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DELAYED DIAGNOSIS OF EXTRAOVARIAN TERATOMA IN RELAPSING ANTI-NMDA RECEPTOR ENCEPHALITIS

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Anti-NMDA receptor (NMDAR) encephalitis is an autoimmune-mediated disease with a wide range of neurologic and psychiatric symptoms including psychosis, cognitive deficits, movement disorders, and epileptic seizures.^{1,2}

Up to 50% of patients have tumors, mainly ovarian teratomas.^{1,2} We describe a 15-year-old girl with a relapsing course of severe and prolonged NMDAR encephalitis in whom an infrathyroidal teratoma was identified with FDG-PET-CT 14 months after symptom onset.

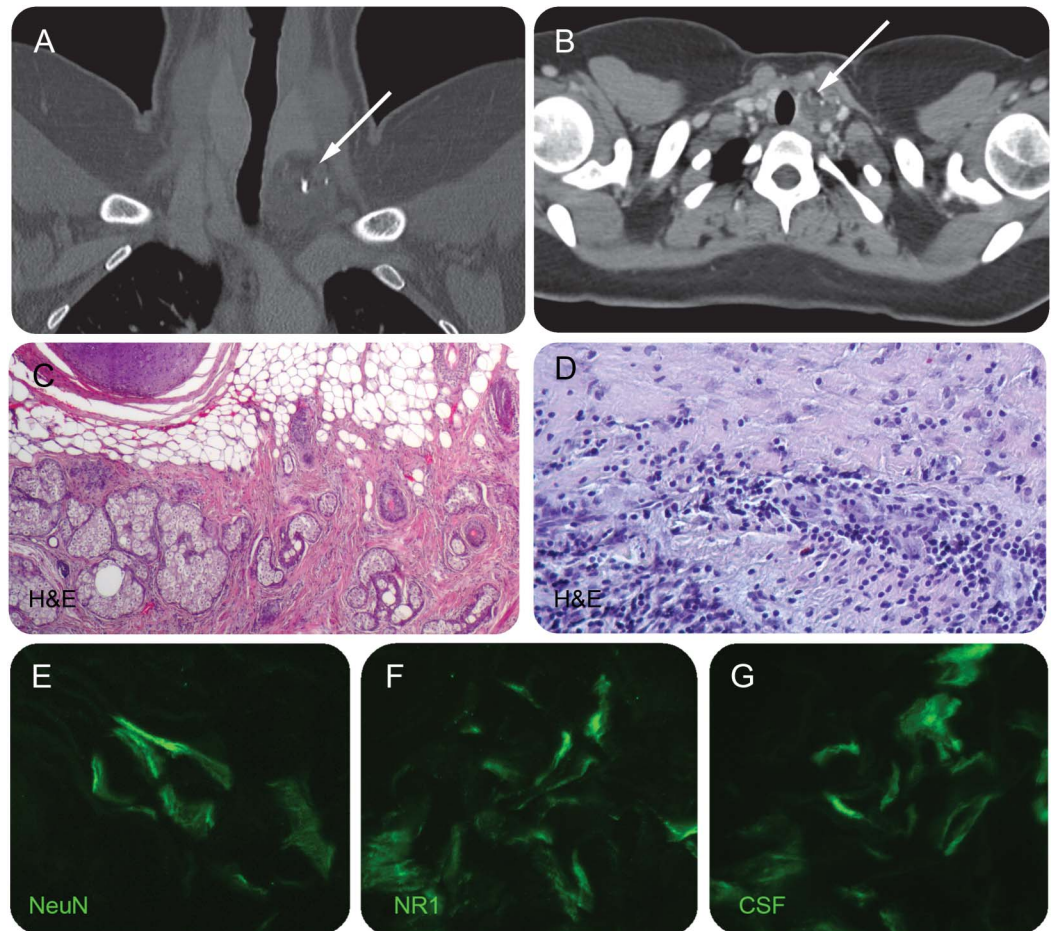
Case report. A 15-year-old girl had been admitted to a local hospital due to ongoing fever and headache as well as abnormal behavior and irritability in March 2014. Subsequently she developed psychosis with visual hallucinations, delirium, fluctuating levels of consciousness, and epileptic seizures as well as dysautonomia with bradycardia. She was referred to our intensive care unit in April 2014 due to 4 episodes of cardiac arrest requiring a transient pacemaker and mechanical ventilation. Cerebral MRI was normal and CSF analysis showed no evidence of viral or bacterial infection. After she tested positive for high-titer NMDAR antibodies (Abs) in serum (immunoglobulin G [IgG] 1:320, immunoglobulin A [IgA] 1:100) and CSF (IgG 1:32, IgA 1:32), IV high-dose glucocorticosteroid and immunoglobulin therapy was initiated. She slowly started to improve after escalating immunotherapy with plasma exchange (PLEX) and subsequent treatment with rituximab (2×1 g). Ultrasound and MRI scan of the pelvis showed no evidence of ovarian teratoma. NMDAR Abs dropped significantly in serum and CSF after PLEX, but fluctuated over time. She experienced a relapse 2 months later with increasingly aggressive behavior and excessive hyperphagia with weight gain. Another PLEX was performed in July 2014 and rituximab continued with another cycle of 500 mg in December 2014. She improved thereafter and was discharged to a rehabilitation hospital. Reassessment in June 2015 still showed significant cognitive dysfunction and NMDAR Abs were again clearly detectable in serum (IgG 1:100, IgA 1:10) and

