CASE REPORT

Anti-AMPA receptor encephalitis associated with Medullary thyroid cancer

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Accepted 6 August 2018

SUMMARY

AMPA receptor (AMPAR) antibodies are a group of recently discovered antibodies which target the neuronal synaptic proteins causing B-cell (immune) mediated neuronal damage, resulting in various neurologic syndromes depending on the area of central nervous system involvement. These syndromes are mostly reversible if treated early. Tumour association has been reported in up to 60% of cases in the most recent case series with lung, breast, ovarian cancers and thymomas being the most commonly associated malignancies with these antibodies. We present here the first case of AMPAR encephalitis associated with medullary thyroid cancer. Our patient presented with cognitive dysfunction and behavioural changes over a period of 3 weeks, with a full recovery after starting immunotherapy, once the diagnosis of AMPAR limbic encephalitis was established. This case highlights the importance of early diagnosis and management of AMPAR encephalitis as these patients respond well to immunotherapy and can have an almost complete recovery.

BACKGROUND

Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of disorders caused by cancers not located in the central nervous system (CNS). The pathophysiology of PNS is different from that of metastases, or other complications of cancer such as metabolic and nutritional deficits, infections, coagulopathy and side effects of cancer treatment.[1] Tumour-mediated immunity plays an important part in the pathogenesis of these disorders. PNS may affect any part of the nervous system. These syndromes (PNS) can be classified into two groups: (A) classical PNS, which strongly suggest an associated malignancy, and (B) non-classical PNS, which may or may not be associated with malignancy. The antibodies responsible for classical PNS target intracellular neuronal antigens (eg, Anti-Hu, Ri, Ma2), and the associated tissue damage is mediated by cytotoxic T cell responses and is often irreversible. In contrast, the non-classical syndromes associated with antibodies against neuronal cell surface or synaptic receptors [eg, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), anti-NMDA, anti-GABA1,2] are mediated primarily by B-cell responses and are usually treatment responsive with substantial neurologic recovery[2] (table 1).

The AMPA receptors (AMPAR) are transmembrane ionotropic glutamate receptor responsible for most of the excitatory synaptic transmission in the vertebrate CNS.[3] They exist as heterotetrameric cation channels composed of various combinations of GluA1 to GluA4 subunits, which are widely expressed in both neurons and glia. In the adult CNS, most assembled AMPAR tetramers contain GluA2, and most glutamatergic synapses on principal neurons consist of GluA1-GluA2 and to lesser extent GluA2-GluA3 heterotetramers.[4] AMPAR encephalitis (AMPAR-E) results from the production of antibodies against these receptors causing mature synaptic AMPAR loss of function due to internalisation and decrease of the number of GluA1/GluA2-containing AMPAR clusters at synapses.[5 6]

CASE PRESENTATION

A 69-year-old female patient was admitted to our hospital for investigations and management of recent abnormal behaviour for 3 weeks. Her main symptoms included paranoid delusions, short-term memory impairment and confusion. There were no reports of seizures during this time.

Her medical history was significant for medullary thyroid cancer (MTC) and she underwent total thyroidectomy without any lymph node clearance in December 2016. Restaging in early 2017 showed persistent cancer with positron-emission tomography (PET) avid cervical lymphadenopathy on the PET scan. She also had a history of sciatica, depression and hysterectomy. Her medications included thyroxine, paracetamol, vitamin D, calcium supplements, risperidone and escitalopram. On the initial neurological examination, she was alert but disoriented in time, place and person. There was marked alteration in executive function with the poor short-term recall. No focal neurological deficits were identified. The rest of the clinical examination was unremarkable except for a thyroidectomy and hysterectomy scar.

