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# Anti-Ma2 encephalitis in a phenotypic female with XY gonadal dysgenesis: A case report

Shaikha Alsuwaidi *, Hamda Kamalboor, Tarig Khairi, Abubaker Almadani

*Rashid Hospital, Dubai, United Arab Emirates*

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ABSTRACT

Anti-Ma2 encephalitis is an autoimmune disorder that typically involves the brainstem, limbic system, and diencephalon. It can be paraneoplastic and is more common in males. We describe an unusual presentation of anti-Ma2 encephalitis in a patient with an XY chromosome and a female phenotype. She experienced various neurological symptoms, including olfactory hallucinations, episodic nausea, per-ictal water drinking, and hypersomnolence, that were poorly controlled by antiseizure medications (ASMs) and immunotherapy. Brain MRI showed abnormalities in right medial temporal and frontal regions, and blood tests detected anti-Ma2 antibodies. Screening for malignancies yielded no tumors. Pelvic CT showed bilateral inguinal masses and the absence of a uterus, while genetic studies revealed an XY karyotype. Surgical removal of the masses, shown to be primitive gonads, offered temporary relief, necessitating ongoing ASMs and immunotherapy.

## Introduction

Anti-Ma2 encephalitis is an autoimmune inflammatory condition that generally affects the brainstem, diencephalon, limbic system or a combination of these regions. It can be paraneoplastic in origin when associated with a tumor. A study showed that among 38 patients with anti-Ma2 encephalitis, 68 % were male (age range: 22 to 70 years), 32 % were female (age range: 53 to 82 years), and over 90 % of them had an underlying tumor [2].

The onconeural Ma proteins exist in three forms: Ma1, Ma2, and Ma3. It has been reported that the Ma1 protein is typically expressed in the brain and testis, Ma2 in the brain, and Ma3 in the brain, testis, and other organs [4]. A study conducted by Voltz et al. [6] revealed that 10 out of 13 individuals with testicular tumors showed Ma2 protein expression. This discovery could explain the observed cross-reactivity in patients presenting with paraneoplastic syndromes associated with anti-Ma2 antibodies and testicular tumors.

Given this information, it is not surprising that the most common neoplasm associated with anti-Ma2 encephalitis is a testicular tumor, especially in males below the age of 45. Lung tumors were observed to be the most prevalent among females or males above the age of 50. Less commonly associated neoplasms include breast, parotid gland, ovarian, colorectal, and renal cancers, as well as choriocarcinomas and lymphomas. Although many have associated neoplasms, neurological symptoms preceded the tumor diagnosis in 62 % of patients. In some patients without evidence of cancer, risk factors for testicular germ-cell tumors such as testicular microcalcification and cryptorchidism were found. [2].

The primary treatment approach in paraneoplastic cases is tumor resection. However, immunotherapy and concurrent symptomatic management is generally also required. Intravenous (IV) steroids, IV immunoglobulin (IVIG), plasma exchange, rituximab and cyclophosphamide have been tried. [2].

We describe an unusual presentation of anti-Ma2 encephalitis in a 50-year-old patient with an XY chromosome and a female phenotype.

## Case presentation

A 50-year-old right-handed female, previously known to have primary infertility, presented with recurrent episodes of pleasant olfactory hallucinations. Within a few days, she developed nausea, fear, social withdrawal, reduced appetite, and disturbed cognitive skills, including memory and speech. In the same month, she experienced a nocturnal focal to bilateral tonic-clonic seizure (FBTCS). Subsequently, she experienced episodes of focal unaware seizures characterized by speech difficulty, slowness and staring. The family history included epilepsy in a distant relative and a significant history of neoplasms, including colon cancer, leukemia, and a lung mass.

* Corresponding author at: Neurology Department, Rashid Hospital, Dubai Academic Health Corporation, United Arab Emirates.
*E-mail address:* Shaikha_al_suwaidi@hotmail.com (S. Alsuwaidi).

