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Mercury Induced Autoimmunity: A Case of CASPR2/LGI1 Autoimmune Encephalitis in a 14-Month-old

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Abstract

Contactin-associated protein-like 2 (CASPR2) autoantibodies are among those associated with several syndromes with effects on both the central and peripheral nervous systems including neuropathy and encephalitis and is most commonly seen in middle-aged to elderly males. We present a case of autoimmune encephalitis in a 14-month-old female presenting with altered mental status, refusal to bear weight, and hypertension in the setting of mercury exposure. This is the youngest reported case of CASPR2/LGI1/VGKC antibody associated autoimmune encephalitis stimulated by mercury exposure.

Keywords

autoimmune encephalitis, mercury, heavy metal, neuropathy

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Introduction:

Contactin-associated protein-like 2 (CASPR2) is a transmembrane cell adhesion protein crucial for localizing voltage-gate potassium channels (VGKC) allowing axon formation and stability.[1–3] CASPR2 autoantibodies disrupt axonal potassium currents causing variable clinical syndromes effecting both the central and peripheral nervous systems (CNS/PNS). Antibodies to leucine-rich glioma inactivated 1 (LGI1) and neuronal (V-G) K + channels (VGKC) have been implicated in similar syndromes.[2,3] The clinical spectrum of CASPR2/LGI1/VGKC autoimmunity includes limbic encephalitis (LE), Morvan syndrome, peripheral nerve hyperexcitability/neuromyotonia (Isaacs syndrome), cerebellar syndromes, weakness/hemiplegia, neuropathic pain, and autonomic dysfunction.[1,3–5] Pediatric patients with anti-CASPR2 encephalitis more commonly have psychiatric symptoms compared to cognitive disturbances, sleep disorders, and epilepsy mainly described in adults, and paraneoplastic causes are rare.[1,6]

Acute mercury toxicity has numerous neurologic, gastrointestinal, and pulmonary symptoms. However even subclinical mercury exposure has been linked to autoimmune disease including CASPR/LGI1/VGKC syndromes, with multiple mechanisms for this pathogenesis proposed.[7,8] Pediatric data is evolving, but our patient's deviation from typical patterns of autoimmunity supports the potential for mercury's causative role in inducing this rare syndrome. To the authors' knowledge, this is the youngest documented case of mercury-induced limbic encephalitis.

Case Description:

A healthy, developmentally typical 14-month-old Caucasian female presented for aproximately2–3 weeks of worsening irritability and fatigue, refusal to bear weight, diarrhea, and regression in both gross motor and language development, most notably loss of words and gait. Her initial neurologic exam was non-focal, and she was discharged from the ER diagnosed

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by respiratory viral panel PCR with rhinovirus/enterovirus infection. However, over 3 days symptoms worsened with ongoing encephalopathy, diffuse motor weakness and sensory loss, hypokinetic movements, lower extremity areflexia, and hypertensive emergency. Extensive work-up including MRI neuroaxis with and without contrast, echocardiogram, renal ultrasound, and CT chest abdomen and pelvis with and without contrast were without findings. Approximately 48 h of long-term video EEG was normal aside from rare background slowing suggesting a mild encephalopathy but no seizures or epileptiform discharges. Two lumbar punctures one week apart had normal cell counts, glucose, and protein. Inflammatory markers, endocrinology studies, and metabolic, infectious, and nutritional labs were normal. Autoimmune encephalitis and paraneoplastic panels from serum and cerebrospinal fluid were also sent.

Blood pressure management initially required nicardipine infusion and ultimately daily anti-hypertensives. Her exam was consistent with severe peripheral neuropathy and encephalopathy, so she was treated empirically with a 5-day course of high dose intravenous (IV) steroids with mental status improvement. This prompted treatment with 2 g/kg of intravenous immunoglobulin (IVIg) and a steroid taper. Her exam further improved with greater engagement, bearing weight, and increasing movement speed.

