hemorrhagic stroke.

Since the patient had experienced a febrile illness one week prior to the onset of symptoms, a post-infectious demyelinating process was hypothesized as a potential cause. Although no T2/FLAIR hyperintensities were detected on MRI, it is well recognized that early-stage demyelinating lesions can sometimes be radiologically occult, leading to clinico-radiological dissociation [14]. This phenomenon has been described in various post-infectious immune-mediated neurological conditions, where inflammatory changes may precede the appearance of structural abnormalities on imaging.

Considering the possibility of an immune-mediated inflammatory response, a short course of oral corticosteroids (prednisolone 60 mg for five days) was initiated, resulting in rapid and complete resolution of symptoms within four days. The favourable clinical response further supports the likelihood of post-infectious demyelination as the underlying aetiology. Steroids were discontinued after five days, and the patient was discharged with instructions for regular follow-up to monitor for recurrence or additional neurological deficits.

8. Conclusion

Plus-minus syndrome remains a rare and underreported neurological entity, typically associated with midbrain structural pathology. However, this case highlights the possibility of an immune-mediated mechanism, particularly in the context of a preceding febrile illness with clinico-radiological dissociation. To our knowledge, there are no previous reports of plus-minus syndrome following a febrile episode in the absence of identifiable midbrain lesions on MRI, making this case a unique contribution to the existing literature.

Given the excellent response to corticosteroid therapy, it is essential to consider post-infectious inflammatory or demyelinating processes as potential differential diagnoses in patients presenting with plus-minus syndrome, particularly when conventional imaging fails to detect an underlying structural lesion. Further research is warranted to explore the full spectrum of aetiologies underlying plus-minus syndrome, including its potential association with post-infectious autoimmune responses [14].

Plus-minus syndrome is an ocular syndrome characterized by unilateral ptosis and contralateral lid retraction. This patient had features of plus minus syndrome following a febrile episode with a clinico-radiological dissociation.

Abbreviations

MRI	Magnetic Resonance Imaging
CE MRI	Contrast Enhanced Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
T1FS	T1 Weighted fat-saturated
CSF	Cerebrovascular Fluid

RNS	Repetitive Nerve Stimulation
WBC	White Blood Cells
RBC	Red Blood Cells

Consent for Publication

An informed consent for publication purpose was obtained from the patient.

Author Contributions

Bharat Rajkumar: Played a primary role in the treatment and management of the patient, retrieved informed consent, and contributed to the preparation of the case report.

Ajay Nathan: Assisted in data collection, manuscript preparation, ensuring communication and verification of data.

Abish Mohan: Assisted in data collection and contributed to the verification of the final manuscript.

Cherukara Nihil: Assisted in the manuscript preparation, served as the corresponding author, compilation of references, and formatting.

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Data Availability Statement

The datasets used are/or analyzed during the current study are available with the author.

Conflicts of Interest

The authors declare no conflicts of interest.

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