Excessive Blinking and Ataxia in a Child With Occult Neuroblastoma and Voltage-Gated Potassium Channel Antibodies

abstract
A previously healthy 9-year-old girl presented with a 10-day history of slowly progressive unsteadiness, slurred speech, and behavior change. On examination there was cerebellar ataxia and dysarthria, excessive blinking, subtle perioral myoclonus, and labile mood. The finding of oligoclonal bands in the cerebrospinal fluid prompted paraneoplastic serological evaluation and search for an occult neural crest tumor. Antineuronal nuclear autoantibody type 1 (anti-Hu) and voltage-gated potassium channel complex antibodies were detected in serum. Metaiodobenzylguanidine scan and computed tomography scan of the abdomen showed a localized abdominal mass in the region of the porta hepatis. A diagnosis of occult neuroblastoma was made. Resection of the stage 1 neuroblastoma and treatment with pulsed corticosteroids resulted in resolution of all symptoms and signs. Excessive blinking has rarely been described with neuroblastoma, and, when it is not an isolated finding, it may be a useful clue to this paraneoplastic syndrome. Although voltage-gated potassium channel complex autoimmunity has not been described previously in the setting of neuroblastoma, it is associated with a spectrum of paraneoplastic neurologic manifestations in adults, including peripheral nerve hyperexcitability disorders.

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ABBREVIATIONS
ANNA-1—antineuronal nuclear autoantibody type 1
CSF—cerebrospinal fluid
OCB—oligoclonal band
OMS—opsoclonus-myoclonus-ataxia syndrome
VGKC—voltage-gated potassium channel

Dr Allen was involved in the clinical care of the patient, wrote the first and edited drafts of the manuscript, as well as editing the accompanying video; Dr McKeon was involved in interpreting the paraneoplastic antibody screen, and in editing and revising the manuscript; Dr O’Rourke was involved in the clinical care of the patient and in making the video; Dr O’Meara was the consultant supervising the oncological care of the patient and in editing the manuscript; Prof King was the consultant involved in the patient’s care, responsible for diagnosis, and edited and supervised the manuscript construction; and all authors have read and approved this final version of the manuscript.

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Paraneoplastic neurologic disorders can cause neuronal degeneration in any part of the nervous system and are likely cytotoxic T cell mediated in some and antibody mediated in others. The prototypic neurologic disorder associated with childhood neuroblastoma (usually ganglioneuroblastoma) is opsoclonus-myoclonus syndrome (OMS). Apart from OMS, patients with neuroblastoma have occasionally presented with other paraneoplastic neurologic disorders, which include encephalomyelitis, Lambert-Eaton myasthenic syndrome, hypothalamic syndrome, and excessive blinking. However, excessive blinking has been described in only 2 other children with neuroblastoma, in which dopamine excess or increased dopaminergic receptor sensitivity was the proposed mechanism.

Antineuronal nuclear autoantibody type 1 (ANNA-1 or anti-Hu), most notably associated with peripheral neuropathy in adults with small-cell lung carcinoma has also been detected in OMS and brainstem encephalitis in association with neuroblastoma in children. More recently, antibodies targeting voltage-gated potassium channels (VGKC) have been identified in adults with various paraneoplastic and nonparaneoplastic neurologic disorders. The phenotypes classically associated with VGKC complex autoimmunity include neuromyotonia, Morvan fibrillary chorea, seizures, limbic encephalitis, and dysautonomia, but they also include peripheral nerve hyperexcitability, myoclonus, neuropathies, myelopathy, and various movement disorders. There are few data regarding VGKC complex antibody-related disorders in children. Recently, they have been identified in a small number of children with limbic encephalitis, status epilepticus, focal epilepsy, movement disorders, and developmental regression. Neoplasm has been reported in up to 33% of adults seropositive for VGKC complex antibodies, but it is distinctly uncommon in children.

A 9-year-old girl with neuroblastoma and a paraneoplastic syndrome of excessive blinking and ataxia with coexisting serum ANNA-1 and VGKC antibodies is reported. Preliminary features of this case were recently presented in a small series of children with VGKC complex autoimmunity.

**PATIENT PRESENTATION**

A 9-year-old previously healthy caucasian girl presented with a 10-day history of progressive unsteadiness of gait, poor balance when dancing and ice skating, indistinct speech, and clumsiness of fine hand movements. In the preceding 2 months, she had reduced appetite, mild weight loss, and emotional lability with mood swings. Neurologic examination showed mild cerebellar ataxia, cerebellar dysarthria, and intention tremor. There was excessive, repetitive blinking upon eye closure at a rate of ~120/minute (age normal ~10/minute) and intermittent subtle perioral myoclonus. Excessive blinking was not noticed by the family before hospitalization. The patient showed mild cerebellar ataxia, mild weight loss, and emotional lability with mood swings. Neurologic examination showed mild cerebellar ataxia, cerebellar dysarthria, and intention tremor. There was excessive, repetitive blinking upon eye closure at a rate of ~120/minute (age normal ~10/minute) and intermittent subtle perioral myoclonus.

**FIGURE 1**

Metaiodobenzylguanidine scan demonstrating abnormal uptake in the region of the celiac trunk (arrow) 48 hours postinjection. Pathologic examination revealed neuroblastoma.
logic examination revealed neuroblastoma.

Posterior to the porta hepatis (arrow). Pathologic evaluation of tumor.

The patient is neurologically normal at 2.5-year follow-up, without recurrence of tumor. Within 1 month, all neurologic signs had completely resolved, including the subtle excessive blinking with- out opsoclonus or limb myoclonus. The patient is neurologically normal at 2.5-year follow-up, without recurrence of tumor.

