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Trauma-Induced Double-Seronegative Ocular Myasthenia Gravis: A Case Report

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Abstract

We present here a 12-year-old child who presented with complaints of blurring of vision and drooping of the left upper eyelid for the past 4 years, which started 1 month after he encountered blunt trauma to the left-sided orbital region. History, examination and pharmacological (neostigmine test) tests were suggestive of ocular myasthenia gravis, however anti-acetylcholine receptor antibodies and anti-musk antibodies were negative. Repetitive nerve stimulation tests and electromyography were also unremarkable. The patient was labelled as a case of trauma-induced double-Seronegative Ocular Myasthenia Gravis and was started on oral Pyridostigmine. The patient reported a drastic improvement in both diplopia and ptosis that he initially presented with. Ocular Myasthenia Gravis can be a diagnostic challenge as its initial presentation can vary to a great degree. Thorough history and examination remain of prime importance which can provide adequate clues to lead us to the diagnosis of ocular myasthenia gravis. Trauma should also be recognized as a triggering factor for myasthenia gravis and more attention needs to be given to understand the pathophysiology of this interesting association.

Keywords: Double-Seronegative Ocular Myasthenia Gravis, Trauma, Auto-Immune Disease, ptosis, diplopia

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1. Introduction

The idea of the fact that our body has a defence system to combat foreign antigens has been long known to humanity; but It wasn't until 1904 when Paul Ehrlich first coined the term *"Horror Autotoxius"*, laying the pioneering concept of a condition in which the immune system acted against one's own body: An Autoimmune disease.[1,2] The idea was not received well by the scientific community, but in the 1950s, Ernst Witebsky and Noel Rose proved the existence of antithyroid antibodies in rabbits. The establishment and escalation of autoimmune disease research followed the discovery of autoimmune thyroiditis.[2] Since then, about 100 autoimmune diseases have been identified. Amongst these, Myasthenia gravis is perhaps the best-understood and most-studied autoimmune disease.[3]

Myasthenia Gravis is a chronic autoimmune disease in which autoantibodies are directed against acetylcholine receptors(or the proteins that are functionally related to acetylcholine receptors), present in the postsynaptic membrane of the neuromuscular junction. [4,5] The motor end plate becomes less responsive than normal, which causes the striated muscle to become rapidly fatigued.[6]

Around 80% of Myasthenia Gravis cases have acetylcholine receptor antibodies (AChR-abs) and nearly all other cases, referred to as 'Seronegative MG', have either antibody to muscle-specific kinase (MuSK) or AChR-abs of low affinity that cannot be detected in solution using the conventional radioimmunoassay.[5] Myasthenia Gravis is typically divided into 5 major types, namely Congenital, Generalized, Ocular, Juvenile and Transient Neonatal. Among these, Ocular myasthenia gravis (OMG) is one of the more well-known forms of myasthenia gravis. It is almost entirely characterized by ocular symptoms such as ptosis and diplopia and can progress to generalized myasthenia gravis (GMG) in about 20–60% of cases.[4,7]

Myasthenia Gravis can be triggered by various factors, including drugs [8], wasp stings[9], neuroborreliosis [10] and HIV infection [11]. It can also develop following trauma such as a minor head injury and has also been reported to develop after cardiac surgery. The time from the instigating event to the onset of symptoms of MG varies from as early as minutes up to days and weeks. [5]

We report a rare case of Double Seronegative Ocular Myasthenia Gravis in a 12-year-old child who developed features of ocular myasthenia gravis 1 month after he had minor trauma to the head. The fact that the patient was negative for both AChR-abs and anti-MuSK antibodies (hence Double Seronegative), along with a history of prior trauma, creates a thought-provoking scenario of a relatively unusual presentation of Ocular Myasthenia Gravis.

