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Letter to the Editor: New Observation

Anti-NMDA Receptor Encephalitis in a Patient with 18p Deletion Syndrome

Marlene Rong and Jennifer A. McCombe
Faculty of Medicine and Dentistry, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Chromosome 18p deletion syndrome (18p-) (OMIM#146390) is a contiguous gene deletion syndrome that results from the deletion of all or a portion of the short arm of chromosome 18. Originally described in 1963, 18p deletions are linked with cognitive impairment, holoprosencephaly, ptosis, strabismus and speech and language difficulties.[1–3]

Autoimmune disorders have been noted in around 10% of patients with 18p-, and phenotypes are variable.[2,3] Rheumatoid arthritis, autoimmune thyroid conditions, celiac disease, alopecia, psoriasis, Sjogren syndrome, lupus and vitiligo have all been reported as manifestations of 18p-.[2–4] Neurological findings have been associated with 18p- in tandem with autoimmune conditions. Movement disorders and tone abnormalities have been described, sometimes accompanied by white matter hyperintensities on brain MRI[3–5]. Seizures have also been noted in patients with 18p deletions.[3]

Neurological autoimmune conditions, however, have not been described in association with 18p deletions. We describe a 24-year-old female patient with 18p- presenting with anti-NMDA receptor (NMDAR) encephalitis. Pre-existing cognitive impairment can make the arrival at a diagnosis of anti-NMDAR encephalitis more difficult. We highlight the importance of considering neurological autoimmune disorders in patients with genetic predisposition to autoimmunity, particularly when new psychiatric or cognitive symptoms arise.

The patient is a 24-year-old white female with 18p- who was born to healthy, non-consanguineous parents. Her medical history includes congenital heart disease, with a patent ductus arteriosus closure at 6 months of age, as well as Duane syndrome. She also has a history of global developmental delay and hypothyroidism, which has been managed with levothyroxine since age 8 years. Prior to symptom onset, she graduated from a special education program, worked in hotel cleaning and participated in Special Olympics bowling. At baseline, she was interactive and verbal and had no psychiatric history.

Six months before presentation, she developed agitation and limb pain, followed by decreased appetite, visual hallucinations and abnormal speech. Over a month, she declined further, losing independence in activities of daily living (ADLs). Olanzapine and escitalopram appeared to worsen her condition. Symptoms included slurred speech, excessive sleep, fatigue, nightmares, urinary incontinence, decreased oral intake, dysphagia and eventual job loss.

CT head found ill-defined areas of subcortical white matter hypoattenuation in bilateral frontal and parietal lobes. A perivascular space was seen in the left inferior basal ganglia. She was weaned off all medications. The patient developed catatonia and movements that her mother described as "shaking and vibrating" suppressible with soothing touch.

MRI imaging revealed scattered T2/T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities in deep and subcortical white matter, with a perivenular/pericallosal distribution, bilaterally symmetrical. No significant involvement of the temporal lobes, cerebellum or brainstem was seen, though periventricular abnormalities were present (Figure 1).

Four months after symptom onset, the patient was evaluated in the emergency department due to progressive unintentional weight loss and mood changes. By this time, she demonstrated significantly diminished oral intake and could no longer perform any ADLs independently. Neurological examination revealed upper and lower extremity rigidity, cogwheeling, decreased spontaneous speech, bradykinesia and slight tremulous upper extremity movements.

An electroencephalogram found diffuse, generalized slow activity, suggesting moderate to severe encephalopathy, possibly linked to her chromosomal abnormality. No history suggested seizures. Repeat brain MRI (T1/FLAIR, T2/FLAIR, postcontrast T1) showed multiple supratentorial white matter lesions with no changes from previous imaging. Lorazepam was started for catatonia to improve reactivity and oral intake.

First lumbar puncture (LP) revealed 53 × 10 ^ 9/L white blood cell count (60% lymphocytes, 20% neutrophils, 20% monocytes) and 0.86 g/L protein. Second LP revealed 51 × 10 ^ 9/L white blood cell count, lymphocytic predominant leukocytosis (93%) with isoelectric focusing electrophoresis revealing 3 IgG bands in CSF that were not seen in serum, along with 0.59 g/L protein. The patient's CSF IgG was elevated at 0.127 g/L normal < 0.050 g/L). Note was made of additional identical bands in CSF and serum. Infectious workup, screening for high-risk paraneoplastic antibodies by immunoblot, anti-AQP4 and anti-MOG antibodies in serum were all negative. The patient was found to have "high positive" anti-NMDA in serum and CSF via cell-based assay, leading to a diagnosis of anti-NMDAR encephalitis.