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Her initial physical examination was unremarkable except for right eye papilledema. Investigations showed hyponatremia, and cerebrospinal fluid (CSF) cells, protein and glucose were unremarkable. Electroencephalogram (EEG) showed focal right temporal epileptiform discharges with occasional ictal evolution. Brain MRI with contrast revealed a non-enhancing right medial temporal and medial frontal region intra-axial lesion, that was hyperintense on T2 sequence with effacement of sulci. Features of the lesion were interpreted as an inflammatory lesion versus low grade glioma. She was started on dexamethasone, levetiracetam 1000 mg BID, and furosemide with good initial response. There were discussions with the patient about the possible glioma that may require resection.

In the following month, the patient reported ongoing symptoms of nausea and weight loss of around 10 kg since symptom onset. Repeat brain MRI imaging demonstrated a reduction in the FLAIR hypersignal, followed by the disappearance of hyperintensity. Due to these changes in imaging, the impression changed from possible brain neoplasm to infectious, inflammatory, or autoimmune etiology. Malignancy screening with colonoscopy, CT of the chest, abdomen and pelvis, and ultrasound of the breasts, axillary and supraclavicular areas did not show any evidence of a tumor. Serum tumor markers were also normal (Table 1).

Over the following six months the patient deteriorated and presented to us for the first time. She continued to experience episodic nausea and olfactory hallucinations, as well as memory and cognitive difficulties, dizziness, hypersomnia, and an unsteady gait. Within the prior two months, she had suffered from two FBTCs. In terms of the patient's antiseizure medication (ASM) history, levetiracetam was switched to phenytoin, and this was followed by the addition of valproic acid 500 mg TID.

Examination at that time revealed a normal physical habitus of an adult female, gaze-evoked nystagmus and abnormal tandem gait. The rest of cranial nerve, motor and sensory examinations were normal. Montréal cognitive assessment (MoCA) test revealed a score of 28/30. Brain MRI brain showed signal changes in bilateral mesial temporal cortices and right insular cortex (Fig. 1). EEG upon presentation showed active focal right temporal epileptiform discharges including lateralized periodic discharges (LPDs) and electro-clinical seizures (Fig. 2). A subsequent video-EEG demonstrated focal unaware seizures with oral and manual automatisms that had a right temporal seizure onset. Serum anti-PNMA2/Ta antibodies were detected, while other autoimmune antibodies were negative (Table 1). Her symptoms, including memory, improved with IV methylprednisolone.

Phenytoin was replaced with brivaracetam, and lacosamide was added. Valproic acid was discontinued due to suspected side effects. At follow-up visits her regimen was modified to lacosamide 200 mg BID, lamotrigine 50 mg BID and topiramate 50 mg BID, along with antiemetics and prednisolone.

Over the following months the patient's symptoms and physical exam findings exhibited further progression. She slept 14–20 h daily with non-refreshing awakening and her unsteady gait required a wheelchair. She had episodes of focal aware seizures consisting of facial twitching, eyelid fluttering, or episodic nausea with peri-ictal water drinking (PIWD) and focal unaware seizures with lip smacking and right-sided or bimanual automatisms that were followed by prolonged post-ictal drowsiness. On examination she had abnormalities in saccades, right eyelid ptosis, dysarthria, ataxia, and scored 21/30 on the MoCA test. She was also having recurrent hyponatremia and was diagnosed with SIADH. EEG showed persistent LPDs, and cortical dysfunction. The patient showed transient improvement following various interventions including IVIG, plasmapheresis, and rituximab, with the greatest benefit noted after plasmapheresis. Her AEDs were adjusted by increasing lacosamide to 300 mg BID and topiramate to 200 mg BID.

33 months following her initial symptoms, we sought further information about the patient's reproductive health and learned that she was born without a uterus. Re-evaluation of abdominal and pelvic CT demonstrated an absence of uterus and ovaries and presence of bilateral inguinal unidentified masses (Fig. 3). Karyotyping showed 46, XY chromosome. And a whole exome sequencing revealed SRY positive, X-linked androgen insensitivity. A whole body fluorodeoxyglucose-positron emission topography (FDG-PET) showed hypermetabolic nodular masses of unknown etiology in the inguinal ring. The patient underwent laparoscopic resection of these masses, which were later identified as abnormal dysgenic gonads. Histopathology showed prepubertal testicular tissue and peripheral ovarian-type stroma; together with a fallopian tube on the right. There were no signs of neoplasia.

