INTRODUCTION

Opsoclonus-myoclonus syndrome (OMS) is seen in 2–3% of children with neuroblastoma [1]. Although most patients with neuroblastoma and OMS have good survival rates, 70–80% of these children will have long-term neurologic deficits [2,3]. OMS is believed to be caused by autoimmune processes elicited by the tumor and directed against nervous system antigens. As in other neurologic paraneoplastic syndromes, onconeural antibodies are believed to play a key role in the development of this disorder. However, most patients are antibody negative [2,4,5]. Clinical improvement has been seen in some children following surgical resection of the tumor, while others may respond to immunomodulatory therapy [2,5]. However, questions regarding optimal treatment strategies and the impact of treatment on long-term neurologic outcome remain largely unanswered.

We report a patient who was diagnosed with OMS 6 months following complete resection of a localized pelvic neuroblastoma. Her initial neurologic symptoms eventually resolved following immunosuppressant therapy. Six years later, she developed anti-Hu associated limbic encephalitis. This case demonstrates the chronicity of this autoimmune disorder and emphasizes the need for long-term follow-up of patients with neuroblastoma and paraneoplastic neurologic syndromes.

CASE REPORT

The patient was diagnosed with a stage 1 pelvic neuroblastoma when she was 14 months old after presenting with a 5-month history of intermittent constipation. The tumor was completely resected and had favorable biologic features. She was followed with no further therapy and remained well for 6 months, at which point she developed cerebellar ataxia and opsoclonus. Re-evaluation for neuroblastoma revealed no evidence for recurrent disease. Brain imaging and tests for onconeural antibodies were negative. CSF cellularity, protein and glucose were normal, and PCA 1 and 2 were all negative. Serum and CSF anti-Hu antibodies were positive, with titers of 1:30,720 in serum and 1:128 in CSF. Serum and CSF anti-VGKC, anti-Anna-2 and 3, anti-CRMP5, anti-VGKC, and anti-CRMP5 were negative. CSF, brain imaging, and magnetic resonance imaging (MRI) of the brain were normal. The patient improved with levetiracetam. PCR viral studies of the cerebral spinal fluid (CSF) for cytomegalovirus, enterovirus, and JC virus were negative. CSF cellularity, protein and glucose were normal, but oligoclonal bands were present. Paraneoplastic autoantibody panels in serum including Anna-2 and 3, CRMP5, anti-VGKC, PCA 1 and 2 were all negative. Serum and CSF anti-Hu antibodies were positive, with titers of 1:30,720 in serum and 1:128 in CSF.

At 7 years of age, she developed signs of precocious puberty including scant pubic hair, breast buds and sudden growth spurt. Hormonal studies showed a pubertal profile. A MRI of the brain showed a normal pituitary gland, but revealed signal change in the left temporal cortex. A fluorodeoxyglucose–positron emission tomography (FDG-PET) scan showed hypermetabolic activity corresponding to the same abnormal area. A video-electroencephalogram showed multiple episodes of subclinical seizures, arising from the left temporal lobe, and correlated with waking from sleep. The patient was started on levetiracetam. MRI scan showed a normal pituitary gland, but revealed signal change in the left temporal cortex. The patient remained on prednisone at 2.5 mg/day for 1 year.

At 20 years of age, she was diagnosed with obsessive–compulsive disorder and started on fluoxetine. Steroids and IVIG were stopped after 3 years of therapy. For the next 2 years, she remained well with mild motor delay and tremor. Thereafter, her anxiety worsened and she developed multiple symptoms of depression. The etiology of the anxiety was not clear. However, it may have been a sequela of the OMS or an initial symptom of her limbic encephalitis. She was re-started on prednisone 2 mg/kg/day. The anxiety improved, and the steroids were weaned after 2 weeks, and the patient remained on prednisone at 2.5 mg/day for 1 year.

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Conflict of interest: Nothing to declare.

*Correspondence to: Susan L. Cohn, MD, Department of Pediatrics, University of Chicago, Chicago, IL 60637. E-mail: scohn@peds.bsd.uchicago.edu

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CSF. Another evaluation for recurrent neuroblastoma was negative. Months later, clinical seizures increased in frequency. Due to the high anti-Hu antibody titer, a diagnosis of a new paraneoplastic syndrome with limbic encephalitis was made and prednisone 2 mg/Kg/day and monthly IVIG 1 gm/kg/dose were initiated. Carbamazepine was added to levetiracetam, but the seizures remained poorly controlled. Because of radiographic progression of the T2 changes in the temporal lobe, a biopsy was obtained in combination with grid implantation for seizure localization. In an effort to control the persistent seizures, resection of a portion of the left temporal lobe and an amygdalo-hippocampectomy was performed. The histologic findings included reactive astrogliosis, patchy areas of microglial infiltrates and marginal gliosis (Fig. 2). Following the surgery, the patient’s seizure activity persisted but with decreased frequency and severity. Repeat serum anti-Hu antibody titers remained high with a value of 1:15,360. Given the poor response to steroids and IVIG, rituximab was administered at 375 mg/m²/week for four doses, with improvement of her seizure activity. Soon after rituximab therapy, anti-Hu antibody titers decreased to 1:3,840 in serum and 1:64 in the CSF. Despite the reduction in antibody titers, she continues to have numerous seizures each day.