Her presentation was suggestive of a subacute encephalitic process with predominant involvement of limbic system. Her differentials at that point included infectious, metabolic, vasculitic and paraneoplastic causes of limbic encephalitis. Further investigations were organised including

To cite: Samad N, Wong J. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-225745

Table 1 Paraneoplastic neurologic syndromes with associated antibodies and cancers

Antibodies	Syndrome	Associated cancers
Against intracellular antigen		
Hu (ANNA1)	Limbic encephalitis	SCLC
Ma2	Limbic encephalitis	Testicular seminoma
GAD	Limbic encephalitis	Thymoma, SCLC
CRMP5	Encephalomyelitis Chorea PCD	SCLC, thymoma
Ri (ANNA2)	Brainstem encephalitis Opsoclonus myoclonus	Breast, SCLC
Yo (PCA1)	PCD	Ovary, breast
Amphiphysin	Stiff-person syndrome Myelopathy and myoclonus Encephalomyelitis	Breast, SCLC
Against synaptic receptors		
NMDA receptor	Encephalitis	
AMPA receptor	Limbic encephalitis	Thymoma, SCLC
$GABA_B$ receptor	Limbic encephalitis	SCLC
$GABA_A$ receptor	Encephalitis	Thymoma
mGluR5	Encephalitis	Hodgkin's lymphoma
Against ion channels and other cell surface proteins		
LGI1	Limbic encephalitis	Thymoma
Caspr2	Morvan's syndrome Limbic encephalitis	Thymoma
DPPX	Encephalitis	Lymphoma

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA, antinuclear-nuclear antibody; CRMP-5, collapsin response mediator protein; DPPX, dipeptidyl-peptidase-like protein-6; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; LGI, leucine-rich glioma-inactivated protein; NMDA, N-methyl-D-aspartate; PCA, Purkinje cell antibody; PCD, posterior cerebellar degeneration; SCLC, small cell lung cancer.

Table 2 Characteristics of previously described patients with AMPAR encephalitis

Median age	50 (7–81 years)
Gender	
Male	24
Female	43
Disease trajectory	
Fulminant	2
Subacute	
Mode of presentation	
Limbic encephalitis±seizures	38
	15 had seizures
Diffuse encephalomyelitis	18
Isolated neurological deficits	5
Psychosis	4
Malignancy	
Data available	52 patients
Present	28
Thymoma	10
Lung	8
Breast	6
Ovary	3
Seminoma	1
Immunological background	
Additional CNS antibodies	13
Systemic antibodies	11
Outcome	
Full or almost full recovery at initial presentation	19
Partial recovery	18
Relapse	9
Death	3
No recovery	5

AMPAR, AMPA receptor; CNS, central nervous system.

lumbar puncture and serological investigations to establish the diagnosis.

INVESTIGATIONS

The significant findings on investigations included a positive treponemal serology on peripheral blood, mildly raised antinuclear antibody at 1:360 titre subclinical hyperthyroidism with thyroid-stimulating hormone of 0.05 mIU/L, T4 19 pmol/L and T3 4.5 pmol/L. The rest of the serology including blood ammonia levels, vitamin B_{12} levels, thyroid antibodies and HIV serology were unremarkable. Also, the antineuronal antibodies were not detected in the serum. Serum calcitonin, which is the biomarker for MTC, was still elevated (normal <5 ng/L in women) at 18.9 ng/L, 4 months after total thyroidectomy, this was highly suggestive of persistent cancer.

Routine cerebrospinal fluid (CSF) analysis showed mildly increased proteins of 0.62 mmol/L and glucose of 3.7 mmol/L. The syphilis serology in the CSF was non-reactive; investigations for autoimmune encephalitis revealed positive AMPAR antibodies against the subunit GluA2 in both serum and CSF using transfected human embryonic kidney-293 cells in the indirect immunofluorescence method. Neuroimaging techniques including MRI and CT brain were performed to exclude any cerebrovascular accident or metastatic disease and to further characterise the neurologic syndrome. Both of the studies were normal.

As mentioned above, the recent whole-body PET fluorodeoxyglucose performed 2 weeks before her presentation showed PET avid cervical lymph nodes suggestive of nodal metastasis from MTC and no signs of any other malignancies.

TREATMENT

The patient was initially treated for possible neurosyphilis while awaiting CSF syphilis serology, but her condition did not improve. Once the results of anti-AMPAR antibodies became available, she was commenced on intravenous immunoglobulin (IVIg) therapy for 3 days.