Heavy metal testing later showed elevated mercury level of 19.4 uG/L ($\leq$ 10.0 uG/L), confirmed with 24-h urine collection elevated at 52.1 uG/L (0.0-5.0 uG/L). Serum autoimmune encephalitis panel was positive for anti-LGI1 without a reported titer, anti-CASPR2 at a titer of 1:100 (reference value negative),, and GAD65 0.11 ($\leq$ 0.02 nmol/L).The serum paraneoplastic panel was positive for neuronal (V-G) K + channel 0.40 nmol/L ($\leq$ 0.02 nmol/L). CT scans of her chest, abdomen, pelvis, and neck revealed no masses. Genetic testing revealed four heterozygous mutations in SCN9A, TSC1, and two in NOD2 all thought to be noncontributory. After 2 weeks she had a strong but incomplete response to steroids and IVIg, with improved motor slowing but continued weakness, refusal to bear weight consistently, and residual sensory deficits. Given persistent disability, the decision was made to initiate immunotherapy with Rituximab as it had been used with success in prior case reports. The infusion was administered approximately 1 month from initial presentation.

She was discharged to acute rehabilitation on labetalol for continued blood pressure management, with a second Rituximab infusion two weeks later. At outpatient clinic follow-up at 2.5 and 6 months from initial presentation, she was at her baseline exam and mental status, and was once again making developmental progress. The home was found clear of exposure sources, and lab error made repeat mercury levels unavailable at time of manuscript publishing.

Discussion/Conclusion:

The constellation of encephalopathy, peripheral neuropathy, and hypertensive emergency in the setting of CASPR2, LGI1, and VGKC autoantibodies positivity and response to immunotherapy in our patient supports the diagnosis of Morvan syndrome, although she demonstrated little neuromyotonia. The most striking feature in younger patients is severe, refractory hypertension without alternate explanation.[5] Double positivity for CASPR2/LGI1 antibodies is reported more frequently in adult patients, and their co-occurrence has been proposed as a specific immunologic marker and pathophysiologic mechanism for Morvan syndrome.[5,8]

In addition to the presence of CASPR2/LGI1/VGKC serum antibodies in our patient, mercury levels were elevated in both the urine and serum. While levels near environmental norms may be difficult to interpret in some clinical scenarios, mercury exposure has been suggested to induce autoimmune dysfunction through direct and indirect mechanisms in combination with environmental and genetic factors.[9] Interpretation may rely on the clinical scenario and her age, lack of neoplasm or family history of autoimmunity, and her triple-positivity of these rare autoantibodies suggests likely mercury induced autoimmunity.[8] As of 2020, a total of 41 cases of mercury-induced Morvan syndrome have been reported ranging from 10 to 70 years of age, making our patient the youngest case of CASPR2/LGI1/VGKC associated autoimmune encephalitis triggered by mercury exposure.[8]

Therapies used in mercury-induced Morvan syndrome included, chelation therapy, corticosteroids, and/or IVIg with gradual resolution of symptoms within 6 months in most patients.[7,8] Our patient's symptoms were diffuse and lacked other organ involvement characteristic of primary mercury toxicity so chelation therapy was not administered. Furthermore, given incomplete response to steroids and IVIg, our patient was treated with Rituximab, previously reported to promote complete resolution of symptoms when glucocorticoids and IVIg alone were unsuccessful.[8] Her striking response after Rituximab is consistent with the findings that case report, and counter to the protracted course seen in other patients who did not receive Rituximab therapy. However, in many other autoimmune conditions where Rituximab is frequently used, responses are typically over weeks to months as well, and more data is needed to confirm Rituximab's benefit in these cases. The source of our patient's elevated mercury level remains unknown, and repeat levels were not able to be obtained. Persist recovery may be explained by the fact the family moved homes shortly after her hospitalization, limiting an unknown exposure source, or due to the ongoing protective effects of rituximab.

While rare, this presentation of mercury induced autoimmune encephalitis in a toddler highlights the importance of a thorough neurologic physical exam. Key findings like the sensory deficits only noted on exam can help narrow a broad differential diagnosis, expedite evaluation and treatment, and ultimately improve prognosis and minimize long term complications.

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Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series. Verbal informed consent was obtained from a legally authorized representative(s), the patient's parents, for anonymized patient information to be published in this article.

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