Ocular Flutter, Generalized Myoclonus, and Trunk Ataxia Associated With Anti-GQ1b Antibodies

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Objective: To describe a movement disorder characterized by ocular flutter, trunk ataxia, and mild generalized myoclonus associated with anti-GQ1b antibodies.

Design: Case report.

Setting: University hospital.

Patient: A 37-year-old woman presented with rapid, conjugated, and periodic oscillations of the eyes with a strict preponderance for the horizontal plane (ocular flutter); trunk ataxia; and occasional arrhythmic muscle jerks (myoclonus) most pronounced at the neck.

Results: Brain magnetic resonance imaging results were normal. Cerebrospinal fluid examination revealed mild lymphocytic pleocytosis. Results of extensive serological tests on viral, bacterial, and fungal infections from blood and cerebrospinal fluid samples were unremarkable. Results of screening examinations for neoplasms and paraneoplastic antibodies, including whole-body fluorodeoxyglucose F18 positron emission tomography, were normal. Positive titers of IgG and IgM anti-GQ1b antibodies were found.

Conclusions: This is the first description of an association between the clinical syndrome of ocular flutter, mild stimulus sensitive myoclonus, and trunk ataxia and anti-GQ1b antibodies. The association with ganglioside antibodies lends further support to the notion of an autoimmune-associated pathology of the syndrome.

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Ocular flutter is a rare oculomotor syndrome that is clinically defined by intermittent bursts of involuntary conjugate eye oscillations with a strict preponderance for the horizontal plane and without intersaccadic interval. Ocular flutter has been considered to be a subform of opsoclonus, probably caused by a loss of tonic stimulation of omnipause neurons. In the healthy brain, omnipause neurons inhibit burst neurons within the paramedian pontine reticular formation. A recent case of ocular flutter after a circumscribed pontine lesion due to multiple sclerosis strongly supports the role of the paramedian pontine reticular formation within the current pathophysiological concept of ocular flutter.

Cogan and Baringer and colleagues are credited for the first descriptions of a movement disorder characterized by brief jerks of conjugated eye movements and postural body tremor. Although ocular flutter and opsoclonus probably share a common pathophysiology, the syndromes are clinically distinct. Whereas the conjugate oscillations of the eyes are strictly horizontal in ocular flutter, irregular oscillations in both the horizontal and vertical planes are observed in opsoclonus. Hankey and Sadka reported a case of ocular flutter associated with postural body tremor and trunk ataxia. In each of these early descriptions, cerebrospinal fluid examination revealed a mild lymphocytic pleocytosis, suggesting a parainfectious origin. Despite the frequent lack of direct serological evidence, the etiology of ocular flutter has been...
Three days before admission, a 37-year-old woman developed brief paroxysmal episodes of blurred vision, illusions of horizontal external motion (oscillopsia), diziness, gait imbalance, and occasional arrhythmic muscle jerks (myoclonus) most pronounced at the neck. The jerks ceased when she lay down in a recumbent position and were provoked by sitting up, standing, or walking. Truncal instability was already present when sitting up. The onset of these symptoms had been preceded by a generalized feeling of discomfort, loss of appetite, and a febrile infection of the upper respiratory tract for 2 weeks.

Neurological examination on admission revealed periodic, rapid, conjugated oscillations of the eyes with a strict preponderance for the horizontal plane (ocular flutter). The eye oscillations were independent of eye position and occurred during fixation (voluntary and guided changes in gaze position), regardless of gaze direction, with eyes open or closed (a video is available at http://www.archneurol.com). The patient had full-range conjugated ocular motion and did not report diplopia. A mild-stimulus sensitive myoclonus (which was most pronounced at the neck and provoked by sitting or standing) as well as mild ataxia of the trunk and gait in the absence of limb ataxia were evident (a video is available at http://www.archneurol.com). The myoclonus was relieved when the patient was in a recumbent position. The remainder of the neurological examination results were unremarkable. Clinical symptom severity increased within 1 week of admission, with the horizontal eye oscillations being more frequent (a video is available at http://www.archneurol.com) and ataxia of the trunk and gait being more pronounced.

Red and white blood cell counts and biochemistry were normal on admission. Cerebrospinal fluid examination on admission revealed a normal opening pressure and mild pleocytosis (75 lymphocytes/mm³). Cerebrospinal fluid protein, lactate, and glucose levels were within the normal range. Oligoclonal bands were positive and quantitative cerebrospinal fluid IgG and IgM indexes were positive. Results of a cerebrospinal fluid examination repeated 10 days later were unremarkable (3 lymphocytes/mm³).

