Prolonged coma and cerebral oedema in a patient with a *ATP1A2* variant.

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Abstract

ATP1A2 (OMIM 182340) encodes the α2 subunit of Na+/K+-ATPase. Variation in this gene has been associated with a spectrum of clinical phenotypes, including familial hemiplegic migraine type 2 (FHM2), epilepsy, and intellectual disability.

A 22-year-old woman with intellectual disability, hemiplegic migraine, and epilepsy, presented with persistent decreased consciousness, unexplained by initial investigations. Two weeks later, repeat imaging showed new, marked cerebral oedema with no identified cause; this eventually resolved. A year later, she had a further milder episode. An epilepsy gene panel identified a likely pathogenic missense variant in the *ATP1A2* gene (NM_000702.3: c.1027A>C, p.(Thr343Pro)). After starting memantine as a targeted treatment, her migraine and seizure frequency reduced.

This case highlights the importance of early genetic testing in certain cohorts of people with epilepsy to determine the cause and enable targeted therapeutic interventions.

Keywords:

***ATP1A2*; epilepsy; familial hemiplegic migraine type 2; intellectual disability; cerebral oedema.**

Case presentation

A 22-year-old woman was found unresponsive by her mother, with a snoring breathing pattern, following a one-week flu-like illness. She had a history of focal impaired aware seizures (unilateral motor jerking, mostly left-sided and loss of contact), and focal to bilateral tonic clonic seizures (previously treated with sodium valproate in childhood, but she had been seizure-free off medication for 10 years before this event), hemiplegic migraine (onset in mid-teens) and intellectual disability. She walked around 15 months. She had one or two words at around the age of one, but language development then stopped at that age, following a generalised tonic-clonic seizure during a febrile illness. Her language has not developed further beyond a few words and echolalia. A consultant paediatrician's letter when she was aged 16 recorded ‘developmental age seems around the age of 5 or 6’, with intellectual disability, severe dyspraxia, and autism. Her family described her migraine symptoms as left-sided weakness and slurring of speech, without loss of consciousness or focal seizure activity. She took no regular medications. Family history was unremarkable, with no prior history of migraine or epilepsy in first-degree relatives.

On arrival in the emergency department, she was tachypnoeic with a low-grade fever of 37.7°C. A 12-lead ECG showed sinus tachycardia. Her Glasgow coma scale (GCS) score was 6 (E2V2M2); reflexes were brisk and plantars downgoing bilaterally. She was tolerating an oropharyngeal airway with stertorous breathing sounds, but the remaining general medical examination was normal. She was intubated and transferred to the intensive care unit.

Initial differential diagnoses included intracranial infection or seizures; she was started empirically on ceftriaxone, acyclovir, with levetiracetam loading. However, the CT scan of head on admission was normal, and a lumbar puncture showed no infective cause; opening pressure was not available. Extensive CSF testing found only that the CSF glucose was 50% of plasma glucose. Over the next 2 weeks, trials of desedation were unsuccessful as she did not awaken; continuous EEG monitoring was not available. Repeat CT and MR scans of brain found no cause for her persistent decreased consciousness.

Two weeks after admission, she began having multiple, focal seizures (left rhythmic facial twitching), which resolved after phenytoin loading. The next day, she was found to have an unreactive right pupil and a CT scan of head showed generalised cerebral oedema and tonsillar herniation, which persisted on serial imaging over the next 4 weeks (*figure 1).* An intracranial bolt was inserted to monitor intracranial pressure; thiopental was added as a third agent to control subsequent seizures.

Serial EEG showed no evidence of status epilepticus (*figure 2).* Extensive serological testing was normal, and testing for common mitochondrial mutations was negative.