Two weeks post-operation, the patient and her husband reported noteworthy improvements in symptoms. The oral and bimanual

**Table 1**
Summary of patient care as a timeline.

| Time from presentation | Clinical features | Laboratory/Genetics | Imaging/ EEG | Management |
|---|---|---|---|---|
| 0–1 month (At symptom onset) | olfactory hallucinations, followed by tonic-clonic seizures, also focal unaware seizures. | Hyponatremia. | EEG: focal subcortical pathology on Right<br>MRI brain: non enhancing right medial temporal & frontal intra-axial lesion | Treatment dexamethasone, levetiracetam, furosemide |
| 2 months | Nausea and weight loss of around 10 kg since symptom onset.<br>Continued nausea and olfactory hallucinations. Neuropsychological test normal. | Serum beta-2-microglobulin, CA 19–9, hCG, AFP, CA 125, CEA, CA 15–3, TSH were normal. | Brain MRI: reduction in FLAIR hypersignal, followed by disappearance of hyperintensity.<br>Maligancy workup: Colonoscopy, CT chest/abdomen/pelvis, ultrasound breasts.<br>showed no evidence of tumor. | Continued dexamethasone taper and levetiracetam. |
| 6 months (Presented to our facility) | Additional signs and symptoms: Sinus tachycardia, mild cognitive impairment, gaze evoked nystagmus and abnormal tandem gait. | Serum: Anti-PNMA2/Ta autoantibodies detected.<br>Anti- amphiphysin, CV2, Hu, Ri, Y, Recoverin, SOX1, Titin, Zic4, GAD65, Tr were negative. | MRI brain: signal changes in bilateral mesial temporal cortices, right insular cortex and gyrus rectus, with minimal swelling | Intravenous methylprednisolone followed by oral prednisolone.<br>Phenytoin and valproic acid stopped replaced by brivaracetam and lacosamide. |
| Follow up visits (During a 2-year period) | Face twitching, vomiting, bilateral automatisms (focal seizures). Abnormal saccades, right eyelid ptosis, dysarthria, ataxia. | Recurrent hyponatremia, diagnosed with SIADH. | EEG: cortical dysfunction with right LPDs. | Lacosamide, lamotrigine, topiramate, levetiracetam.<br>IVIG, plasmapheresis, and rituximab. |
| 33 + months | Transient parital improvements with immunotherapy and antiseizure medications (ASMs).<br>Still requiring assisstance in activities of daily living. | Karyotyping: XY chromosome SRY positive, X-linked androgen insensitivity | CT abdomen and pelvis re-evaluated: absence of uterus and ovaries.<br>PET: hypermetabolic nodular masses in inguinal ring. | Resection of dysgenic gonads with partial improvement.<br>Continued ASMs, plasmapheresis, physiotherapy. |

