CASE REPORT

Unusual case of anti-N-methyl-D-aspartic acid-receptor (NMDA-R) encephalitis and autoimmune polyglandular syndrome (APS)

Simona Frunza-Stefan,[1] Hilary B Whitlatch,[1] Gautam G Rao,[2] Rana Malek[1]

[1]Department of Medicine, Division of Endocrinology, Diabetes and Nutrition, University of Maryland Medical Center, Baltimore, Maryland, USA
[2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Maryland Medical Center, Baltimore, Maryland, USA

Correspondence to
Dr Simona Frunza-Stefan, simonastefan@gmail.com, sfrunza@som.umaryland.edu

Accepted 13 April 2018

SUMMARY

Anti-N-methyl-D-aspartic acid-receptor (NMDA-R) encephalitis is a novel disease discovered within the past 10 years. It is an autoimmune disease (AD) that has been associated with other ADs, such as Graves' disease. However, association with autoimmune polyglandular syndromes (APS) has not been previously described.

A 58-year-old woman presented with altered mental status and an 8-month history of weight loss, apathy and somnolence. Laboratory evaluation confirmed Graves' disease with thyrotoxicosis and type 1 diabetes mellitus. Despite treatment, she continued to have a fluctuating mental status. Further diagnostic evaluation included an abdominal MRI that showed a cystic lobular left adnexal mass. Serum anti-NMDA-R antibodies were positive, raising concern for NMDA-R encephalitis. Bilateral salpingo-oophorectomy was performed, with pathology consistent with cystadenofibroma. She had a favourable recovery with marked clinical improvement. Anti-NMDA-R antibodies were negative 2 months following surgery. The concomitant occurrence of APS and anti-NMDA-R encephalitis suggests a shared mechanism of autoimmune pathophysiology.

BACKGROUND

Anti-N-methyl-D-aspartic acid-receptor (NMDA-R) encephalitis is a rare autoimmune antibody-mediated form of limbic encephalitis (LE) that presents with a combination of psychiatric, neurological and autonomic features.[1] Reported immunological triggers of this autoimmune encephalopathy include benign tumours, malignancy and preceding infection. Autoimmune diseases (ADs) share genetic, pathophysiological and environmental characteristics.[2,3] This is reflected clinically in coincidence of more than one AD in a single patient. When a specific combination of ADs occurs, the diagnosis of an autoimmune polyglandular syndrome (APS) can be made. We are presenting a unique case of altered mental status in a patient with concomitant Grave's disease, type 1 diabetes mellitus (T1DM) and anti-NMDA-R encephalitis.

CASE PRESENTATION

A 58-year-old woman was transferred to our tertiary medical centre with altered mental status. Symptoms began 8 months prior to presentation and included weight loss (unsure how much), apathy and depression. One week prior to admission, she was noted to have a sharp decline in her mental status characterised by excessive somnolence, gait disturbances and poor appetite. Her husband brought her to a local hospital after she collapsed at a funeral. Biochemical evaluation was significant for a blood glucose level of 590 mg/dL (70-99), potassium of 2.3 mmol/L (3.5–5.1), sodium of 151 mmol/L (136-145), CO_2 of 7 mmol/L (21-30), anion gap of 41 (4-16) and pH of 7.17 (7.35–7.45), and urinalysis was positive for glucose and ketones without evidence of infection. She was treated for diabetic ketoacidosis with fluids and insulin infusion and was transferred to our tertiary medical centre given her worsening mental status.

Medical history was significant for gestational diabetes. She was not on any long-term medications and had no known drug allergies. She was not a smoker. Family history was notable for a sister with amyotrophic lateral sclerosis, a deceased sister with early-onset Alzheimer's disease.

INVESTIGATIONS

On examination, she was afebrile with sinus tachycardia at a heart rate of 107 bpm. Blood pressure was 107/63 mm Hg, respiratory rate of 24 breaths/min with a pulse oximetry of 87% on room air. She appeared older than stated age, pale and cachectic with temporal muscle wasting. Right eye proptosis was noted. Thyroid examination was normal without palpable nodules. Crackles were noted in the left posterior chest on inspiration. She was easily arousable, followed simple commands and was oriented to person and year, but not to place. She had a flat affect and did not engage in conversation. The rest of her examination was unremarkable.