CSF (IgG 1:3.2, IgA 1:10). Therefore, another diagnostic workup for possible tumor with whole-body FDG-PET-CT was performed and revealed a cystic mass with calcifications and fatty tissue inferior to the left thyroid gland suggesting teratoma (figure, A and B). Serum levels of β -human chorionic gonadotropin (β -HCG) and α -fetoprotein (AFP) were unremarkable. Diagnosis of teratoma was confirmed histopathologically after tumor removal without evidence of malignancy (figure, C and D). Therapy with rituximab was repeated and the patient was able to return to school.

Paraffin-embedded teratoma tissue was stained with CSF of a patient with high-titer NMDAR antibodies after fluorescence labeling of immunoglobulins.² The teratoma contained neuronal elements detectable with immunohistochemistry for the neuronal protein NeuN, which were also immunopositive when probed with a commercial anti-NR1 antibody and the labeled CSF on adjacent sections (figure, E–G).³ Written informed consent was obtained from the parents according to the Declaration of Helsinki, and immunologic blood and CSF investigations approved by the local ethics committee.

Discussion. The association of NMDAR encephalitis with teratomas is well-known, usually found in the ovaries or testis. It has become common practice to restrict the exclusion of a tumor in women with NMDAR encephalitis to ultrasound and MRI scans of the pelvis as extragonadal teratomas are exceptionally rare and FDG-PET-CTs are performed restrictively to avoid radiation in female adolescents. Extragonadal teratomas may occur in the head, neck, thyroid, and mediastinum.⁴ A large mediastinal teratoma was reported in a male adolescent with severe and prolonged NMDAR encephalitis who started to improve after resection of the teratoma and with immunosuppressive therapy.⁵

Serum levels of β -HCG and AFP may serve as additional disease markers indicating the presence of an undetected teratoma, although they may not be evident at diagnostic workup, as in our case. Recently the presence of CSF IgA NMDAR Abs has been described as a potential biomarker for ovarian teratomas.⁶ Indeed, positive testing of CSF IgA NMDAR Abs together with persisting cognitive dysfunction prompted us to perform an extensive tumor search including FDG-PET-CT.



(A, B) CT scan shows a tumor with calcifications and fatty tissue inferior to the left thyroid gland (arrows). (C) Histologic analysis reveals a mature teratoma containing cartilage, fatty tissue, and hair follicles. (D) Some areas contained dense lymphocyte infiltrates, which are common in NMDA receptor encephalitis-associated teratomas.³ (E) Atypical neuronal elements in the teratoma detected with NeuN immunohistochemistry. (F, G) A similar neuronal staining was seen when sections were incubated with either a commercial anti-NR1 antibody (F) or CSF of a patient with high-titer NMDAR antibodies after immunoglobulin fluorescence labeling (G). For this, CSF was conjugated with N-hydroxysuccinimide-ester of Alexa Fluor 594 (Life Technologies, Carlsbad, CA) as described previously.²

Rapid detection of a teratoma is important since clinical improvement is linked to removal and prevents ongoing disease activity as well as relapses.⁷ In fact, only after surgical removal was sustained improvement of NMDAR encephalitis-associated symptoms achieved in our patient. The demonstrated binding of CSF immunoglobulins to neuronal elements in the teratoma suggests that this extraovarian tumor triggered and sustained the NMDAR encephalitis.

This case illustrates 2 important points in NMDAR encephalitis: (1) exclusion of ovarian teratomas with MRI or ultrasound is not sufficient in some patients as extragonadal teratomas may occur; and (2) tumors should be considered in patients with a prolonged relapsing disease course and persistent CSF NMDAR antibody titers, including the IgA isotype.

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