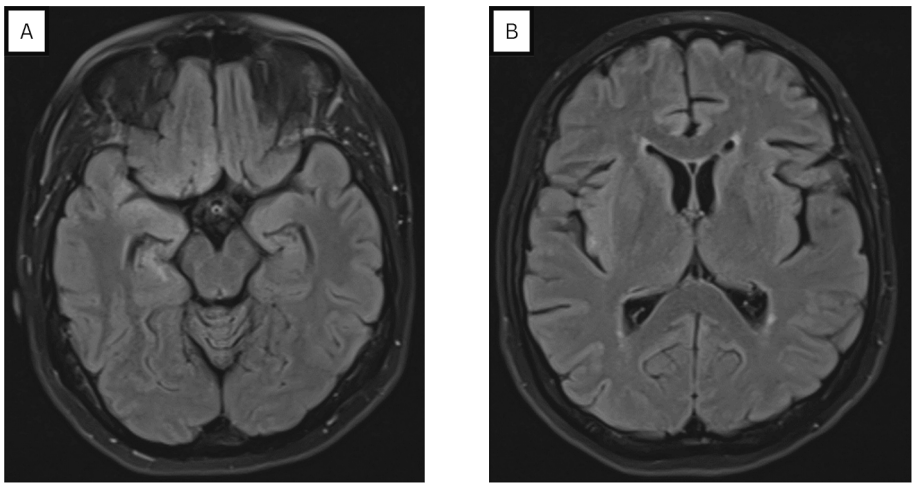


**Fig. 1.** Axial T2/FLAIR brain MRI revealed confluent hyperintense signal changes in both mesial temporal regions (image A) and insular cortices (image B) as well as gyri recti with some localized swelling more seen on the right side.

automatisms were no longer present, and there was reduction in nausea, PIWD and slurred speech. Hypersomnia also improved, as sleep duration reduced to 10–14 h with refreshed awakening and absence of daytime sleepiness. Additionally, the patient showed improvement in sitting posture and notable enhancement in mood and memory. However, she still complained of exertional fatigue, mild nausea, mainly while looking down, and severe ataxia requiring assistance with mobilization out of the wheelchair. MoCA score improved to 26/30.

Nine months post-procedure, the patient began experiencing a gradual recurrence of her previous symptoms, and was readmitted to the hospital for further management and malignancy re-evaluation. She had ongoing complaints of fatigue and somnolence but no recurrence of nausea attacks or PIWD. During the examination, the patient could maintain attention during verbal interaction but struggled with performing tasks, and there was also evidence of short-term memory impairment. She had visual fixation impairment, including bilateral slow upward drift of eyes and horizontal nystagmus, along with a right facial droop. Involuntary movements were observed in the form of intermittent upper chest myokymia, episodes of right facial twitching, and right shoulder jerky movements, all with intact awareness. A tonic-clonic seizure occurred during admission, linked to a urinary tract infection and hyponatremia.

Overnight video-EEG study revealed multiple nocturnal focal unaware seizures with lip smacking, bimanual automatisms and eyelid fluttering. Repeat brain MRI indicated disease regression with a reduction of swelling and FLAIR hyperintensities, accompanied by evidence of atrophy in the affected regions. CSF studies revealed elevated protein but normal glucose, no pleocytosis, normal CSF hypocretin levels, and negative anti-Ma1 and anti-Ma2 antibodies. Repeat malignancy screening found no tumors. The patient was started on 7 sessions of plasmapheresis and noted improvement from the third session. However, she still had ongoing complaints of hypersomnolence and a continued need for assistance in activities of daily living. She was placed on lacosamide 300 mg BID, lamotrigine 200 mg BID, topiramate 200 mg BID, levetiracetam 500 mg BID.

A multidisciplinary team, including neurologists, neuroradiologists, nuclear medicine specialists, and geneticists has been involved since previous admissions. During this latest admission, they recommended continuing prednisolone 10 mg OD, the combination of ASMs, 5–7 sessions of plasmapheresis every 6 weeks, and rituximab every 3–6 months, as well as continued regular malignancy screening every 6 months.

## Discussion

This case illustrates the presentation and therapeutic challenges of autoimmune limbic and rhombencephalitis due to Ma-2 antibodies in a 50-year-old phenotypically female patient with XY gonadal dysgenesis.

Anti-Ma2 encephalitis is a rare autoimmune disease. In the study by Dalmau et al. [2], 95 % of patients developed isolated or mixed limbic, diencephalic, or brainstem encephalopathy. Excessive daytime sleepiness affected 32 % of the patients, sometimes with narcolepsy-cataplexy and low CSF hypocretin. Eye movement abnormalities and SIADH were also observed. Atypical presentations, such as isolated cerebellar dysfunction or peripheral nervous system syndrome [3], may result in delayed syndrome detection.