Her conscious level slowly improved over the next 2 weeks. One month after admission, a percutaneous tracheostomy was inserted, and she was discharged from the intensive care unit to the neurology high dependency unit. After 10 weeks in hospital, she was discharged having recovered well with physiotherapy; the tracheostomy had been removed, and she had a good neurological outcome overall. However, she was more irritable than before, with reduced engagement in activities previously enjoyed; she had poorer balance and required a wheelchair for long distances. Brain imaging post-discharge showed the cerebral oedema had resolved (*figure 1).*

The following year, she presented to the emergency department with dense left-sided hemiplegia and drowsiness (GCS score 13 (E4V4M5)). Her family reported an increased frequency of focal seizures (left-sided facial twitching) over the previous few days. On examination, she had increased tone in the left arm and leg, as well as left facial droop and left upper and lower limb weakness; right-sided tone and strength were normal. Reflexes were brisk on the left, with downgoing plantars bilaterally. Initial CT scan of head and venogram showed no acute intracranial findings and a lumbar puncture was normal; however, the opening pressure was not measured and there was no paired plasma glucose to allow for comment on CSF: plasma glucose.

Her level of consciousness fluctuated over the following fortnight (GCS score 8–13). She had frequent focal seizures throughout the admission (left-sided facial twitching with eye deviation to the left), which evolved into epilepsia partialis continua one week into the admission; this terminated after phenytoin loading. The left-sided weakness persisted for 10 days before gradually improving. At the end of the three-week admission, she had recovered to her baseline and was discharged. Repeat imaging performed after the onset of epilepsia partialis continua showed right-sided cerebral oedema *(figure 3)*.

After discussion with the medical genetics team, she was tested with an epilepsy gene panel (clinical exome sequencing with a filter applied). This identified a missense variant in the *ATP1A2* gene (NM_000702.3: c.1027A>C, p.(Thr343Pro)). Following ACGS Best Practice Guidelines for Variant Classification, the variant was classified as likely pathogenic based on absence from population databases (PM2), predicted deleterious by *in silico* tools (PP3), absence of variant in parental samples (PM6), and a different missense variant (c.1028C>T, p.(Thr343Ile); ClinVar variant ID 529750) has been reported as pathogenic at the same residue (PM5)[1]. Furthermore, *ATP1A2* is a gene with a low rate of benign variation (PP2) and the Thr343Pro variant is in the proton-ATPase domain, a key functional region of the protein, with little nearby variation in the general population (PM1). We submitted details of the

variant to the DECIPHER database (Patient 433613) (https://www.deciphergenomics.org/patient/433613/).

Treatment

The genetic panel provided the key to linking the triad of hemiplegic migraine, epilepsy, and intellectual disability. It also explained the two episodes of cerebral oedema, which had been otherwise suspected to have an infective or inflammatory cause. Identifying this genetic variation helped inform future acute treatment options, and ongoing management. Small case series in children and adolescents have reported improvements in overall function, including speech, cognition, behaviour, alertness and attention span after memantine treatment as a targeted treatment for *ATP1A2*-related encephalopathy. Some children also showed improved motor function, including fine motor skills and gait; memantine was generally well-tolerated with few side effects[2,3].

After discussion with the patient and her mother, and hospital approval for unlicensed use, she started memantine at 10 mg twice daily four years after the first admission. Follow-up at 3, 6 and 12 months showed that the memantine was well tolerated and had reduced the frequency of hemiplegic migraine (from monthly to one in 12 months), and the frequency of focal to bilateral tonic-clonic seizures (from two to one in 12 months). The frequency of catamenial focal seizures was unchanged. Whilst there was no significant difference in objective tests to assess learning, her mother reported improved behaviour, language, and increased focus and desire to engage in tasks such as reading and drawing. There was a further recent hospital admission, almost 7 years since her first presentation, with a generalised tonic-clonic seizure, decreased consciousness, post-ictal headache, and hemiplegia that resolved over 4 weeks, and no cerebral oedema on CT or MR imaging.

Discussion

Whilst paediatric neurologists frequently diagnose developmental and epileptic encephalopathies, many remain undiagnosed when they reach adulthood. Thus, adult neurologists should consider a genetic basis for complex epilepsy and revisit previous negative genetic tests as genetic testing advances[4].

There are many different genetic testing techniques, and so multidisciplinary discussions between clinical geneticists and neurologists are important in determining the appropriate technique. A study using whole-exome sequencing looked at 71 adult patients with developmental and epileptic encephalopathies, 90.1% of whom had previous negative genetic testing. Whole-exome sequencing identified 24 likely pathogenic variants in 18 patients, giving an overall diagnostic yield of 25.3%. This discovery influenced the clinical management of half the patients in whom a genetic variant was identified[4]. As genomic testing for intellectual disability and epilepsy becomes more widely available, a higher proportion of

children will have a definite genetic diagnosis with implications for management and improved future treatment.

