Parkinsonism and Related Disorders 15 (2009) 792–794

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Letter to the Editor

Opsoclonus myoclonus after human papilloma virus vaccine in a pediatric patient☆

1. Introduction

Opsoclonus-Myoclonus Syndrome (OMS) is a rare neurologic condition comprised of the two hallmark signs of dysmetric ocular ataxia and myoclonic jerks of the extremities. The eye movements have been described as "dancing eyes". The eyes dart involuntarily away from the point of visual fixation or pursuit in a manner that can be considered a myoclonic jerk of the extra-ocular muscles. When the patient attempts to align the gaze on a point, there may be dysmetric overshoot of the eye movement. Myoclonic movements of the extremities occur at rest, and intended actions are ataxic. The mean age of presentation of OMS in childhood is 14 months, and it presents as a paraneoplastic syndrome associated with an underlying tumor in 50–60% of the cases [1,2], most commonly neuroblastoma or ganglioneuroblastoma. Recent research has revealed the presence of several auto-antibodies including anti-Hu, anti-Ri, α-Enolase, KSRP and NLK [3] in patients with OMS. These antibodies bind to an array of targets in the cerebellum and may manifest as oligoclonal bands in cerebrospinal fluid. The syndrome is often associated with behavioral changes such as aggression, irritability, and insomnia. Post-vaccine OMS is not well described in the pediatric population.

2. Case report and discussion

The patient was a fully vaccinated and developmentally appropriate 11-year-old female with seasonal allergies and mild asthma. Her initial symptoms consisted of a sudden onset of increased "moodiness" causing uncharacteristic anger and depression. These symptoms presented approximately 15 days after receiving her first human papilloma virus (HPV) (Gardisil®) vaccination on 11/26/2007. The uncharacteristic behavior persisted and 1 month after the initial mood changes she noted that her "eyes were doing weird things" and she perceived that visual images went "back and forth in circles". The abnormal ocular movements occurred with her eyes closed or open, and could be only minimally suppressed with great effort. There were no other symptoms at this time, however, her eye symptoms became more frequent and troubling to her. She then received a second HPV vaccination 2 months later in addition to a meningococcal (Menactra®) vaccine. Four days after these vaccinations she developed noticeable worsening of the eye movements and acute perception of dizziness, which she described as the "room is spinning." This was accompanied by leg weakness requiring assistance to walk and "jumpy arms." Family history reveals a cousin with childhood epilepsy, maternal great aunt with lupus, maternal grandfather died of a ruptured aneurysm at age 40, and mother with fibromyalgia, but no movement disorders or paraneoplastic syndromes.

Initial examination revealed conjugate opsoclonus with or without eyelid closure that worsened with attempts to maintain visual fixation. Optic discs were sharp. Cranial nerves were intact. There was mild weakness and impersistence of force in quadriceps, hamstrings, tibialis anterior, hip adductors, abductors and iliopsoas. Myoclonus was noted in upper and lower extremities, but was worse in the upper extremities. Trunk strength was preserved in the supine position with the patient able to perform sit-ups, but weakened with standing. Sensation to all modalities was intact. Myotactic tendon reflexes were brisk except that ankle reflexes were difficult to elicit. Extensor Babinski sign was not present. Clonus was not present. Dysmetria was noted in the upper extremities. Gait ataxia was severe. There were no telangiectasia on skin or sclerae, or any other signs of neurocutaneous phakomatoses. The general physical exam was otherwise normal.

No laboratory investigations (Table 1) established a toxic, metabolic, infectious, immunologic or paraneoplastic cause for the patient's OMS. Anti-Ro was slightly elevated, but repeat was normal. There were no oligoclonal bands in the cerebrospinal fluid (CSF). Electroencephalogram was normal and multiple imaging studies were normal (Table 1), with no evidence of neuroblastoma, ganglioneuroma or other mass. The ophthalmologist's examination found no evidence of retinitis, cherry red spots, or optic pallor.

The patient was treated with high dose methylprednisolone (2 mg/kg) daily in divided doses for 1 week, but developed headache and worsening myoclonus and hyperglycemia (354 mg/dL), so methylprednisolone was discontinued. Intravenous immunoglobulin (IVIG) 2 g/kg in divided doses for 48 h, but there was no improvement. Levetiracetam was started and was associated with improvement after 5 days. She had elevated lactate and was therefore treated presumptively for mitochondrial disease with thiamine 25 mg twice daily, riboflavin 50 mg BID and Co-enzyme Q-10 while waiting more definitive mitochondrial testing. The lactate normalized, and there were no additional signs of mitochondrial disease (normal mitochondrial genome analysis, methylglutaconic acid, and head MRI). Over the next month she was admitted to

☆ The review of this paper was entirely handled by the Co-Editor-in-Chief, Professor R.F. Pfeiffer.

1353-8020/$ – see front matter
doi:10.1016/j.parkreldis.2009.04.002

Table 1
Laboratory investigations.