**DISCUSSION**

In this 9-year-old girl, neuroblastoma diagnosis was preceded by a paraneoplastic neurologic disorder characterized by mood alteration, cerebellar ataxia and dysarthria, perioral myoclonus, and excessive blinking without opsoclonus or limb myoclonus. The presence of OCBs in CSF and the subacute onset prompted a search for an underlying paraneoplastic process such as an occult neuroblastoma or ganglioneuroblastoma.

The mean rate of spontaneous blinking increases from 2/minute in early infancy to 10/minute at the end of the first decade. In a prospective study of 99 children with excessive blinking, Coats et al 14 found that most children had benign and/or self-limiting ophthalmologic conditions. Although there was a history of neurologic disease in 22%, this was not causally related to the excessive blinking in most. Although cerebellar ataxia and OMS are well-recognized paraneoplastic disorders accompanying neuroblastoma, excessive blinking has been reported in only 2 other children with this disorder. Ramadan et al 16 reported repetitive blinking in a 3-year-old boy 1 year before ganglioneuroblastoma diagnosis, whereas Maeoka and Maegaki 7 identified a 13-month-old girl with hyperexcitability of the blink reflex, OMS, and neuroblastoma. In isolated excessive blinking, in the absence of unexplained neurologic symptoms or progression of the blinking (as in the recent case of a boy with juvenile Huntington disease), 15 an underlying neurologic disorder is unlikely. However, it must be noted that the boy with neuroblastoma described by Ramadan et al had excessive blinking for 1 year before neuroblastoma diagnosis, and, apart from mild speech and motor delay, he did not have any specific signs, having had pediatric ophthalmology, neurology, psychology, and behavioral evaluations. The blinking was resolving at the time of diagnosis and resolved completely after treatment. 6

As is frequently the case in paraneoplastic neurologic disorders, our patient had a multifocal presentation that defied 1 unique neurologic localization. The anatomic regions pertinent to this case likely include the brainstem reticular formation and/or the pontine blink premotor area and facial nucleus (excessive blinking), cerebral cortex (mood alteration and myoclonus), and the cerebellum (ataxia and dysarthria). In both previously described patients with neuroblastoma and excessive blinking (increased blink reflex in one), urinary catecholamine metabolites were elevated (not observed in our patient), and the mechanism proposed was neuronal hyperactivity in the brain-stem reticular formation possibly due to oversecretion of dopamine or increased sensitivity of dopaminergic receptors. More recently, Yonekawa et al 16 identified a boy with OMS and hyperexcitability of the blink reflex (but without neuroblastoma), postulating hyperexcitability in the pontine blink premotor area and facial nucleus as a potential mechanism. Autoantibody data were not presented in these reports.

The exact mechanism of immune-mediated neural dysfunction in this patient is unknown. ANNA-1 is a well-characterized onconeural antibody, and, although it is not pathogenic, it is rather a marker of cytotoxic T-cell-mediated neurologic injury. VGKC complexes, on the other hand, are plasma membrane proteins and thus may become dysfunctional when targeted directly by pathogenic antibodies. VGKC complexes are critical for the regulation of neuronal excitation, axonal conduction, and neurotransmitter release. VGKC complex autoimmunity has recently been implicated in a broad spectrum of neurologic disorders in adults, including ataxia, limbic encephalitis, seizures, and hyperexcitability manifestations. Thus, the authors hypothesize that the excessive blinking seen in this patient may have been mediated by an antibody targeting the VGKC or a related complexed protein such as CASPR2 or LGI1, which have recently been described as the antigenic target in some patients seropositive for VGKC complex antibodies.
In the present case, serum antibody testing revealed ANNA-1 and VGKC complex antibodies. In adults, ANNA-1 and VGKC complex antibodies have been reported to coexist in small-cell lung carcinoma, another neoplasm of neuroendocrine cell lineage, but coexistence in childhood neoplasia has not been reported. ANNA-1 has also been described in neuroblastoma with and without the OMS but not in patients with excessive blinking. In general, cytotoxic T-cell-mediated paraneoplastic neurologic disorders do not respond well to immunotherapies such as corticosteroids. In contrast, patients with VGKC complex antibody-mediated neurologic disorders frequently improve with immunotherapy (including antibody-depleting modalities such as plasma exchange). It is also possible that there are other, as yet unidentified, antigenic targets in the VGKC complex.

CONCLUSIONS
Occult neuroblastoma (and related neoplastic syndrome) may present subacutely with a range of nonspecific neurologic symptoms, in addition to the well-known OMS or dancing eyes-dancing feet syndrome. This case draws attention to repetitive blinking, rarely reported in neuroblastoma, but which may be part of the neurologic complex and a useful clue to an occult paraneoplastic process, when associated with other neurologic symptoms. In addition, the case highlights useful and emerging ways of detecting paraneoplastic autoimmunity, including testing for the presence of CSF OCBs (the diagnostic importance of which has not been emphasized in the pediatric literature). VGKC complex (and other) antibodies are associated with a variety of neurologic manifestations in adults but have only recently been studied in children. As in adults, VGKC complex antibody testing (on serum) should be part of a comprehensive serological and CSF evaluation for investigating unexplained subacute neurologic disorders in children. Such cases should include those in whom hyperexcitability occurs, but presentations including epilepsy, suspected limbic encephalitis, myopathy, movement disorders, ataxia, and acute/subacute onset developmental regression in a previously healthy child, have all been described. Although VGKC antibodies have not been described in neuroblastoma, in adults, VGKC autoimmunity appears to define immunoresponsive conditions. The child in this report was treated early with adjuvant immunotherapy and has had an excellent outcome to date at 2.5 years follow-up, emphasizing the importance of recognizing and treating early, this emerging group of autoimmune neurologic disorders in children.

REFERENCES


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