2. Case Presentation

Patient Zakariya, 12 years 12-year-old school-going child presented with complaints of doubling of vision for the past 4 years and drooping of the left upper eyelid for the past 3.5 years. Doubling of vision was binocular, variable throughout the day as it worsened by the night and was worst on the primary gaze and elevation. Drooping was unilateral (left-sided) and variable (worse as the day progressed). The Patient also reported immediate improvement in the drooping of the lid when he woke up from sleep. There was also an associated history of blunt trauma to the left-sided orbital region during a scuffle, 1 month before the appearance of these signs and symptoms. There was no reported localized bleeding, loss of consciousness, ENT bleeding, or history of seizures after the trauma. There was no associated history of dysarthria, dysphagia, generalized muscle weakness, or difficulty in breathing. A General physical examination revealed a young child conscious and oriented in time, place and person with no obvious dysmorphic features or facial drooping. There was a slight upward head tilt which was intermittent. There was no nasal tone/hoarseness of voice, and neither was there any evidence of proximal muscle weakness. Ocular examination revealed a shortened palpebral fissure of the left eye. Extraocular movements showed restricted elevation in all gazes with reduced vertical saccadic velocity in the left eye. There was primary gaze left hypotropia (15 Degrees at the pupillary margin) on Hirschberg's Test. Ptosis examination of the left eye depicted the following results: Marginal Reflex Distance: -1mm, Palpebral Fissure Height: 5mm, Levator Function Test: 11mm. Bell's phenomenon was normal, while Fatigability, Cogan Lid Twitch Sign, and Sleep Tests were positive. Ice pack tests and Neostigmine tests were conducted, which were also positive. Forced Duction Test and Force Generation Test were negative. His CBC, PT/APTT/, Serum Electrolytes, LFTs, RFTs, ESR, TFTs, anti-acetylcholine receptor antibodies, and anti-MuSk antibodies were also negative. Repetitive Nerve Stimulation Test (RNS) was unremarkable and revealed no electrophysiological evidence of peripheral neuromuscular disorder. CT Scan Brain and MRI Brain were unremarkable. CT Chest with contrast revealed borderline enlarged thymus. Consultation was arranged with a pediatrician and a neurophysician was arranged to rule out generalized myasthenia gravis. Based on history, examination and investigations, a diagnosis of Post Traumatic Double Seronegative Ocular Myasthenia Gravis was established and the patient was started on Oral Pyridostigmine 7mg/kg/day, which resulted in drastic improvement of ptosis and diplopia. A monthly follow-up of the patient is planned.

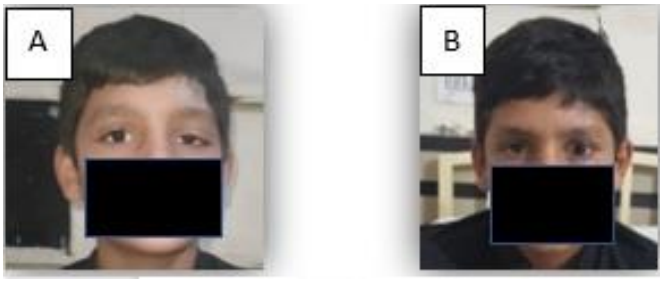

Figure 1: A) Pre Ice-Pack Test B) Immediately Post Ice-Pack Test (All pictures were taken with parent's consent and permission of the child)

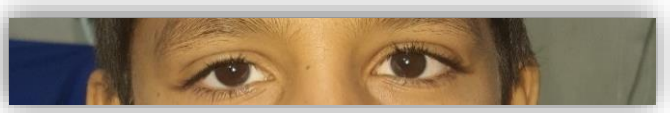

Figure 2: A) Pre Neostigmine Test B) 15min Post Neostigmine Test. Drastic imorovement in ptosis can be seen

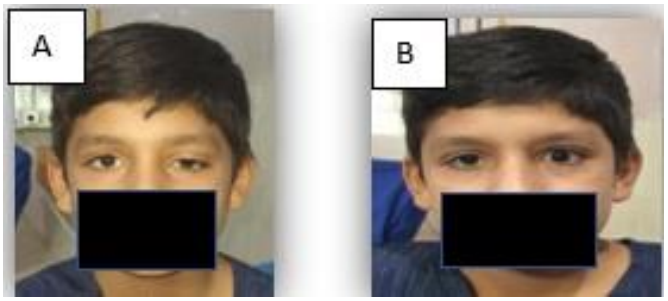

Figure 3: Close-up view Post-Neostigmine test. Corrected ptosis and hypotropia (Central Hirschberg's Reflex) can be seen

3. Discussion

Owing to the extremely diverse presentation of the disease, Myasthenia Gravis is known as "The Great Masquerader". [12] This report's main goal is to draw attention to the frequent delay in MG diagnosis, especially when it happens in circumstances like the one our patient encountered and renders the diagnosis of this serious, yet treatable condition difficult.