OUTCOME AND FOLLOW-UP

The patient showed substantial neurocognitive improvement and was discharged home. She underwent a left neck dissection 4 weeks later that showed six nodes involved with MTC, and subsequently received adjuvant prophylactic radiotherapy. She showed a complete neurological recovery at her 6 month out-patient follow-up.

DISCUSSION

Encephalitis associated with AMPAR antibodies usually has an acute to subacute onset, and the symptoms depend on the

part of the brain involved, namely limbic encephalitis, brainstem encephalitis or encephalomyelitis with widespread neuraxis involvement. It usually affects middle-aged women and presents as subacute limbic encephalitis (<8 weeks) with symptoms of behavioural disturbance, short-term memory loss and cognitive dysfunction associated with seizures in less than 50%. About two-thirds of the cases are associated with underlying malignancies involving lung, breast and thymus.[7]

Diagnostic workup includes careful history and examination, neuroimaging, CSF studies, electroencephalography (EEG) and exclusion of other causes. Majority of the patients with AMPAR-E have abnormal MRI[2] with fluid-attenuated inversion recovery signal abnormality in the medial temporal lobes. CSF studies often show predominant lymphocytic pleocytosis and presence of AMPAR antibodies. EEG usually shows non-specific abnormalities including focal or generalised slowing, epileptiform activity and periodic lateralised epileptiform discharges, and is helpful in excluding other causes of non-convulsive seizures and encephalitis.

We identified 66 cases of AMPAR-E after conducting a literature search until June 2017 using PubMed[5 8–23] (table 2).

Patients' median age was 50 years (range 7–81 years). Women were affected more commonly than men (F:M ratio of 43:24). Most of the patients had a subacute presentation similar to our case. However, a few fulminant cases have also been described in the literature.[8] Our patient presented with typical symptoms of limbic encephalitis, which is the most frequent mode of presentation. It is defined as the subacute onset of short-term memory loss, seizures, confusion and psychiatric symptoms, which can develop with or without seizures.[24] Based on symptomatology, four modes of presentations were observed: (1) symptoms of limbic dysfunction, seen in 56.7% (n=38), of which half of them developed seizures; (2) diffuse encephalitis with clinical manifestations of multiple areas of CNS involvement in addition to limbic encephalitis, for example, optic neuropathy, sensory deficits, motor symptoms, ataxia and dyskinesias, observed in 27.2% (n=18); (3) isolated neurological symptoms without limbic encephalitis were noted in 7.4% (n=5); and (4) four (5%) patients presented with new-onset psychosis. Cancer status was available in 52 patients, of which 28 (53.8%) had cancer, including lung cancer (n=8), thymomas (n=10), breast cancer (n=6), ovarian cancer (n=3) and 1 case of seminoma. Our patient had the recent diagnosis of MTC associated with lymph node metastases and had no evidence of any other malignancy on the PET scan. To the best of our knowledge, there has been no previous reported case of AMPAR-E associated with MTC. She made a rapid and complete recovery after the initiation of immunotherapy once the diagnosis was confirmed. Immunotherapy and tumour control are the mainstay of treatment with overall 72% of patients showing a response. Most (44%) of them had a partial response but some (31%) had almost full or complete recovery. More recent case series and reports have reported fewer relapses as compared with those in early literature.[5] This could be explained by early recognition and improved treatment regimens available at present although the follow-up period in more recent case reports was much shorter. The neurological outcome was also influenced by the presence of additional onconeuronal antigens likely due to the influence of the overlapping immune responses.[8 9]

Learning points

- The knowledge of autoimmune encephalitides and in particular AMPA receptor (AMPAR)-associated encephalitis is continually expanding. Despite this information, occasionally AMPAR encephalitis can be difficult to diagnose due to considerable phenotypic heterogeneity.
- AMPAR encephalitis can present as a paraneoplastic neurologic syndrome in a cancer that does not have a previously known association with AMPAR antibodies.
- Early recognition and prompt treatment (institution of immunotherapy) can lead to improved outcomes in this otherwise serious and potentially life-threatening disorder.

Acknowledgements The authors thank Dr Ho Pui San Sarah, 5th year MBBS student, Monash University, for her assistance in collection of data.