ATP1A2 (OMIM 182340) is a gene which encodes the α2 subunit of Na+/K+-ATPase. Variation in the *ATP1A2* gene is associated with a spectrum of disease phenotypes, including familial hemiplegic migraine type 2 (FHM2), epilepsy and intellectual disability. The relationship between *ATP1A2* genotype and phenotype is still being defined. Recent evidence suggests reduced Na^+/K^+-ATPase activity is correlated with increased severity of familial hemiplegic migraine phenotypes and intellectual disability.[5] Most patients with early-onset sporadic hemiplegic migraine have either *ATP1A2* or *CACNA1A* mutations, and around three-quarters of these are de novo[6].

There have been other case reports of people with *ATP1A2* variations who have developed cerebral oedema following hemiplegic migraine and/or status epilepticus[7,8]. In a 15-year follow-up of 12 family members with *ATP1A2* variations, 9/12 had episodes of altered consciousness, lasting days to weeks; only two had abnormalities on CT/MR scan of the brain during these episodes[8]. Over the follow-up period, several patients had recurrent episodes, with three requiring rehabilitation to regain full motor function[8]. Along with the case we describe, this provides evidence that *ATP1A2*-related coma/cerebral oedema can have a good functional outcome and provide reassurance to family members and treating clinicians during these episodes of reduced consciousness.

Animal models have suggested that neuronal dysfunction in *ATP1A2*-related encephalopathy results from glutamate excitotoxicity[9]. Memantine is a noncompetitive NMDAR antagonist, typically used in Alzheimer's dementia, which restores homeostasis in the glutamatergic system[10]. As discussed above, this has been shown in case reports/series, as well as in this case, to reduce seizures and/or improve overall function, including behaviour and learning[2,3]. Improvements in function and reduced severity of seizure are also reported in a patient with *ATP1A2*-related epileptic encephalopathy treated with intramuscular ketamine injections[2].

This case highlights the importance of genetic workup for people with epilepsy and intellectual disability and/or other neurodevelopmental disorders, especially in those with unexplained neurological presentations. Discussion with genetic multidisciplinary teams allows for appropriate testing and aids in the interpretation of results. Identifying genetic variation can allow for targeted treatment options, which can reduce seizure frequency and/or lead to an improvement in overall function.

Key points

1. Multi-disciplinary discussions between neurology and clinical genetics are crucial to determine the most appropriate technique and panel for genetic testing.

2. As genetic panels expand, adult neurologists should consider re-visiting the possibility of a genetic diagnosis in selected patients, even with previous negative results.
3. Genetic diagnoses can unlock targeted treatments.
4. Case reports/series are an important source of information for rare diseases.

Suggested further reading

Minardi R, Licchetta L, Baroni MC, et al. Whole-exome sequencing in adult patients with developmental and epileptic encephalopathy: It is never too late. Clin Genet 2020; 98: 477–485.

Moya-Mendez ME, Mueller DM, Pratt M, et al. Early onset severe ATP1A2 epileptic encephalopathy: Clinical characteristics and underlying mutations. Epilepsy & Behavior 2021; 116: 107732.

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Figure legends

Figure 1. 1A) CT scan of head showing bilateral cerebral oedema. 1B) CT scan of head 4 days later showing ongoing bilateral cerebral oedema with an intracranial pressure bolt in situ. 1C) Follow-up CT scan of head at 3 months showing resolution of previous cerebral oedema.

Figure 2. 2A) Prolonged EEG performed whilst on midazolam and 24 hours after thiopental was withdrawn, showing low amplitude with little/no cortical activity. There were no visible epileptiform discharges. 2B) Repeat EEG 4 days later after withdrawal of all sedation, showing diffuse generalised slow wave activity. There was greater amplitude than previously, and no epileptiform discharges were seen. 2C) Repeat EEG 9 months after first admission, showing resolution of these changes.