In up to 80% of cases of Generalized Myasthenia Gravis, autoantibodies against the nicotinic acetylcholine receptor (AChR) can be found, but this percentage

reduces to only 50% in patients with Ocular Myasthenia Gravis. No antibodies against AChR and MuSK are found in approximately 15% of patients with Generalized Myasthenia Gravis and up to 50% of patients with ocular forms of the disease. Such cases are classified as double-seronegative MG cases (SMG). [13]

Two possibilities have been speculated in patients who are double seronegative, but have all the characteristic clinical features of generalized/ocular myasthenia gravis: 1) The Presence of low-affinity antibodies that could induce disease but were undetectable by the conventional radioimmunoassay 2) Possibility that antibodies may be targeted toward other antigens/membrane proteins present in the motor end-plate and produce a similar clinical and neuromuscular disorder. [14]

LRP4 (low-density lipoprotein receptor-related protein 4) is a membrane protein that acts as an agrin receptor in the neuromuscular junction. The binding of agrin to LRP4 causes MuSK to be activated, leading to the phosphorylation of cortactin, which promotes AChR clustering. This AchR clustering increases receptor availability to synaptic acetylcholine, allowing for greater muscle excitability. Antibodies directed against LPR4 are primarily of the IgG1 subclass, which can impair Agrin-LRP4 signalling, eventually leading to decreased Acetylcholine receptor availability and neuromuscular transmission.[4]

In A retrospective cross-sectional study conducted in Barcelona, Spain, 38 out of 250 patients of Myasthenia Gravis were found to be double-seronegative. Cortactin antibodies were identified in 28 patients with MG: 9 of 38 (23.7%) who had dSNMG, 19 of 201 (9.5%) who had MG with AChR antibodies (significantly lower than those with dSNMG: 9.5% vs 23.7%; P = .02).[14] Other antibodies that have been identified to cause a similar pathology include anti-agrin, anti-collagen Q and anti-voltage gated Potassium Channel antibodies. The pathogenic mechanisms of these autoantibodies, however, have not yet been thoroughly understood.[4]

Multiple trigger factors have been reported in the literature that have instigated Myasthenia Gravis; with trauma, though relatively rare, being one of them. The mechanism by which trauma leads to MG is not very well understood, but some theories have been proposed as possible explanations. Acetylcholine receptor antibodies are generally considered pathogenic for Myasthenia Gravis, however, there seems to be a safety threshold before the neuromuscular control is overridden. This barrier might be crossed if certain events, such as trauma, cause a higher autoimmune response and raise the levels of AChR antibodies. The theory is that tissue microtrauma causes an abrupt rise in muscle permeability, which increases receptor exposure to antibodies and impairs neuromuscular transmission. [5]

Seropositive Myasthenia gravis has been reported following minutes after trauma to the neck and chest, in a previously asymptomatic 68-year-old man. [15] Myasthenic symptoms have been observed after 3 months of an RTA in a 55-year-old man, who had multiple rib fractures.[5]

In 1996, a similar case was reported when a 17-year-old male, a collegiate football player, developed left-sided unilateral ptosis, a few hours after minor trauma to the left side of his orbital area during a scrimmage. This patient also had symptoms of generalized fatiguability which worsened after a period of exercise. His Acetylcholine receptor antibody test was negative, however, RNS showed a decremental response. A diagnosis of trauma-induced, very mild, antibody-negative generalized myasthenia gravis was made.[16]

