Rare disease

Presentation of opsoclonus myoclonus ataxia syndrome with glutamic acid decarboxylase antibodies

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Summary

In this rare case, the patient presented with opsoclonus, myoclonus and ataxia. Serological and imaging studies revealed high glutamic acid decarboxylase antibody (GAD-Ab) levels. High-dose corticosteroids were of no benefit and subsequent intravenous immunoglobulin (IVIg) administration proved resolution of the condition. Levetiracetam proved useful in symptomatically controlling the myoclonus. Follow-up GAD-Ab levels were within normal limits.

BACKGROUND

Opsoclonus myoclonus ataxia syndrome (OMAS) is a very rare syndrome. Hypothesised to be due to an underlying autoimmune mechanism, multiple antibodies have been linked to it. Glutamic acid decarboxylase antibody (GAD-Ab) is one of many antibodies, but only two cases have reported GAD-Ab positive OMAS. Up to date, this is the third case in the literature that involved GAD-Ab with OMAS, and the second in an adult. The use of intravenous immunoglobulin (IVIg), in this case, demonstrates the likelihood that the underlying mechanism in OMAS is actually autoimmune. Moreover, to the author's knowledge, it is the first described report of levetiracetam use in symptomatically treating OMAS-related myoclonus. Thus, this rare presentation should be mentioned in the literature so that it can assist in our further understanding of OMAS.

CASE PRESENTATION

A 34-year-old Caucasian women with no significant medical history presented with a right earache while on vacation in California, USA. She developed marked lethargy, delirium and a pressure headache that prompted an emergency room visit. She was diagnosed with aseptic meningoencephalitis and warranted a 48 h stay at the local hospital. One week after improvement, she travelled back to Texas, but along the way back she developed limb and truncal ataxia. Within a day, she noted ocillopsia and 4 days later developed sudden jerking of her extremities frequently throughout the day. She was not on any medications significant to this case. Medication allergies included penicillin. Family and social histories were non-contributory.

On physical examination vital signs were within normal limits. She was alert, awake and in no distress. Testing of cognition and language did not reveal any abnormalities. Upon examination of cranial nerves, marked multidirectional, high amplitude and fast frequency, conjugate eye movements were seen. Myoclonus of her extremities was seen to be intermittent. The rest of

her cranial nerves, motor and sensory exam did not reveal deficits. Truncal ataxia, dysmetria and dysidiadochokinesis were notable findings in testing coordination. Due to these findings, she could not even stand to ambulate properly.

Comprehensive workup of the aetiology was undertaken (as seen below). Comprehensive workup to locate a possible cancer source, such as a neuroblastoma, was undertaken (see below). Infectious disease consultation led to a diagnosis of underlying recovering aseptic meningoencephalitis. Gynaecologic consultation was unrevealing. She began to develop severe anxiety and psychiatry was consulted. Treatment was initiated (as seen below).

INVESTIGATIONS

No abnormalities on complete blood count or serum chemistries. Ammonia, vitamins B12 and E, thyroid panel, urine/serum catecholamines, cortisol, paraneoplastic panel and various tumour markers, blood, urine and sputum cultures were unrevealing. In addition various cerebrospinal and serological virus antibody panels including Epstein-Barr virus, echo/coxsackie, cytomegalovirus, arbovirus, enterovirus, West Nile virus and St Louis encephalitis virus were unrevealing. Cerebrospinal fluid studies revealed 310 white cells/mm³ (91% lymphocytes), 20 red cells/mm³, glucose 78 mg/dl, protein 57 mg/dl, no oligoclonal bands, negative gram stain and cultures, no cytological evidence for cancers and negative HSV-1 and HSV-2 PCR. Serological anti-N-methyl-D-aspartate antibodies were negative and glutamic acid decarboxylase antibodies were markedly elevated at 239.4 IU/ml (normal <5 IU/ml).

EEG: Normal awake and stage II sleep routine study.

MRI brain with and without contrast: Unremarkable.

Abdominal CT, chest CT, bone scan and mammogram: Unremarkable.

DIFFERENTIAL DIAGNOSIS

Paraneoplastic syndromes associated with neuroblastoma or ganglioneuroma, cerebellar ataxia, cerebellar degeneration,

epilepsy, aseptic meningitis, neurosarcoidosis, limbic encephalitis, brainstem encephalitis, hyperosmolar nonketotic coma, medication induced (ketamine, tricyclic antidepressants), pheochromocytoma, prion encephalopathy, demyelinating disease, myasthenic syndrome and conversion disorder

TREATMENT

Initially, due to the underlying diagnosis of aseptic meningoencephalitis, prednisolone 1 g/day intravenous was given for 5 days with no benefit. Subsequently, since the opsoclonus, myoclonus and ataxia did not improve, IVIg 0.4 g/kg/day for 5 days was initiated. Levetiracetam 750 mg twice daily was started to treat the myoclonus. The IVIg and levetiracetam regimen led to marked improvement in the ataxia, opsoclonus and myoclonus. Escitalopram was initiated for the anxiety.