**DISCUSSION**

OMS, the most frequent paraneoplastic syndrome in childhood, remains a treatment challenge. There is no standard management and long-term neurological sequelae are reported in 70–80% of the patients [1,6]. Various immunomodulatory therapies have been used including steroids, IVIG, cyclophosphamide, and, more recently, rituximab [1]. Although many children initially respond, each treatment approach is associated with significant

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**Fig. 1.** Brain MRI: (A,B) coronal and axial views show increased FLAIR signal involving the left hippocampus. C: Fluorodeoxyglucose-PET scan showing area of hypermetabolism in the left hippocampus.

**Fig. 2.** A: H&E stained histologic sections show marginal gliosis and reactive astrogliosis. No neoplastic infiltrate was found. B: GFAP staining highlights the presence of uniformly spaced reactive astrocytes. C: CD163 labeling highlights the presence of patchy microglial cell clusters.

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toxicity, and relapses frequently occur when the immunosuppression is decreased [2]. The impact of specific treatment strategies on neurologic outcome remains controversial. However, there is some evidence that chemotherapy may decrease the severity of long-term neurologic deficits [3].

In our patient, OMS developed 6 months after the child underwent a complete resection of her locoregional neuroblastoma. OMS more commonly antedates the diagnosis of neuroblastoma, offering an opportunity for early detection of this neoplasm [2]. Similar to other reported cases of neuroblastoma and OMS, our patient had frequent relapses of her neurologic symptoms when immunosuppression was weaned. However, it is extremely unusual for a child to develop a second classic paraneoplastic neurologic disorder, limbic encephalitis, 6 years following the initial diagnosis of neuroblastoma and OMS.

Limbic encephalitis is an inflammatory process that is mediated by anti-neural autoantibodies and cytotoxic T-lymphocytes that cause neurologic damage [4]. Anti-Hu associated limbic encephalitis is largely observed with adult malignancies including small cell lung cancer (SCLC), Hodgkin’s lymphoma, testicular cancer, and breast cancer [4,7]. Only two cases of limbic encephalitis associated with neuroblastoma have been reported, and neither of these had prior OMS. One patient was a 12-year-old male with a pelvic neuroblastoma and the other was a 23-year-old woman with an abdominal neuroblastoma [8,9]. In both cases limbic encephalitis preceded the diagnosis of the tumor and was associated with anti-Hu antibodies. Neurologic symptoms can precede the diagnosis of the neoplasm or more rarely, as in our patient, develop after diagnosis and treatment. Neuropsychiatric symptoms such as anxiety, depression, delirium, short-term memory deficits, seizures, dementia, and hypothalamic dysfunction with endocrine abnormalities have been reported. Retrospectively, our patient’s anxiety and precocious puberty were probably initial symptoms of limbic encephalitis. Brain MRI reveals abnormalities in the medial temporal lobes in T2 or FLAIR sequences, and these abnormalities may be hypermetabolic by FDG-PET scan. Electroencephalogram usually shows uni- or bilateral temporal lobe epileptic discharges. Pleocytosis in the CSF is common as these abnormalities may be hypermetabolic by FDG-PET scan. Treatment consists of immunotherapy, and in cases with coincident malignancies, specific antitumor therapy [5]. If no tumor is found at the time of diagnosis of the limbic encephalitis, as in our patient, frequent tumor re-evaluations have been recommended for at least 3 years. Irrespective of treatment, partial neurologic recovery has been seen in less than 40% of patients [5].

Our patient had characteristic neuropsychological symptoms in addition to typical MRI, FDG-PET, EEG findings, high serum and CSF anti-Hu titers, and positive oligoclonal bands. Anti-Hu antibodies target the intracellular antigen Hu, and are one of the most well-recognized paraneoplastic onconeural antibodies. The presence of the anti-Hu antibody is associated with a worse prognosis, with neurologic improvement in only 5–7% of the cases [14].

Our patient’s limbic encephalitis symptoms did not respond to steroids and IVIG. Rituximab has been used in small numbers of patients, and some responses have been reported [13,14]. The anti-Hu titers decreased in our patient after treatment with rituximab, and her symptoms have improved somewhat with decreased frequency and severity of seizure activity. However, the pathogenic role of onconeural antibodies is not fully understood. Due to the rarity of paraneoplastic syndromes and coincident neuroblastoma, international collaboration will be needed to conduct clinical trials evaluating the efficacy of treatment strategies.

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