Our patient presents a rather interesting scenario. He had an episode of blunt trauma to the left orbital region 1 month before the development of doubling of vision and left-sided ptosis, which aggravated by the end of the day. He had been experiencing these symptoms for the past 4 years, and as per his parents, he had visited multiple health facilities regarding this concern, but to no avail. They had this general perception that trauma might have led to some “nerve damage” that was the cause of these symptoms. When we examined the patient, his fatiguability test and ice-pack test (Figure 1) were strongly positive. We therefore decided to proceed with the neostigmine test. Intramuscular Inj. Neostigmine was injected (0.02mg/kg), which resulted in drastic improvement of ptosis and hypotropia in the left eye after 15 minutes. (Figure 2, Figure 3). The patient also reported radical improvement in diplopia. His anti-AchR Antibodies and anti-MuSK antibodies came out to be negative. A Repetitive nerve stimulation test (RNS) was ordered which did not reveal any decremental response in the tested muscles/nerves. We did not rule out myasthenia gravis as our diagnosis because of a negative RNS as the literature states that in Cases of General Myasthenia Gravis (GMG), declining responsiveness will be seen with repetitive nerve stimulation (RNS). However, In the absence of widespread symptoms, its diagnostic significance is low because it is abnormal in

only 30 to 50 per cent of OMG patients. [17] LRP4 and anti-cortactin antibodies were not done because of the non-availability of these investigations.

Positive clinical findings (ice pack test, fatiguability test, cogan lid twitch sign, sleep test) and strongly positive pharmacological test (Neostigmine test), in the absence of anti-AchR and anti-MuSK, after the relevant history of trauma to the left-sided orbital region, led to the diagnosis of Trauma induced Double-Seronegative Ocular Myasthenia Gravis. The pharmacological test alone may be sufficient for the diagnosis of Myasthenia Gravis [18] It may be used as an alternative to electrodiagnosis as a second-line method, especially in ocular myasthenia gravis.[19]

The patient was commenced on acetylcholinesterase inhibitor, pyridostigmine. Initially, he was given a lower dose of 30mg twice daily. Two weeks follow-up revealed only a mild improvement in ptosis and diplopia. Therefore, the dosage was increased to 7mg/kg/day (60mg TDS). Two weeks follow-up showed drastic improvement in ptosis and mild improvement in diplopia which tended to manifest especially during the night.

Owing to the drastic improvement in signs and symptoms with which the patient presented both objectively and subjectively, he has not been offered any immunosuppressive therapy as yet. He will be kept on a monthly review so that his signs and symptoms are re-evaluated. Although Some patients of ocular myasthenia will experience complete resolution of symptoms with acetylcholinesterase inhibitor alone, most of them require additional immunosuppression to achieve full clinical remission. Options include glucocorticoids and steroid-sparing agents, most commonly azathioprine and mycophenolate mofetil.[20]

4. Conclusion

This case is a true reflection of the masquerading nature of myasthenia gravis. It reiterates the importance of the very basics; history and examination. Just by obtaining a thorough history and performing relevant examination, though atypical, the presence of Ocular Myasthenia Gravis seemed likely. Trauma should also be recognized as a triggering factor for myasthenia gravis and more attention needs to be given to understand the pathophysiology of this interesting association. Lastly, we propose that anti-LRP4 antibodies and anti-cortactin antibodies should be routinely ordered specially in the cases of seronegative, or double-seronegative myasthenia gravis, which appear to play an important role in the development of these forms of Myasthenia Gravis.

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References

1. Cabral-Marques O, Moll G, Catar R, Preuß B, Bankamp L, Pecher AC, et al. Autoantibodies targeting G protein-coupled receptors: An evolving history in autoimmunity. Report of the 4th international symposium. Autoimmunity Reviews. 2023 May;22(5):103310. https://doi.org/10.1016/j.autrev.2023.103310
2. Ahsan H. Origins and history of autoimmunity—A brief review. Rheumatology & Autoimmunity. 2023;3(1):9–14. https://doi.org/10.1002/rai2.12049
3. Behera S, Kumari P, Das D, Dora J, Tilak A. Ocular myasthenia gravis. Odisha J Ophthalmol. 2022;29(1):19. https://doi.org/10.4103/odjo.odjo_15_22
4. Behbehani R. Ocular Myasthenia Gravis: A Current Overview. EB. 2023 Feb; 15:1–13. https://doi.org/10.2147/eb.s389629
5. Siriratnam P, Zhang W, Faragher M. Trauma-induced myasthenia gravis: coincidence or causal relationship? BMJ Case Rep. 2021 Apr;14(4):e238415. https://doi.org/10.1136/bcr-2020-238415
6. Yulianto F, Gusti Ngurah Made Suwarba I, Sutriani Mahalini D, Agung Mas Putrawati Triningrat A, Paramita Wijayati M. Juvenile Ocular Myasthenia Gravis: A Case Report. CNN. 2020;4(4):86. https://doi.org/10.11648/j.cnn.20200404.14
7. Hendricks TM, Bhatti MT, Hodge DO, Chen JJ. Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study. American Journal of