Our patient exhibited symptoms indicative of temporal lobe seizures, including olfactory hallucinations, fear, nausea,automatisms and PIWD. She also experienced hypersomnia, despite having normal hypocretin levels in the CSF. Additionally, she had hyponatremia attributed to SIADH and eye movement abnormalities, characterized by upward drift of the eyes and nystagmus.

PIWD is a rare phenomenon described in literature as the action of drinking during or within two minutes of an electroclinical seizure. According to Pietrafusa et al. [5] PIWD may be classified as a rare automatic behavior, akin to other automatisms frequently observed in temporal lobe epilepsy patients. In their article, 51 patients with focal epilepsy and PIWD were described. All cases being associated with temporal lobe epilepsy, predominantly involving the right hemisphere. Hence, there is some suggestion that PIWD might have lateralizing significance in the non-dominant temporal lobe. Our patient had several episodes of PIWD, one of which was witnessed by us, in association with severe nausea attack that was presumed to be ictal in origin. Although this unique seizure semiology was not captured by our video-EEG studies, the patient had several abnormal EEG studies capturing seizures with ictal onset from right temporal lobe. Also, MRI brain showed signal changes in the right (more than left) mesial temporal and insular cortices.

Dalmau et al. [2] described brain MRI findings in patients with anti-Ma2 encephalitis. 70 % of patients had abnormal MRI findings in the initial MRI, seen as a T2 or FLAIR hyperintensity. The regions involved were varied and included unilateral or bilateral medial temporal lobes, amygdala, diencephalon, basal ganglia, brainstem, cerebellar peduncles, and one patient with cerebellar atrophy. The initial MRI brain scan of our patient revealed an intra-axial lesion in the right medial temporal and medial frontal regions, accompanied by edema. This led to the suspicion of a brain neoplasm and, as a result, it led to a delay in initiating the proper treatment. This emphasizes the importance of considering alternative interpretations of MRI images, as they can occasionally be misinterpreted, potentially affecting the course of treatment. In hindsight, it is possible that the MRI findings could have been attributed

