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Brief Communication

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Acute Ophthalmoparesis Associated With Anti-GM1, Anti-GD1a, and Anti-GD1b Antibodies After Enterovirus Infection in a 6-Year-Old Girl

Carlo Fusco, MD, Gianna Bertani, MD, Angela Scarano, MD, and Elvio Della Giustina, MD

This article presents a 6-year-old girl who developed acute unilateral third cranial nerve palsy in the absence of any other sign of central nervous system involvement. Raised titers of immunoglobulin M antibodies against GM1, GD1a, and GD1b ganglioside components were demonstrated. Ten days earlier, the girl had experienced acute gastroenteritis with positive specific immunoglobulin M antibodies against enterovirus. The results of all other laboratory tests usually performed for infectious diseases were negative, and neuroradiologic findings were also normal. Oral prednisone was administered for a few days, and the ophthalmoparesis fully resolved within 1 month. Two months later, a second episode of isolated ophthalmoparesis occurred, again associated with a positive immunoglobulin M reaction against GM1, GD1a, and GD1b antigens. This report discusses the relationship between acute isolated ophthalmoparesis and antiganglioside antibodies.

Keywords: antiganglioside antibodies; ophthalmoparesis; GM1; GD1a; GD1b

Considerable progress has been achieved in understanding the link between peripheral neuropathy and antiganglioside antibodies. Particularly in acute ophthalmoparesis, a frequent overlap is described with anti-GQ1 antibodies, whereas anti-GM1 and anti-GD1a/GD1b antibodies are usually detected in axonal forms of Guillain-Barré syndrome.[1] We report an unusual case of acute ophthalmoplegia with anti-GM1, anti-GD1a, and anti-GD1b antibodies after enterovirus infection, and the dysimmune pathogenic pathway underlying isolated ophthalmoparesis is discussed.

Case Report

A 6-year-old girl was admitted to our Child Neurology Unit complaining of unilateral ophthalmoplegia and diplopia in the absence of ptosis. She was born to healthy, nonconsanguineous parents, and no remarkable events took place in the perinatal period. Motor and mental developmental milestones were achieved normally, and she appeared to be very healthy until the acute ophthalmoparesis episode.

On admission, the neurologic examination revealed right myosis-induced anisocoria and severe limitation of the right eye adduction and vertical movements. The other cranial nerves were normal. No muscle weakness and hypotonia or unstable gait and dysmetric movements were observed. The plantar responses were flexor, deep tendon reflexes were normally evoked, and sensory stimuli were correctly perceived.

She had developed fever and gastroenteritis 10 days earlier. Findings from brain electroencephalographic (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) studies were normal. Routine laboratory test results were also normal, and blood serum did not contain antibodies for adenovirus, *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus (1 and 2), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, Epstein-Barr virus, and influenza A and B virus. Test results for antiphospholipid antibodies were negative, as were antinuclear antibody, antineutrophilic cytoplasmic antibodies, and antineuronal immunologic reaction. The stool culture was negative for *Shigella* and *Campylobacter* infection and for virus isolation. Antistreptolysin O and antideoxyribonuclease B titers were raised, although a throat culture was negative for streptococcal infection.

From the Child Neurology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Address correspondence to: Carlo Fusco, MD, Arcispedale Santa Maria Nuova, Child Neurology Unit, Viale Risorgimento 80, 42100 Reggio Emilia, Italy; e-mail: Fusco.Carlo@asmn.re.it.

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Table 1. Laboratory Findings

Antigens	Normal Value	Ophthalmoparesis First	Ophthalmoparesis Second	3 Months Later	10 Months Later
GM1 IgM	< 50	59	87	6	10
GM1 IgG	< 50	0	0	0	0
GD1a IgM	< 50	80	230	0	0
GD1a IgG	< 50	0	0	0	0
GD1b IgM	< 50	56	0	0	0
GD1b IgG	< 50	0	0	0	0
IgM enterovirus	N	P	N	N	N
IgG enterovirus	N	N	P	N	N

NOTE: Ig = immunoglobulin; N = negative; P = positive.

The only laboratory abnormality was the immunoglobulin M titer to GM1, GD1a, and GD1b, which was significantly raised in the serum during the acute phase of the ophthalmoparesis. Test results for immunoglobulin G antibodies against gangliosides were negative. At that time, the specific immunoglobulin M against enterovirus was detected.

The girl was given oral prednisone (1 mg/kg daily) for 10 days, which led to a gradual reduction of paretic complaints and a complete recovery of the right oculomotor nerve palsy within a month. Meanwhile, the immunoglobulin M titer to enterovirus and raised specific immunoglobulin G in the serum normalized. The finding from a cranial MRI was normal, with no contrast enhancement.

Two months later, the girl had a second identical episode of ophthalmoparesis. Raised immunoglobulin M anti-GM1 and anti-GD1a and positive specific immunoglobulin G against enterovirus were observed in the serum. On that occasion, the ophthalmoparesis resolved spontaneously in a few days. The antiganglioside antibody titer was tested 3 and 10 months later and was negative in both cases. No further episodes of ophthalmoparesis have been experienced since. All laboratory findings are reported in Table 1.