CT of the brain showed no acute intracranial process. Laboratory evaluation was notable for thyroid stimulating hormone (TSH) <0.005 uIU/mL (0.47–4.68), free T4 3.3 ng/dL (0.6–2.5) and elevated serum thyroid-stimulating immunoglobulin 479% (0–139), consistent with thyrotoxicosis due to Graves' disease. Her A1C was 9.7% (4.6–6.2) with glutamic acid decarboxylase (GAD) antibodies titre 1702.3 U/mL (0.0–5.0) and C-peptide 0.5 ng/mL (1.1–4.4), consistent with type 1 diabetes. Adrenal insufficiency was ruled out with a normal morning

To cite: Frunza-Stefan S, Whitlatch HB, Rao GG, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-224821

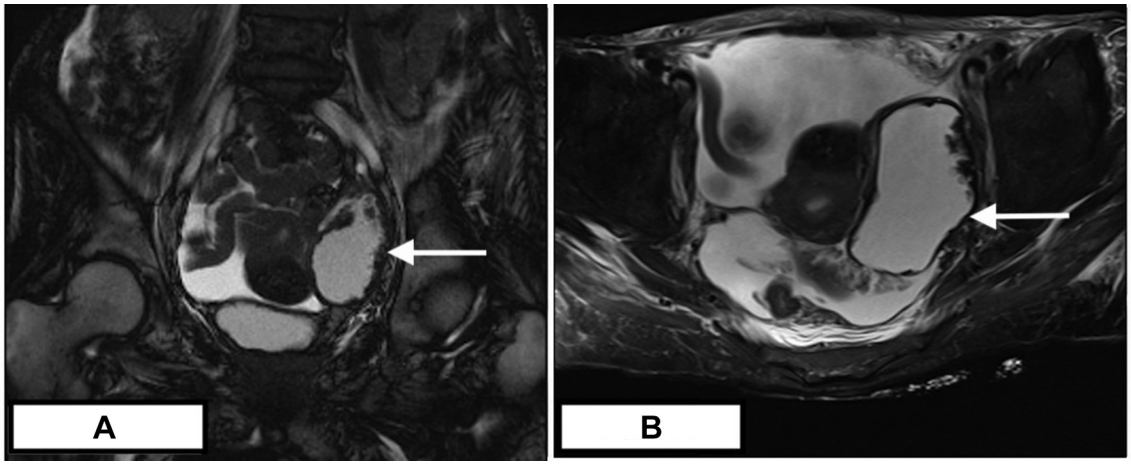

Figure 1 (A) Coronal section view and transverse section view (B) of abdominal MRI scan reveals an elongated, tubular, T2 bright lesion in the left adnexa with a thick wall, an incomplete septum and diffuse irregular mural excrescences, measuring 6.2×7.4×4.2 cm (arrow).

serum cortisol and adrenocorticotrophin levels. The co-occurrence of Graves' disease and type 1 diabetes established the diagnosis of APS type 3.

Since her mental status persistently fluctuated despite treatment, additional diagnostic testing was performed, including evaluation for paraneoplastic disease.

Serum anti-Hu, Yo and Ri antibodies were negative <1:10, but anti-NMDA-R antibody was positive with titre 1:160 (<1:10). Abdominal images, both CT scan and MRI with contrast, showed a cystic lobular left adnexal mass with peripheral enhancing soft tissue (figure 1).

TREATMENT

She was admitted to the medical intensive care unit and treated with methimazole 20 mg two times per day and insulin infusion therapy.

After gynaecological evaluation, the patient underwent bilateral salpingo-oophorectomy and pelvic washing. Pathology was consistent with a left serous cystadenofibroma (figure 2).

OUTCOME AND FOLLOW-UP

Within hours of surgery, she had a marked clinical improvement. She became more alert, oriented and was able to communicate. She was discharged on a basal/bolus insulin regimen and methimazole 20 mg daily. Serial anti-NMDA-R antibody testing revealed clearance of the serum antibodies within 2 months of surgery. Clinically, she completely recovered, with weight gain and resumption of her normal daily activities.

DISCUSSION

LE is a condition characterised by the subacute development of short-term memory loss, behavioural change and seizures involving the medial temporal lobes and the amygdalae, with variable evidence of Cerebrospinal fluid (CSF) inflammation and neuronal antibodies.[4 5]

Anti-NMDA-R encephalitis is an autoimmune antibody mediated form of LE that was initially reported by Delmau *et al* in 2007.[1] It predominantly affects young women of reproductive age.[6 7] The presence of a tumour, most commonly an ovarian

