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 hepatitis. 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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Authors: Nicholas M. Allen, MBCh, MD, Andrew McKeon, MBCh, MD, Declan J. O’Rourke, MBCh, Anne O’Meara, MBCh, MD, and Mary D. King, MBCh

Department of Pediatric Neurology and Clinical Neurophysiology, Children’s University Hospital, Dublin 1, Ireland; Department of Neurology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; and Department of Paediatric Oncology, Our Lady’s Children’s Hospital, Crumlin, Dublin, Ireland

Key Words: neuroblastoma, autoimmune, excessive blinking, cerebellar ataxia, VGKC antibody

Abbreviations

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

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Address correspondence to Nicholas M. Allen, MBCh, MD, Department of Pediatric Neurology, Children’s University Hospital, Temple Street, Dublin 1, Ireland. E-mail: nicholasallen@physicians.ie

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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. Neoplasia 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. School report and academic grades remained unchanged, but difficulties with motor coordination and speech articulation had been noted by school teachers. There was no opoclonus or limb myoclonus. During the period of investigation, there was additional deterioration in behavior with refusal to undergo investigations, but the other neurologic signs were unchanged. Repetitive blinking can be observed (see Supplemental Video).

The results of the following investigations were normal: hematologic indices, complete blood cell count and smear, urea, creatinine, electrolytes, liver transaminases, ammonia, lactate, creatine kinase, quantitative plasma amino acids, vitamin B12, folate, thyroid function, copper, ceruloplasmin, and plasma metanephrines. Viral serologies were also negative. The results of urine tests, including toxicology screen, catecholamines, and organic acids, were negative. Cerebrospinal fluid (CSF) cell count, protein, glucose, culture, and viral polymerase chain reaction results were also normal. Electrophysiologic investigations, including electroencephalography and nerve conduction studies as well as MRI of the brain and spine, chest radiograph, and abdominal ultrasound examination, were all reported as normal.

Oligoclonal bands (OCBs) were detected in CSF. The CSF:serum albumin quotient was 3.3 (normal <9), indicating an intact blood-CSF barrier. CSF immunoglobulin G index was 0.77 (value >0.78 indicates increased intrathecal immunoglobulin G synthesis). Neuron-specific enolase was mildly elevated at 15 µg/L (0–12.5). Metaiodobenzylguanidine scan showed abnormal uptake in the region of the celiac trunk (Fig 1). Computerized tomography of the abdomen identified a 4-cm mass with calcification posterior to the porta hepatis suggestive of neuroblastoma (Fig 2).

Paraneoplastic serological evaluation revealed seropositivity for ANNA-1 (1:3840 [normal ≤240], detected by indirect immunofluorescence) and coexisting serum VGKC complex antibodies (0.45 nmol/L [normal ≤0.02 nmol/L, detected by radioimmunoprecipitation)

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). Patho-

ing. The patient is neurologically normal within 1 month, all neurologic signs had completely resolved, including the subtle excessive blinking with-

terial formation and/or the pontine 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 blink-
ing (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 in-

creased sensitivity of dopaminergic receptors.6,7 More recently, Yonekawa et al16 identified a boy with OMS and hyperexcitability of the blink reflex (but without neuroblastoma), post-

ulating hyperexcitability in the pontine blink premotor area and facial nucleus as a potential mechanism. Autoanti-

body 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.17 VGKC complexes, on the other hand, are plasma membrane proteins and thus may become dysfunc-
tional when targeted directly by patho-

genic antibodies. VGKC complexes are critical for the regulation of neuronal ex-

citability, axonal conduction, and neuro-

transmitter release.18,19 VGKC complex autoimmunity has recently been impli-
cated in a broad spectrum of neurologic disorders in adults, including ataxia, limbic encephalitis, seizures, and hyper-

excitability manifestations.9,10 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 re-
cently been described as the antigenic target in some patients seropositive for VGKC complex antibodies.20,21

FIGURE 2
Computed tomography scan of the abdomen demonstrating a 4 × 4 cm mass with calcification posterior to the porta hepatis (arrow). Patho-

logic examination revealed neuroblastoma.

DISCUSSION
In this 9-year-old girl, neuroblastoma diagnosis was preceded by a paraneo-

plastic neurologic disorder characterized by mood alteration, cerebellar ataxia and dysarthria, perioral my-

oclonus, and excessive blinking without opsoclonus or limb myoclonus. The presence of OCBs in CSF and the sub-
acute 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 inf-

nancy to 10/minute at the end of the first decade.13 In a prospective study of 99 children with excessive blinking, Coats et al14 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 disor-

der. Ramadan et al6 reported repetitive blinking in a 3-year-old boy 1 year before ganglioneuroblastoma diagno-
sis, whereas Maeoka and Maegaki7 identified a 13-month-old girl with hyperexcitability of the blink reflex, OMS, and neuroblastoma. In isolated excessive sleeping, in the absence of un-

explained 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.14 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.6 The blinking was resolving at the time of diagnosis and resolved completely after treatment.6

As is frequently the case in paraneo-

plastic neurologic disorders, our pa-

tient had a multifocal presentation that defied 1 unique neurologic localization. The anatomic regions pertinent to this case likely include the brainstem re-
ticular formation and/or the pontine
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.8 In general, cytotoxic T-cell-mediated paraneoplastic neurologic disorders do not respond well to immunotherapies such as corticosteroids.22 In contrast, patients with VGKC complex antibody-mediated neurologic disorders frequently improve with immunotherapy (including antibody-depleting modalities such as plasma exchange).9,22 It is also possible that there are other, as yet unidentified, antigenic targets in the VGKC complex.

**CONCLUSIONS**

Occult neuroblastoma (and related neural crest tumors) 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).23 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.20 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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