Discussion

A case of a child with unilateral ophthalmoparesis and immunoglobulin M antibodies against enterovirus and antibodies to GM1, GD1a, and GD1b is reported. In childhood, isolated palsy of cranial nerves with good prognosis is encountered fairly frequently in clinical practice and can be caused by trauma, ophthalmoplegic migraine, infectious or dysimmune disease with inflammation, and neoplasm, or it can be idiopathic.[2] The significance of raised antiglycolipid antibodies in peripheral neuropathies has been extensively reviewed in recent times,[1] stating that in acute ophthalmoparesis, there may be overlap between the clinical picture and the positive increase in anti-GQ1b immunoglobulin G antibodies. Conversely, anti-GM1, anti-GD1a, and anti-GD1b antibodies are usually raised in the axonal form of Guillain-Barré syndrome, in chronic ataxic neuropathy, and in multifocal motor neuropathy, whereas they are not generally observed in acute ophthalmoparesis.[1] Very few reports describe the occurrence of paresis of the extraocular muscles in association with GM1 and, notably, GQ1b antibodies,[3-7] but not with anti-GD1a and anti-GD1b antibodies.

Patients reported by Kowal et al[4] had no previous infectious disease, and a single patient experienced right hypertropia 10 days after an influenza vaccination, with elevated immunoglobulin G and M anti-GM1. The patient described by Lavallée et al[5] developed a postinfectious ophthalmoparesis and showed positive anti-GM1 antibodies; however, electroneurography showed a conduction block in the peroneal nerve, suggesting a benign form of Guillain-Barré syndrome. Ryo et al[6] focused on a 19-year-old woman with recurrent ophthalmoplegia and anti-GM1 antibodies but within the context of a chronic inflammatory demyelinating polyneuropathy. Several points of discussion deserve special consideration.

To our knowledge, this is the first report illustrating the overlap between anti-GM1, anti-GD1a, and anti-GD1b antibodies and acute ophthalmoparesis in childhood. It is generally recognized that there is a link between acute ophthalmoparesis and either anti-GQ1b immunoglobulin G antibody production or the Miller Fisher variant of Guillain-Barré syndrome.[8,9] Yuki et al[7] examined 21 patients with ophthalmoparesis and anti-GQ1b immunoglobulin G antibodies in the absence of ataxia and diagnosed them as having a mild form of Miller Fisher syndrome or a regional variant of Guillain-Barré syndrome, both showing a possible clinical overlap. From a clinical point of view, our patient might be considered as having had an atypical form of Miller Fisher syndrome that does not show either ataxia or arreflexia.

It is interesting to note that in humans, GM1, GD1a, and GD1b are present in both dorsal and ventral roots and in peripheral nerves, whereas GQ1b is especially enriched at the nodes of Ranvier of oculomotor nerves.[1] We would suggest that a regional variant of Guillain-Barré syndrome developed in our patient; more precisely, an acute axonal motor neuropathy or nerve conduction block of the third right cranial nerve could be suggested. Anti-GM1, anti-GD1a, and anti-GD1b antibodies are primarily specific markers of these clinical syndromes, and the unilateral involvement of the oculomotor nerve would appear to confirm this diagnostic suggestion.

Several infectious agents are described as antecedents of peripheral neuropathies, including enterovirus associated with ophthalmoparesis, but no previous reports focus on the overlap between enterovirus infection (gastroenteritis) and acute ophthalmoparesis and anti-GM1, anti-GD1a, and anti-GD1b immunoglobulin M antibody production. As it does

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happen in the axonal form of Guillain-Barré syndrome after *Campylobacter jejuni* infection, we assume a possible molecular mimicry between microbial structures and nerve tissue as a cause and the immune cross-reactivity of antibodies for the enterovirus to react against physiologic components of the peripheral nervous system as a consequence.[10]

The finding of raised antistreptolysin O and anti-deoxyribonuclease B antibodies deserves a brief comment. This suggests a previous streptococcal infection, and isolated cranial nerve involvement has actually been associated with streptococcal infection and high anti-GQ1b antibody titer, presumably subsequent to an autoimmunization. We excluded this etiology and pathogenesis because of the negativity of the throat culture, the wide diffusion of streptococcal infection in the pediatric population, and especially, the suggestive time lag between clinical gastroenteritis and ophthalmoparesis and between gastroenteritis and evidence of specific immunoglobulin M against enterovirus coinciding with the acute onset of the ophthalmoparesis.

Conclusion

Although acute ophthalmoparesis after infection or immunization is frequently associated with anti-GQ1b antibody reaction, we think that investigation for antibodies against several antiganglioside subtypes should be strongly recommended to support the clinical work-up. Also, isolated ophthalmoparesis with anti-GM1, anti-GD1a, and anti-GD1b immunoglobulin M antibodies should be included as a separate entity within the broad spectrum of postinfectious diseases after a dysimmune process. The dysimmune pathogenesis of the ophthalmoparesis in our patient is clearly demonstrated by the cross-reacting antiganglioside antibodies; in addition, we successfully treated our patient with oral prednisone for a short time during the first episode. We believe that this therapeutic approach should be strongly recommended at least in the acute phase of the disease. Further investigations will help to better correlate the clinical phenotype with the kind of antiganglioside antibody reaction.

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