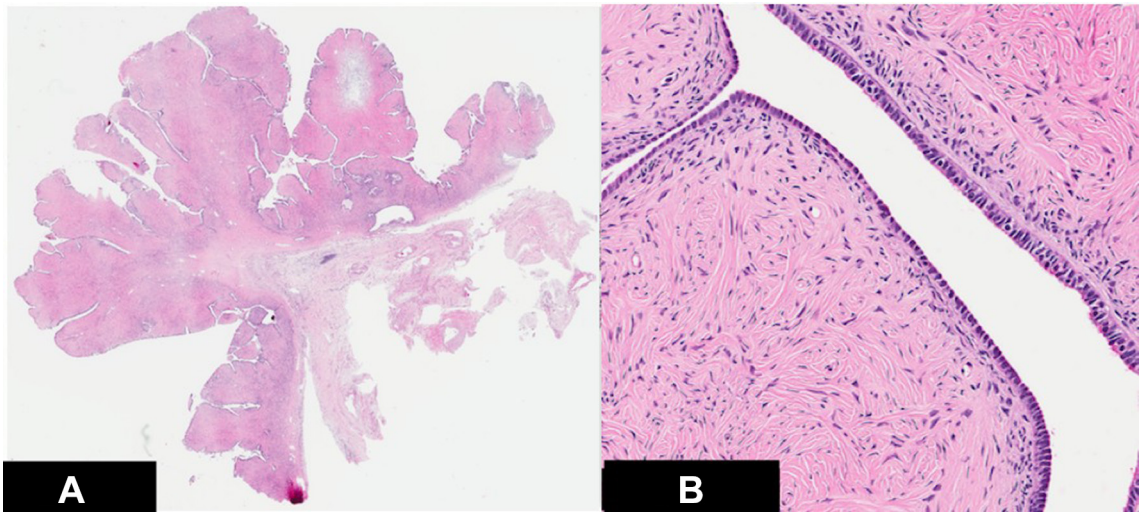

Figure 2 Histopathology of the ovarian mass on H&E stain shows projections of hypocellular fibroblastic stroma into a cystic space (A, low magnification), lined by a single layer of epithelium, which ranges from ciliated and columnar to non-ciliated and cuboidal (B, high magnification). No cytological atypia, invasion or capsular involvement was identified.

teratoma, is found in approximately half of the cases.[8] The clinical presentation is highly variable, which poses a diagnostic challenge. Typical presentations include acute personality and behavioural changes, memory loss, hallucinations, dyskinesia, dystonia, autonomic dysfunction and seizures.[8] The biochemical hallmark of the disease is the presence of anti-NMDA-R antibodies. Diagnosis is based on the detection of IgG antibodies against the GluN1 subunit of NMDA receptors that can be found in both the serum and the CSF.[8]

While the pathogenesis of Anti-NMDA-R to date remains unclear, it is believed to be T cell mediated, resulting in a loss of self-tolerance. Although the presence of a tumour that expresses NMDA receptors may contribute to breaking immune tolerance in some patients, 41% of patients do not have a clinically detectable tumour, suggesting other immunological triggers are involved, such as infection.[8]

Management of anti-NMDA-R encephalitis includes immunotherapy and the detection and removal of a causative mass, if present. First-line immunotherapy includes steroids, intravenous immunoglobulin and plasma exchange.[6 9] Patients who do not respond to first-line therapy have been treated with immunomodulators such as cyclophosphamide and rituximab.[6 10] The overall prognosis of anti-NMDA-R encephalitis is favourable. In Dalmau *et al*'s 2008 case series of 100 patients, 75 patients had substantial recovery or mild sequelae.[8] Out of these patients with positive outcomes, 59% had a tumour, most commonly an ovarian teratoma. The reported mortality is 4% within 3–5 months of disease onset.[8] Detection of a teratoma is a good prognostic factor, probably because a surgical cure is possible.[7]

While teratoma is the most common tumour associated with anti-NMDA-R encephalitis, other associated tumours have been reported, one patient with a neuroblastoma and another with Hodgkin's lymphoma.[11 12] Sanmaneechai *et al* in 2015 reported the first case of an adolescent girl linking ovarian cystadenofibroma to anti-NMDA-R encephalitis. She was treated with immunotherapy and removal of an ovarian cystadenofibroma, which led to full resolution of her symptoms and resolution of serum NMDA-R antibodies.[13] Our patient is the second case with ovarian cystadenofibroma described on final pathology report without evidence of a teratoma.

To our knowledge, this is the first case of coincident Grave's disease, type 1 diabetes and anti-NMDA-R encephalitis. The co-occurrence of these autoimmune conditions suggests common genetic, immunological and/or environmental factors underlying the induction of organ-specific autoimmunity. It also suggests that anti-NMDAR encephalitis may be a feature of APS.