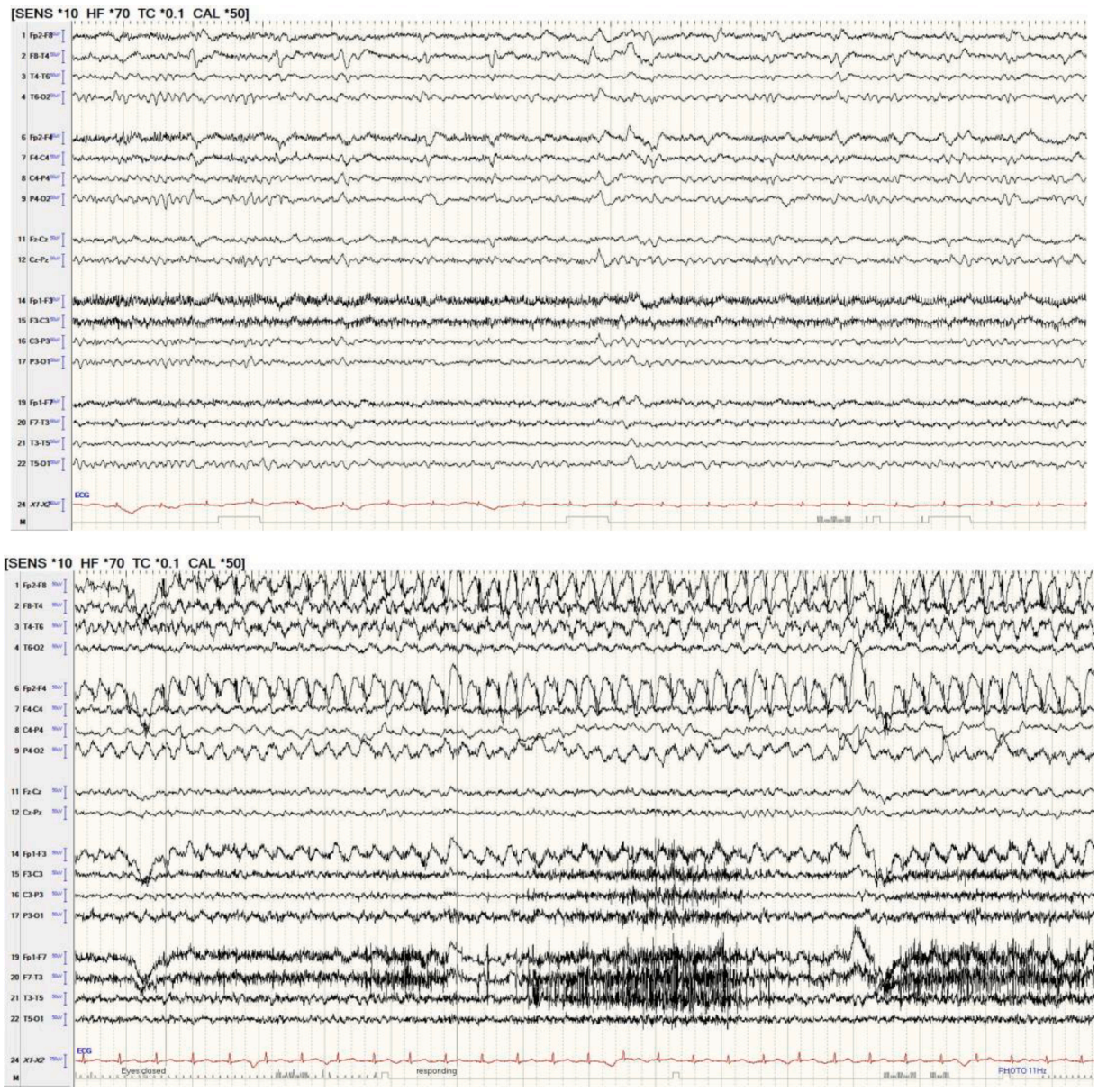


**Fig. 2.** Samples of interictal and ictal EEG findings in longitudinal bipolar montages. Top epoch shows lateralized periodic discharges (LPDs) over right anterior temporal area. Bottom epoch demonstrates an ictal onset from right temporal lobe during a seizure characterized by intact awareness and eyelid fluttering.

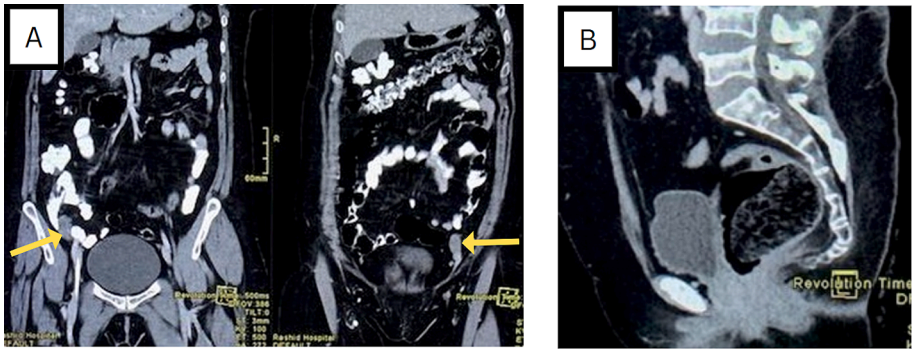


**Fig. 3.** Contrast-enhanced CT abdomen images. (A) Coronal sections with yellow arrows demonstrating oval solid structures in iliac fossae adjacent to external iliac vessels with minimal enhancement. Linear rope-like structures are seen communicating distal poles of both structures to inguinal canal, and look very much like the gubernaculum testis in males. (B) No uterus could be identified on mid-sagittal plane. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to edematous inflammation or even post-ictal changes. Unfortunately, since these initial images were captured at a separate facility, some in a different country, we only had access to the accompanying reports. Brain MRIs obtained at our facility showed signal changes in bilateral mesial temporal cortices, insular cortex and gyrus rectus without significant swelling.