Immune studies
NeoCerebellar degeneration and paraneoplastic profile (at Athena Labs)
- Anti-Hu: normal
- Anti-Ma 1 and Ma 2: normal
- Anti-Yo, Ta, Ri, CV2, and ZiO4: normal

Infectious studies
- Mycoplasma IgG and IgM: normal
- Anti-Streptolycin O Titer and Anti-DNAse B: normal
- Lyme disease antibodies: normal
- HIV antigen: normal
- Total Plasma IgG = 1484 (high); total IgA and IgM: normal
- Human Herpes Virus 6: normal
- Complete blood count: normal

Additional auto-antibodies
- ANA: = >1:80 (positive)
- Anti-DNA: negative
- c-ANCA and p-ANCA: negative
- Myeloperoxidase (PR2) : normal
- Anti-cardiolipins: normal; ACA IgM: normal
- Anti-SCL70: normal
- Anti-LA: normal
- Anti-RO: = 1.7, high, but followup was normal at 0.2 normal value is <1)
- Anti-SM: normal
- Anti-JO1: normal
- Anti-U1RNP: normal
- Anti-MPO: normal
- Anti-Proteinase 3 (PR3): normal
- Anti-gliadins, anti-tissue transglutaminase, and celiac DQ genes: normal

Endocrine studies
- ACE : normal for age
- Urine spot HVA: 3.1 ug/mg Cr (normal <7.0)
- Urine spot VMA: 6.0 ug/mg Cr (normal <12.0).
- TSH, free T4, and AM Cortisol: normal

CSF studies
- Protein 37 (normal); Glucose 71 (normal)
- Myelin Basic Protein: normal
- Oligoclonal bands: negative
- WBC 0, RBC 30334, no xanthochromia

General toxic and metabolic studies
- Electrolytes, transaminases, bilirubin, lipase, urea nitrogen, creatinine, electrolytes: normal
- Urinalysis: normal
- Vitamin E level: normal
- Urine drug of abuse screen: no evidence of cocaine, opiate, amphetamine, benzodiazepine or other agents
- Blood lead: normal; urine arsenic and mercury: normal

Mitochondrial studies
- Blood lactate 6.6mMol/L, but followup tests were normal, on and off vitamin therapy
- CPK normal
- Acyl-Carnitine: normal
- Mitochondrial genome analysis in blood, especially for associations with myoclonus: mutations at: 3243; 3251; 3252; 3260; 3271; 8344; 8356; 8363; 8851; 8993; 9176; 14 709; 14 459; deletions at 9480; 5 kb; and 7.4 kb: all normal

Neurodegenerative disorder studies
- Spinocerebellar atrophy genes (Types 1–3, 5–8, 10, 14, 17; DRPLA; FRDA1; SETX; POLG1; SIL1; TTPA; KCNC3): normal
- Lafora body disease genes (EPM2A; EPM2B): normal
- Sjogren-Larson disease genes (ALDH3A2/FALDH): normal
- Spinal muscular atrophy genes (SMN1, SMN2): normal

Electrophysiological studies
- 24 h Video electroencephaogram: normal
- Electromyogram and nerve conduction studies: normal
- Audiogram and otoacoustic emissions: normal
- Electrocardiogram: normal

Imaging studies
- Magnetic resonance imaging of head, full spine, chest and abdomen, with and without contrast: normal, with no mass such as neuroblastoma or ganglioneuroma
- Chest X-ray: normal
- Abdominal ultrasound: normal
- Head computed tomography: normal
- Radionuclide scans (octreatide and meta-iodobenzylguanidine): normal

a rehabilitation center, during which her opsoclonus improved, but she was still unable to walk or reach accurately and a second course of IVIG (2 g/kg divided BID) failed to improve her symptoms, including her mood changes. After 9 months, all her symptoms abated and she returned to her baseline function with only mild difficulty with walking up stairs.

3. Discussion

There is one case report of post-vaccine OMS in a 30-year-old female with an allergic diathesis [4]. Her symptoms began two weeks after a vaccine. She failed to improve with corticosteroid therapy, but IVIG was not used. She derived clinical benefit from benzodiazepines and her symptoms resolved completely within 10 months.

In both the prior reported case, and this case, symptoms began with behavioral change 2 weeks after vaccination, and symptoms worsened acutely after the second vaccination, which was associated with progression to severe opsoclonus, myoclonus and ataxia. Laboratory investigations in both cases revealed no other pathological explanations for the OMS. In both cases symptoms resolved completely by 10 months. Lack of oligoclonal bands in the CSF has been reported in other cases of OMS [5]. This report describes a case of post-vaccinic OMS due to Gardasil® in a child and documents that although the illness resolved after 10 months and did not benefit from IVIG therapy, it had a significant toll on her quality of life for a year.

References

[1] Wilson J. Neuroimmunology of dancing eyes syndrome. Dev Med Child Neurol 2006;48:693–6.
[2] Tate E, Allison T, Pranzatelli M, Verhulst S. Neuroepidemiologic trends in 105 cases of pediatric opsoclonus myoclonus syndrome. J Pediatr Oncol Nurs 2005;22:8–19.
[3] Kirsten A, Beck S, Fuhlhuber V, Kaps M, Kreutz T, Korfei M, et al. New autoantibodies in pediatric opsoclonus-myoclonus syndrome. Ann N Y Acad Sci 2007; 1110:256–60.
[4] Lapenna F, Lochi L, de Mari M, Iliceto G, Lamberti P. Post-vaccinic opsoclonus myoclonus syndrome: a case-report. Parkinsonism Relat Disord 2000;40: 241–2.
[5] Antunes N, Khakoo Y, Matthay K, Seeger R, Strum D, Gestner E, et al. J Pediatr Hematol Oncol 2000;22:313–20.

James E. McCarthy*
Department of Pediatrics,
Children's Hospital at Dartmouth-Hitchcock Medical Center,
One Medical Drive, Lebanon, NH 03766, USA
* Corresponding author. Tel.: +1 8022998774.
E-mail address: james.e.mccarthy@hitchcock.org

James Filiano
Department of Pediatric Neurology,
Children's Hospital at Dartmouth-Hitchcock Medical Center,
Lebanon, NH 03766, USA
Department of Pediatric Critical Care,
Children's Hospital at Dartmouth-Hitchcock Medical Center,
Lebanon, NH 03766, USA

26 January 2009