Brain magnetic resonance imaging, including 2-mm sections through the brainstem and the cerebellum, showed no abnormality before or following application of gadolinium–diethylenetriamine pentaacetic acid. Analysis of ocular movements using electrooculography revealed bursts of rapid horizontal, symmetric, and sinusoidal movements without intersaccadic interval (Figure). Results of electrophysiological examinations, such as somatosensory, acoustic, and visual evoked potentials and electroencephalography, were normal. Results of duplex Doppler ultrasonography of the extracranial and intracranial vessels were also normal.

Serological tests, cultures, and polymerase chain reactions performed on blood and cerebrospinal fluid samples were negative for viral, bacterial, and fungal infections. Tests included screenings for infection with Epstein-Barr virus, mumps, measles, rubella virus, adenovirus, influenza virus type A and B, cytomegalovirus, herpes simplex virus type 1 and 2, varicella-zoster virus, enterovirus, human immune deficiency virus type 1 and 2, Chlamydia pneumoniae, Borrelia burgdorferi, Haemophilus influenzae, Neisseria meningitidis, Campylobacter jejuni, Mycoplasma pneumoniae, Yersinia, Listeria monocytogenes, Streptococcus pneumoniae, Mycobacterium tuberculosis, and Treponema pallidum.

Results of screening examinations for neoplasms, including abdominal ultrasonography, computed tomography of the abdomen and chest, as well as whole-body fludeoxyglucose F18 positron emission tomography, were all unremarkable. Serological tests of blood and cerebrospinal fluid for paraneoplastic antibodies, such as anti-Ri (ANNA-2), anti-Hu (ANNA-1), anti-Yo (PCA1), anti-Ma2, anti-CV2 (collapsin response mediator protein 5), and anti-amphiphysin, were negative. Ganglioside antibodies were negative for GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GT3, and asialo GM1. IgG and IgM antibodies against GQ1b were found.

The patient was initially treated with acyclovir (750 mg, 3 times a day intravenously) and ceftriaxone (2000 mg once a day intravenously) for 14 days. Prednisolone acetate (1000 mg once a day intravenously) was given to the patient for 5 days together with the antiviral and antibiotic therapy and then was switched for an oral regimen (100 mg once a day orally) for 11 days. Plasmapheresis therapy began 21 days after admission, with daily immunoadsorption of 500 mL of plasma for 2 days but had to be discontinued owing to low fibrinogen levels.

Figure. Oculographic recording showing bursts of rapid horizontal, conjugated, and sinusoidal movements without intersaccadic interval with eyes open and closed.
Twenty-three days after admission, immunoadsorption therapy was started (3 L) for 3 days. Twenty-six days after admission, the patient was given intravenous immunoglobulins (10 g, 3 times a day for 5 days). The symptoms gradually resolved after the second day of immunoadsorption and continued to improve after the administration of intravenous immunoglobulins during the following 2 weeks.

COMMENT

This is the first description of an association between anti-GQ1b antibodies and the clinical syndrome of ocular flutter, stimulus sensitive myoclonus, and truncal ataxia. The association of ocular flutter with elevated serum titers for ganglioside antibodies lends further support to the notion of an autoimmune-associated pathology of the syndrome. The origin of ocular flutter appears to be related to a malfunction of the inhibitory control of saccadic burst neurons in the paramedian pontine reticular formation.1-2 Postural ataxia of the trunk in the absence of limb ataxia may be associated with a circumscribed dysfunction of the vestibulocerebellum, including the flocculus and the nodulus, the nucleus fastigii, the ventral uvula, and the ventral paraflocculus.7 Generalized myoclonus most likely results from a dysfunction within the Guillain-Mollaret triangle between the nucleus ruber, the inferior olive, and the dentate nucleus of the cerebellum.

It is typical of the syndrome that brain imaging does not demonstrate an anatomical lesion,5-11 and therefore the clinical symptomatology is probably caused by a functional rather than a structural disturbance within the network of areas specified. The brainstem and cerebellar features found in our patient suggest that anti-GQ1b antibodies target central nervous system epitopes in these neuroanatomical regions. Indeed, an association between ganglioside antibodies and central nervous brainstem malfunction causing oculomotor deficits (not cranial nerve dysfunction as obvious as in Miller-Fisher syndrome10) has recently been described.14 Generally, this syndrome has a benign course, and an appropriate treatment regimen remains to be established given its rare occurrence. Intravenous high-dose immunoglobulin and plasmapheresis have been recommended, while oral steroids are less effective.4-12,14 In our case, antibiotics and steroid treatment did not result in profound clinical improvement. The favorable course in many reported cases is probably caused by spontaneous remission.4,5,7 An association with anti-GQ1b antibodies should be considered when confronted with a movement disorder that is related to dysfunction of the brainstem (ocular flutter and myoclonus) and the vestibulocerebellum (trunk ataxia), and additional clinical or instrumental data suggesting other etiologies are lacking.

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Additional Information: Videos are available online at http://www.archneurol.com.

REFERENCES