The origins and progression of CNS autoimmunity
Nature, nurture, and tumor

Neuroblastoma is the most common extracranial solid cancer of childhood, accounting for 15% of cancer deaths in children.1 A small proportion (up to 4%) of children with neuroblastoma develop opsoclonus-myoclonus ataxia syndrome (OMAS), a paraneoplastic autoimmune CNS disorder.2 Of note, neuroblastoma associated with OMAS is frequently of low stage, incurring a better prognosis,3 suggesting that this tumor-triggered autoimmunity may also have a protective role.

In this issue of Neurology®, Amini et al.4 describe an intriguing and complex case that provides further glimpses at this important facet of CNS autoimmunity. The case in question initially presented at age 5 with OMAS, a para-aortic neuroblastoma, and anti-Hu antibodies; the tumor was successfully treated.

Ten years later, the patient presented with a complex autoimmune CNS syndrome, with limbic encephalitis features plus opsoclonus and sensorineu-ral deafness. The tumor had recurred and mutated, now with MYCN gene amplification (having previously been negative) and chromosome 1p deletion. Further tumor therapy plus IV methylprednisolone induced a surprisingly good recovery from the neurologic illness, allowing return to full time academic education. The patient developed a further suspected autoimmune complication 1 year later (chronic intestinal pseudo-obstruction), and then had a recurrence of the CNS syndrome, which responded to corticosteroids and plasma exchange, resulting in a return to normal functioning.

In this patient, the breadth of evolving, overlapping, and relapsing nervous system features of suspected autoimmune origin, OMAS, limbic encephalitis, reversible sensorineural deafness, and pandyrsomotility syndrome (brain, ear, autonomic gut involvement) is highly unusual, although the co-occurrence of autoimmune nervous system syndromes is increasingly recognized, such as myasthenia gravis plus neuromyelitis optica and anti-NMDA receptor encephalitis plus CNS demyelination syndromes.5,6

The most interesting aspect of this case is the mutating neuroblastoma, which alongside other potential, yet unidentified, host factors is likely to have generated the diversity of autoimmune syndromes in this patient. Neural crest tumors make intellectually appealing triggers of paraneoplastic CNS disease, given the “neural-like” features of the tumor. Although there is currently little evidence of a “cell surface antibody” in the majority of patients with OMAS,7 the consistent immunotherapy responsiveness and histopathologic evidence of inflammatory infiltrate observed in neuroblastoma tumors associated with OMAS strongly support an autoimmune response both toward the tumor and also against the brain.8 Furthermore, this immuno-therapeutic tumor effect has been successfully used in treating neuroblastoma with antibodies or, more recently, engineered T cells against highly expressed tumor antigen such as disialoganglioside (GD2).9

The impressive reversal of symptoms with only modest immune suppression at each relapse in this case is more typical of that seen in cell surface antibody-associated syndromes rather than classic paraneoplastic syndromes associated with onconeural antibodies (such as anti-Hu antibodies). It is conceivable, even likely, that this patient had a reversible immunologic process (humoral or cellular) throughout the disease course that was not detectable by current standard measures or antibody assays.

The tumor mutation at the time of relapse in the patient reported by Amini et al.4 suggests that alteration of the cellular nature of the tumor is likely to have “reactivated” the paraneoplastic autoimmune CNS syndrome, by means of exposure of the host to “cryptic antigens” causing resultant loss of prior established immune tolerance, as hypothesized by the authors. This observation augments our understanding of the origins of autoimmune nervous system disease in a similar way to the recent recognition that the destructive pathology of herpes simplex virus encephalitis can provoke a secondary autoimmune response associated with anti-NMDA receptor antibodies or other cell surface antibodies,10 with the putative unifying process being the “release of previously cryptic neuronal antigens in an inflammatory milieu.”

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The careful longitudinal serum antibody analysis at presentation and through the relapsing phases of the disease in this case provides further insights into the natural history and evolution of the autoimmune process. Only anti-Hu antibodies were present throughout the clinical course, which are unusual in pediatric OMAS, and only rarely reported in children with inflammatory brain disease.\(^{11}\) Testing for a panel of cell surface antibodies was negative, and initial screening for a cell surface antibody using cultured live hippocampal neurons was negative at disease onset, although became positive in the relapsing stages of the illness over a decade after presentation. The fact that the patient only developed a potentially pathogenic cell surface antibody during the relapsing phase of disease further emphasizes the evolving nature of disease in this patient, hypothetically due to "epitope spreading" of the autoimmune response, potentially triggered by the mutating tumor. What is also intriguing is that during the early stages of disease, despite having no immunoglobulin binding to live hippocampal neurons, the patient’s serum inhibited proliferation of neuroblastoma cells, suggesting the serum contained immunoglobulin or other immune or drug factors that had direct effects on neuronal-like cells.

There are a number of approaches that could have improved our understanding of this notable case, such as longitudinal CSF testing, the use of purified immunoglobulin rather than serum testing in the pathogenic experiment, and pathologic and molecular examination of the tumor. Regardless, this thought-provoking case sheds light on the initiation and persistence of CNS autoimmunity.

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**REFERENCES**