APS are characterised by the coexistence of at least two glandular ADs, endocrine or non-endocrine.[14] APS is distinguished by age of presentation, characteristic patterns of disease combinations and different modes of inheritance. Based on clinical criteria, in 1980, Neufeld and Blizzard published a classification of the APS describing four main types.[15] APS 1, most commonly characterised by mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency, is an autosomal recessive disorder caused by mutations in the AIRE gene (autoimmune regulator gene) found on chromosome 21.[14 16 17] AIRE is most highly expressed in thymic medullary epithelial cells. Deletion of this regulator leads to decreased expression of tissue-specific self-antigens. This is hypothesised to allow autoreactive T cells to avoid clonal deletion, which normally occurs during T cell maturation in the thymus.[18 19] APS 2 is characterised by the association of Addison's disease, type 2 diabetes and autoimmune thyroid disease (ATD). Adrenal insufficiency is present in a high percentage of patients. In contrast to APS 1, the precise pathogenesis of APS 2 is unknown. It is usually associated with class II human leukocyte antigen (HLA) alleles, DR3/DQ2 and DR4/DQ8.[14 16 17]

APS 3 is defined as the coincidence of an ATD and at least one other AD (endocrine or non-endocrine). Examples of associated ADs include type 1 diabetes mellitus, pernicious anaemia, coeliac disease, atrophic gastritis and vitiligo.[15] Women are more often affected than men. Similar to APS 2, APS 3 exhibits polygenic inheritance and is associated with HLA class II haplotype. HLA DRB-1 is found in this group of patients. APS 3 is the most common APS, likely due to the high prevalence of the combination of ATD and T1DM.[20] If the autoimmune polyendocrinopathies do not fulfil the criteria of APS 1 to 3, the disease may be categorised as APS 4.

Central nervous system disease, due to endocrine, metabolic or autoimmune conditions, has rarely been described in association with APS.[21] There are several cases of cerebellar ataxia with antibodies against GAD reported in literature.[22–25] Vogt-Koyanagi-Harada syndrome, an autoimmune-mediated disease with ocular, neurological and dermatological manifestations, has been reported in a patient with APS 1.[26] Facchini *et al* reported a case of a child with combined subacute degeneration who presented with severe subacute sensory ataxia, unusual skin hyperpigmentation and megaloblastic anaemia. The child who had Hashimoto's thyroiditis without clinical manifestation was also found to have pernicious anaemia, consistent with a diagnosis of APS 3.[27] Demyelinating lesions and multiple sclerosis (MS) have been reported in a few cases of both APS 2[28 29] and APS 3.[29–32] The cases of MS associated with APS 3 had concomitant diabetes mellitus and thyroiditis.

In the literature to date, a correlation between anti-NMDA-R encephalitis and ATD has been reported in only two cases. Leu and colleagues described a case of repetitive seizures and concomitant encephalopathy in a young patient with Graves' disease who initially did not respond to antithyroid, antiviral or antiepileptic measures, but gradually recovered consciousness and cognition after corticosteroid treatment. Serological NMDA-R antibodies were positive.[33] A second case described a patient with concomitant Graves' disease and anti-NMDA-R encephalitis in pregnancy.[34]

Learning points

- Our case is the first reported association of anti-N-methyl-D-aspartic acid-receptor (NMDA-R) encephalitis and autoimmune polyglandular syndrome 3. It underscores the importance of considering autoimmune encephalopathy in those patients with a personal or family history of autoimmunity.
- It is difficult to predict clinically whether an individual will develop one or multiple autoimmune disorders; however, knowledge of these diseases and their associations can lead to earlier diagnosis and management.
- Early treatment of anti-NMDA-R encephalitis results in a better neurological outcome for patients.[35]

Contributors SF-S: contributed to the conception and design of the work as well as acquisition of data; major contributor in writing/ drafting the manuscript; gave final approval of the version to be published. HBW: contributed by helping design, conduct, draft and revise the case and also helped with figures, data interpretation and approved the final version. GGR: contibuted to publication by conception, acquisition of data and its interpretation; discussed planning and approved the final vision to be published. RM: contributed by discussing the conception and design, conducted the work, revised it critically for important intellectual content and