Ophthalmology. 2019 Sep;205:99–105. https://doi.org/10.1016/j.ajo.2019.04.017
8. Binu A, Kumar SS, Padma UD, Madhu K. Pathophysiological basis in the management of myasthenia gravis: a mini review. Inflammopharmacol. 2022 Feb;30(1):61–71. https://doi.org/10.1007/s10787-021-00905-9
9. Ruwanpathirana P, Priyankara D. Clinical manifestations of wasp stings: a case report and a review of literature. Trop Med Health. 2022 Oct 28;50(1):82. https://doi.org/10.1186/s41182-022-00475-8
10. Briciu V, Flonta M, Leucuța D, Lupșe M. The Diagnostic Challenges and Clinical and Serological Outcome in Patients Hospitalized for Suspected Lyme Neuroborreliosis. Microorganisms. 2022 Jul 11;10(7):1392. https://doi.org/10.3390/microorganisms10071392
11. Leopardi V, Chang YM, Pham A, Luo J, Garden OA. A Systematic Review of the Potential Implication of Infectious Agents in Myasthenia Gravis. Front Neurol. 2021 Jun 14;12:618021. https://doi.org/10.3389/fneur.2021.618021
12. Cleanthous S, Mork AC, Regnault A, Cano S, Kaminski HJ, Morel T. Development of the Myasthenia Gravis (MG) Symptoms PRO: a case study of a patient-centred outcome measure in rare disease. Orphanet J Rare Dis. 2021 Dec;16(1):457. https://doi.org/10.1186/s13023-021-02064-0
13. Masi G, O'Connor KC. Novel pathophysiological insights in autoimmune myasthenia gravis. Current Opinion in Neurology. 2022 Oct;35(5):586–96. https://doi.org/10.1097/wco.0000000000001088
14. Hayashi M. Pathophysiology of Childhood-Onset Myasthenia: Abnormalities of Neuromuscular Junction and Autoimmunity and Its Background. Pathophysiology. 2023 Dec 2;30(4):599–617. https://doi.org/10.3390/pathophysiology30040043
15. El-Wahsh S, Triplett J, Robertson A, Yiannikas C. Post-traumatic myasthenia gravis with head drop: insights into pathogenesis. Neurol Sci [Internet]. 2023 Apr 17 [cited 2023 Jun 22]; Available from: https://link.springer.com/10.1007/s10072-023-06797-7. https://doi.org/10.1007/s10072-023-06797-7
16. Andersen LK, Aadahl M, Vissing J. Fatigue, physical activity and associated factors in 779 patients with myasthenia gravis. Neuromuscular Disorders. 2021 Aug;31(8):716–25. https://doi.org/10.1016/j.nmd.2021.05.007
17. Rousseff RT. Diagnosis of Myasthenia Gravis. JCM. 2021 Apr 16;10(8):1736. https://doi.org/10.3390/jcm10081736
18. Katz NK, Barohn RJ. The history of acetylcholinesterase inhibitors in the treatment of myasthenia gravis. Neuropharmacology. 2021 Jan;182:108303. https://doi.org/10.1016/j.neuropharm.2020.108303
19. Nguyen TT, Kang JJ, Chae JH, Lee E, Kim HJ, Kim JS, et al. Oculomotor fatigability with decrements of saccade and smooth pursuit for diagnosis of myasthenia gravis. J Neurol. 2023 May;270(5):2743–55. doi: https://doi.org/10.1007/s00415-023-11611-7
20. Farrugia ME, Goodfellow JA. A Practical Approach to Managing Patients With Myasthenia Gravis—Opinions and a Review of the Literature. Front Neurol. 2020 Jul 7;11:604. https://doi.org/10.3389/fneur.2020.00604