EEGs obtained in the study by Dalmau et al [2] demonstrated unilateral or bilateral epileptic foci, mainly involving the temporal lobes. One patient had LPDs that predominated in the right frontotemporal lobe, similar to our patient. The CSF analyses in the study were abnormal in 78 % of patients, some had increased protein concentration with or without pleocytosis, while others had pleocytosis with normal protein. A few had oligoclonal bands.

The mainstay of therapy in autoimmune encephalitis centres around detecting and resecting an underlying tumor, as well as immunotherapy. Our patient underwent extensive malignancy screening which did not reveal any tumors. Re-evaluation in the context of sex differentiation disorder led to the identification and removal of primitive gonads, which showed no signs of malignancy on histopathology. A combination of therapies, including ASMs, steroids, IVIG, rituximab, and plasmapheresis, achieved only temporary and incomplete relief. The most significant improvement was observed with plasmapheresis and gonadectomy, implying a potential role of dysgenic gonads in the disease process. While prior cases showed symptom improvement with gonadectomy, in some instances, it did not provide lasting relief (Dalmau et al., 2013). In the aforementioned study, 33 % of patients with anti-Ma2 encephalitis experienced neurological improvement, 21 % had long-term stabilization, and 46 % deteriorated. Features associated with improvement of symptoms included male gender, age <45 years, testicular tumor with complete response to treatment, absence of anti-Ma1 antibodies and limited central nervous system involvement.

Relevant to our case, a published report by Al-Thubaiti et al. [1] described a patient with Swyer syndrome presenting with anti-Ma encephalitis. Individuals with Swyer syndrome have an XY chromosome, female appearance, and are at higher risk of gonadal neoplasia. The patient in the report displayed limbic and hypothalamic dysfunction, along with the presence of anti-Ma1 and anti-Ma2 antibodies. An adenexal dysgerminoma was found. Initial improvement followed tumor resection, but the patient succumbed to an unknown cause after two months.

## Conclusion

Anti-Ma2 encephalitis is a rare autoimmune disorder that can be challenging to diagnose and treat. This case highlights the importance of considering underlying genetic conditions in some autoimmune diseases, particularly when tumors are not identified, and pursuing alternative treatment options. Further research is needed to better understand the pathogenesis of this disorder and to identify effective treatment options.

## Ethical statement

Shaikha Alsuwaidi is the corresponding author that takes full responsibility for the data, and all authors have agreed to conditions of authorship.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The patient has provided informed consent for the publication of this case report, including the use of medical images and clinical information.

## Ethical publication statement

We affirm our compliance with the journal's ethical publication guidelines and confirm that the patient has provided informed consent, including the use of medical images, for this case report's publication.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

[1] Al-Thubaiti I, Al-Hayek K, Binfalah M. Anti-Ma-associated encephalitis due to dysgerminoma in a woman with Swyer syndrome. Neurology 2013;80(15):1439–40. https://doi.org/10.1212/WNL.0b013e31828c2f0c.
[2] Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004;127(8):1831–44. https://doi.org/10.1093/brain/awh203.
[3] Lamby N, Leypoldt F, Schulz JB, Tauber SC. Atypical presentation of anti-Ma2-associated encephalitis with choreiform movement. Neurology Neuroimmunol Neuroinflamm 2019;6(3):e557.
[4] Sahashi K, Sakai K, Mano K, et al. Anti-Ma2 antibody related paraneoplastic limbic/brain stem encephalitis associated with breast cancer expressing Ma1, Ma2, and Ma3 mRNAs. J Neurol, Neurosurg, Psychiatry 2003;74:1332–5.
[5] Pietrafusa N, Trivisano M, de Palma L, et al. Peri-ictal water drinking: A rare automatic behavior in temporal lobe epilepsy. Epileptic Disorders 2015;17(4):384–96. https://doi.org/10.1684/epd.2015.0776.
[6] Voltz R, Gultekin SH, Rosenfeld MR, Gerstner E, Eichen J, Posner JB, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. New Engl J Med 1999;340(23):1788–95.