approved the final version to be published. All authors agreed to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Dalmau J, Tüzün E, Wu HY, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;61:25–36.
2 Anaya JM. The diagnosis and clinical significance of polyautoimmunity. *Autoimmun Rev* 2014;13:423–6.
3 Eisenbarth GS, Gottlieb PA. Medical progress: autoimmune polyendocrine syndromes. *N Engl J Med* 2004;350:2068–79.
4 Graus F, Delattre JY, Antoine JC, *et al*. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
5 Gultekin SH, Rosenfeld MR, Voltz R, *et al*. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000;123(Pt 7):1481–94.
6 Titulaer MJ, McCracken L, Gabilondo I, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157–65.
7 Dalmau J, Lancaster E, Martinez-Hernandez E, *et al*. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
8 Dalmau J, Gleichman AJ, Hughes EG, *et al*. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–8.
9 Ramanathan S, Mohammad SS, Brilot F, *et al*. Autoimmune encephalitis: recent updates and emerging challenges. *J Clin Neurosci* 2014;21:722–30.
10 Liba Z, Sebronova V, Komarek V, *et al*. Prevalence and treatment of anti-NMDA receptor encephalitis. *Lancet Neurol* 2013;12:424–5.
11 Lebas A, Husson B, Didelot A, *et al*. Expanding spectrum of encephalitis with NMDA receptor antibodies in young children. *J Child Neurol* 2010;25:742–5.
12 Argov Z, Mckee D, Agus S, *et al*. Clinical / Scientific Notes. 2008:28–31.
13 Sanmaneechai O, Song JL, Nevadunsky N, *et al*. Anti-N-methyl D-aspartate encephalitis with ovarian cystadenofibroma. *Pediatr Neurol* 2013;48:232–5.
14 Eisenbarth GS, Gottlieb PA, Eisenbarth GS, a GP. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004;350:2068–79.
15 Kakleas K, Soldatou A, Karachaliou F, *et al*. Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus (T1DM). *Autoimmun Rev* 2015;14:781–97.
16 Cutolo M. Autoimmune polyendocrine syndromes. *Autoimmun Rev* 2014;13:85–9.
17 Kahaly GJ. Polyglandular autoimmune syndromes. *Eur J Endocrinol* 2009;161:11–20.
18 Abramson J, Husebye ES. Autoimmune regulator and self-tolerance - molecular and clinical aspects. *Immunol Rev* 2016;271:127–40.
19 De Martino L, Capalbo D, Improda N, *et al*. APECED: a paradigm of complex interactions between genetic background and susceptibility factors. *Front Immunol* 2013;4:1–10.
20 De Marchi SU, Cecchin E, De Marchi S. Autoimmune spontaneous chronic urticaria and generalized myasthenia gravis in a patient with polyglandular autoimmune syndrome type 3. *Muscle Nerve* 2015;52:440–4.
21 Kattah JC, Kattah WC. Neurologic complications of multiple endocrine syndromes. *Handb Clin Neurol* 2014;120:799–808.
22 Bayreuther C, Hieronimus S, Ferrari P, *et al*. Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes mellitus. *Diabetes Metab* 2008;34:386–8.
23 Manto M, Jissendi P. Brain imaging in cerebellar ataxia associated with autoimmune polyglandular syndrome type 2. *J Neuroimaging* 2012;22:308–11.
24 Berger JR, Weaver A, Greenlee J, *et al*. Neurologic consequences of autoimmune polyglandular syndrome type 1. *Neurology* 2008;70:2248–51.
25 De AC. Cerebellar ataxia with anti–glutamic acid decarboxylase antibodies. *Library* 2008;58.
26 Jovic NS, Nesovic M, Vranjesevic DN, *et al*. The Vogt-Koyanagi-Harada syndrome: association with autoimmune polyglandular syndrome type 1. *Postgrad Med J* 1996;72:495–7.
27 Facchini SA, Jami MM, Neuberg RW, *et al*. A treatable cause of ataxia in children. *Pediatr Neurol* 2001;24:135–8.
28 Sastre-Garriga J, Tintoré M, Montalban X. Polyglandular autoimmune syndrome type II and multiple sclerosis. *J Neurol* 2001;248:330–1.
29 Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler J* 2004;10:575–81.
30 Boz C, Velioglu S, Altunayoğlu V, *et al*. Central nervous system involvement in autoimmune polyglandular syndrome. *Clin Neurol Neurosurg* 2003;105:102–4.
31 Donadio V, Cortelli P, Liguori R, *et al*. Multiple sclerosis-like disease in polyglandular autoimmune syndrome. *J Neurol* 2001;248:61–2.
32 Yokote H, Nagasawa M, Ichijo M, *et al*. Autoimmune polyendocrine syndrome-3 in a patient with late-onset multiple sclerosis. *Neurologist* 2012;18:83–4.
33 De Leu N, Unuane D, Poppe K, *et al*. Seizures and posticta l stupor in a patient with uncontrolled Graves' hyperthyroidism. *BMJ Case Rep* 2012;2012:bcr0220125929..
34 Lu J, Samson S, Kass J, *et al*. Acute psychosis in a pregnant patient with Graves' hyperthyroidism and anti-NMDA receptor encephalitis. *Case Reports* 2015;2015.
35 Finke C, Kopp UA, Prüss H, *et al*. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2012;83:195–8.