Corresponding author: Jennifer A. McCombe; Email: jmccombe@ualberta.ca
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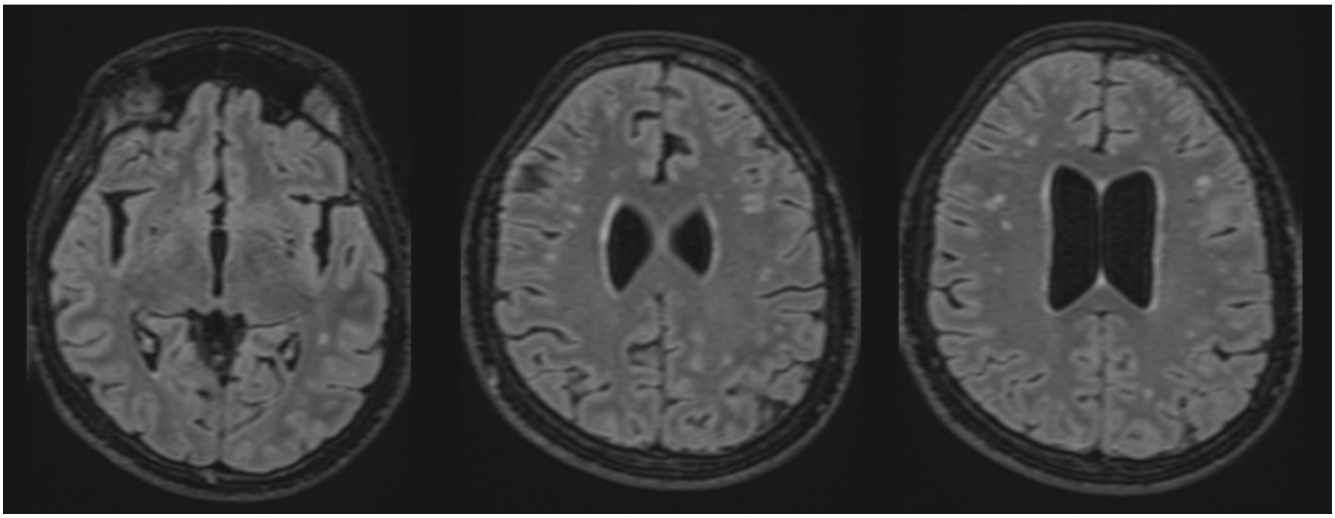

Figure 1. Nonspecific T2 fluid-attenuated inversion recovery hyperintensities noted throughout the deep white matter, some of which were subcortical in distribution.

Despite transient improvement with corticosteroids, she experienced further clinical decline, developing waxy catatonia and oral dyskinesias. Pelvic MRI was ordered to look for ovarian teratoma given the diagnosis of anti-NMDAR encephalitis, which reported two teratomas (3 and 6 mm) in her left ovary. Her right ovary was normal. She underwent a left salpingoophrectomy. Surgical pathology found unilocular mucinous fluid-filled cysts with no evidence of teratoma. Repeat treatment with methylprednisolone was initiated, along with intravenous immunoglobulin and rituximab. Over several months, the patient gradually returned to her baseline level of functioning.

Anti-NMDAR encephalitis is an immune-mediated disease marked by serum or CSF IgG antibodies against the GluN1 subunit, often linked to ovarian teratomas and herpes simplex virus.[6] Diagnosis is challenging due to variable presentation. Psychiatric or behavioral symptoms appear in 90% of cases, often mimicking primary psychiatric illness.[7] Neurological complications, including movement abnormalities, dysautonomia, hypoventilation and seizures, typically emerge over weeks to months.[7] In cognitively impaired patients, new psychiatric symptoms warrant high suspicion if prior regression was absent.

Although anti-NMDAR encephalitis is commonly linked to human leukocyte antigen alleles, other genetic risk factors remain uncertain.[7] The *PTPN2* gene, located on chromosome 18p, is known to contribute to autoimmunity.[2] It is possible that deletions affecting this region increase susceptibility to anti-NMDAR encephalitis, warranting further genetic investigation.

Approximately 80% of anti-NMDAR encephalitis patients recover with immunotherapy and, if present, tumor removal.[8] Delayed treatment can lead to lasting cognitive deficits, making early diagnosis essential.[7] This case links 18p- with autoimmune neurological conditions, specifically anti-NMDAR encephalitis. Patients with a genetic predisposition to autoimmunity should be evaluated for autoimmune neurological disease when presenting with suggestive symptoms, even when confounded by cognitive impairment or imaging features attributable to their genetic condition.

Data availability statement. De-identified data may be provided upon reasonable request.

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