Contributors NS: conception or design of the work; data collection, data analysis and interpretation; drafting the article; principal guarantor; involved in management of the patient. JW: critical revision of the article; final approval of the version to be published.

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 Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med* 2003;349(16):1543–54.
2 Josep D, Rosenfeld MR. Overview of paraneoplastic syndromes of the nervous system. 2018. www.uptodate.com/contents/overview-of-paraneoplastic-syndromes-of-the-nervous-system
3 Shepherd JD, Huganir RL. The cell biology of synaptic plasticity: AMPA receptor trafficking. *Annu Rev Cell Dev Biol* 2007;23:613–43.
4 Lu W, Shi Y, Jackson AC, *et al*. Subunit composition of synaptic ampa receptors revealed by a single-cell genetic approach. *Neuron* 2009;62:254–68.
5 Lai M, Hughes EG, Peng X, *et al*. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009;65:424–34.
6 AMPA receptors. *Dynamics and targets of disease Benarroch*. Rochester, Minnesota: Eduardo E MD, 2016.
7 Myrna R. Autoimmune encephalitis with antibodies to cell surface antigens. *Neurology in Clinical Practice*;82:1196–200.
8 Joubert B, Kerschen P, Zekeridou A, *et al*. Clinical spectrum of encephalitis associated with antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: case series and review of the literature. *JAMA Neurol* 2015;72:1163.
9 Höftberger R, van Sonderen A, Leypoldt F, *et al*. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. *Neurology* 2015;84:2403–12.
10 Zhu M, Yu X, Liu C, *et al*. Hashimoto's encephalitis associated with AMPAR2 antibodies: a case report. *BMC Neurol* 2017;17:37.
11 Li X, Mao YT, Wu JJ, *et al*. Anti-AMPA receptor encephalitis associated with thymomatous myasthenia gravis. *J Neuroimmunol* 2015;281:35–7.
12 Linnoila JJ, Binnicker MJ, Majed M, *et al*. CSF herpes virus and autoantibody profiles in the evaluation of encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e245.
13 Quaranta G, Maremmani AG, Perugi G. Anti-AMPA-Receptor encephalitis presenting as a rapid-cycling bipolar disorder in a young woman with turner syndrome. *Case Rep Psychiatry* 2015;2015:1–5.
14 Yang S, Qin J, Li J, *et al*. Rapidly progressive neurological deterioration in anti-AMPA receptor encephalitis with additional CRMP5 antibodies. *Neurol Sci* 2016;37:1853–5.
15 Ances BM, Vitaliani R, Taylor RA, *et al*. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005;128(Pt 8):1764–77.
16 Graus F, Boronat A, Xifró X, *et al*. The expanding clinical profile of anti-AMPA receptor encephalitis. *Neurology* 2010;74:857–9.
17 Spatola M, Stojanova V, Prior JO, *et al*. Serial brain 18FDG-PET in anti-AMPA receptor limbic encephalitis. *J Neuroimmunol* 2014;271(1-2):53–5.
18 Wei YC, Liu CH, Lin JJ, *et al*. Rapid progression and brain atrophy in anti-AMPA receptor encephalitis. *J Neuroimmunol* 2013;261(1-2):129–33.
19 Kubota A, Tajima T, Narukawa S, *et al*. [Anti-Ma2, anti-NMDA-receptor and anti-GluRε2 limbic encephalitis with testicular seminoma: short-term memory disturbance]. *Rinsho Shinkeigaku* 2012;52:666–71.
20 Bataller L, Galiano R, García-Escrig M, *et al*. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. *Neurology* 2010;74:265–7.

21 Dogan Onugoren M, Deuretzbacher D, Haensch CA, *et al*. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. *J Neurol Neurosurg Psychiatry* 2015;86:965–72.
22 Gleichman AJ, Panzer JA, Baumann BH, *et al*. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. *Ann Clin Transl Neurol* 2014;1:180–9.
23 Elamin M, Lonergan R, Killeen RP, *et al*. Posterior cortical and white matter changes on MRI in anti-AMPA receptor antibody encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e118.
24 Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. *Neurologist* 2007;13:261–71.