OUTCOME AND FOLLOW-UP

Upon marked improvement, she was transferred to an inpatient rehabilitation facility for a short duration. In a month, she had fully recovered. On subsequent clinic visits, her neurological examination did not reveal any sequelae and she returned to baseline. At a year, her serum glutamic acid decarboxylase antibodies were normalised to 4.1 IU/ml (normal <5 IU/ml).

DISCUSSION

OMAS is a unique syndrome that was first described in infants in 1962.¹ OMAS is a very rare condition with orphan status that is seen in one in 10,000,000 people per year.² Most neurologists may not see a single case in their lifetime. In the pediatric population, it is closely linked with neuroblastoma. Although it is much more common in children than in adults, even in that population, 2–3% of patients with neuroblastoma experience OMAS.³ Therefore, full workup should be undertaken to locate a possible neuroblastoma. This includes urine and/or serum catecholamines, paraneoplastic panel, in addition to full body imaging (CT scans and bone scan). In adults, the majority are paraneoplastic in origin, but other aetiologies include demyelinating disease, infectious, drug induced and other autoimmune processes.^{4–5} But classically, the autoimmune hypothesis of OMAS has been the mainstream among those in the field. The main evidence stems from multiple classes of antibodies that have been linked to OMAS, including anti-Hu, anti-Ri, anti-Yo, anti-Ma1, anti-Ma2, antineurofilaments, alpha enolase, *N*-methyl-D-aspartate receptor (NMDAR) IgG and GAD-Ab, among many others.^{3–8}

GAD-Ab have been linked to multiple neurological conditions including stiff person syndrome, palatal myoclonus, Parkinson's disease and cerebellar ataxia, and up to now, only two cases involving OMAS had high GAD-Ab levels.⁴ This would be the third such case. Thus in this case, it is surmised that the high GAD-Ab levels may be due to the initial presentation of aseptic meningoencephalitis. With its resolution, an autoimmune process, involving GAD-Ab, was initiated; this process leads to the OMAS.

Glutamic acid decarboxylase is the enzyme that catalyses glutamate to gamma-aminobutyric acid (GABA).

Thus, GAD-Ab directly impair the conversion of glutamate to GABA leading to depreciated GABAergic transmission, especially in key areas involving the brainstem and cerebellum.^{4–9} These GAD-Ab have been directly linked to stiff person syndrome and cerebellar ataxia,⁹ and logically based on the components of opsoclonus, myoclonus and ataxia making up OMAS, could readily be involved in its pathogenesis. For example, it is hypothesised that opsoclonus may be due to damage of the fastigial nucleus of the cerebellum.⁸

False-positive GAD-Ab has been reported with OMAS. In one case report, increased GAD-Ab levels were noted after administration of IVIg; these levels normalised after the cessation of the infusions.¹⁰ Prior to the infusion, the authors note the GAD-Ab levels were normal; additionally, as suggested by the authors, it is prudent to check GAD-Ab levels prior to IVIg administration to avoid confounding the possibility of the OMAS aetiology being due to false-positive GAD-Ab.¹⁰

Once the underlying aetiology of OMAS is determined, treatment can commence. Up to now, no prospective controlled trials involving comparison of treatments in OMAS have been undertaken. Besides treating the underlying tumour or encephalitis, if they exist, the use of high-dose corticosteroids and/or IVIg have been used as it seems to catalyse recovery.^{7–8–11} In refractory cases, cyclophosphamide, mycophenolate, azathioprine and plasmapheresis have been described.⁸ Adrenocorticotrophic hormone has been used anecdotally, and it is thought to act at the level of neurotransmitter modulation.¹¹ Due to low risk, high-dose corticosteroids were used initially in the patient described in this case. With no improvement noted, IVIg was initiated with marked improvement. This bolsters the hypothesis of an autoimmune process in OMAS. Additionally, as the IVIg was used to treat the underlying process, for the symptomatic relief of myoclonus, levetiracetam was used especially due to its low side effect profile. It has been used effectively in cortical myoclonus, as cited in review.¹² This is the first case of OMAS where levetiracetam was used to relieve myoclonus with good results.

In conclusion, OMAS is a very rare syndrome. The case presented here is even more so due to its link with GAD Ab; this is only the third case of this kind reported. In the literature, OMAS is believed to be due to an autoimmune mechanism; but multiple antibodies have been cited to have caused OMAS. It may be that as it is a syndrome, multiple underlying processes can lead to the same phenotype. Moreover, as per the literature, if no underlying aetiology is uncovered use of high-dose corticosteroids and/or IVIg is recommended. Additionally, in symptomatic control of myoclonus, levetiracetam has proven useful. As fascinating as this syndrome is, further research needs to be done to understand it.

Learning points

- Opsoclonus myoclonus ataxia syndrome (OMAS) is a very rare disease process with only three reported cases of glutamic acid decarboxylase antibody positive OMAS.

- Multiple aetiologies can cause OMAS, so full workup involving serological and imaging studies should be undertaken, inclusive of full workup to locate possible neuroblastoma as almost half of all OMAS cases occur with it.
- The underlying processes involved in OMAS are likely autoimmune mediated.
- High-dose corticosteroids and/or intravenous immunoglobulin may be of benefit in treating OMAS
- Levetiracetam may be used to symptomatically treat myoclonus.

Competing interests None.

Patient consent Obtained.

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