Figure 3. 3A) CT scan of head showing right-sided cerebral oedema. 3B) MR scan of brain 2 days later showing slightly improved right-sided cerebral oedema and increased signal in the right cerebral cortex compared with the left, with decreased intensity of the right subcortical white matter compared with the left. 3C) Subsequent CT scans showed resolution of the unilateral cerebral oedema.

Competing interests

None.

Contributorship

SV and KH were directly involved in patient care, conception and design of the case report, as well as acquisition of the case data. SV drafted the manuscript. SV, AF and KH edited, reviewed and approved the final manuscript. KH is the guarantor.

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Ethical approval information, institution and number(s)

Not applicable.

Data sharing statement

Not applicable.

Patient and Public Involvement, see the journal's submission guidelines

Not applicable.

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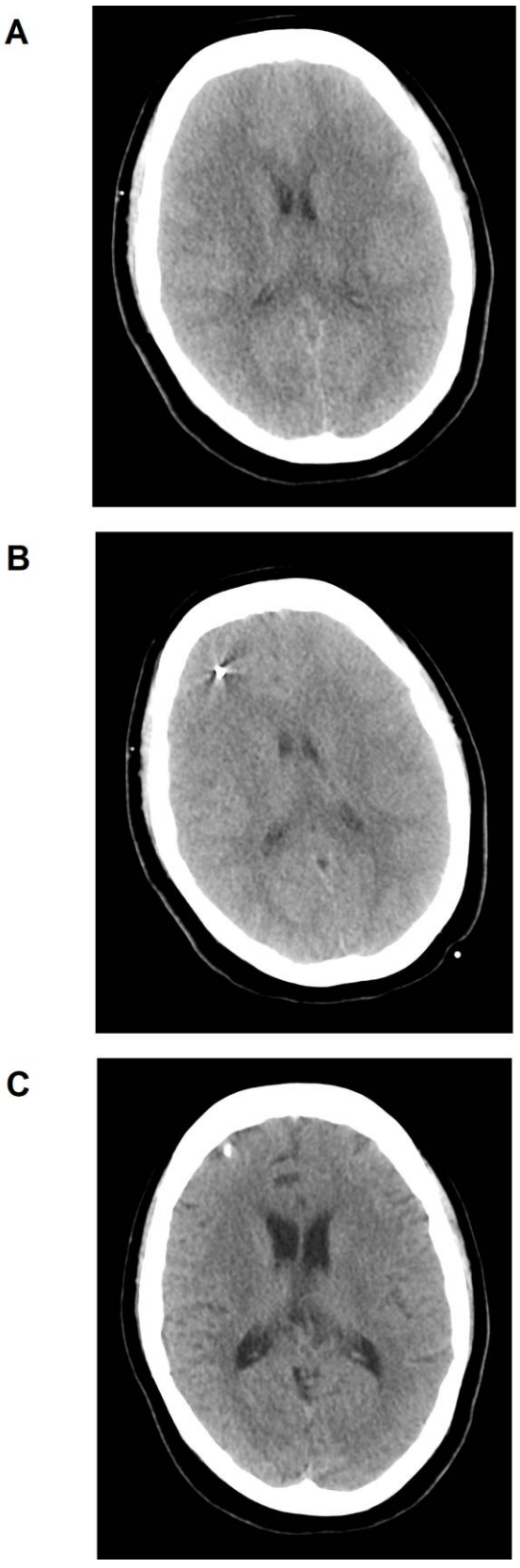
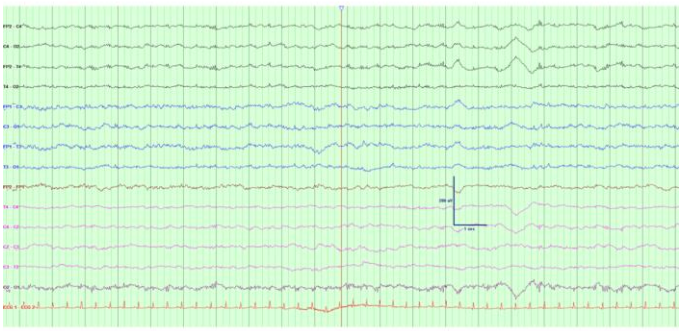


Figure 1

A



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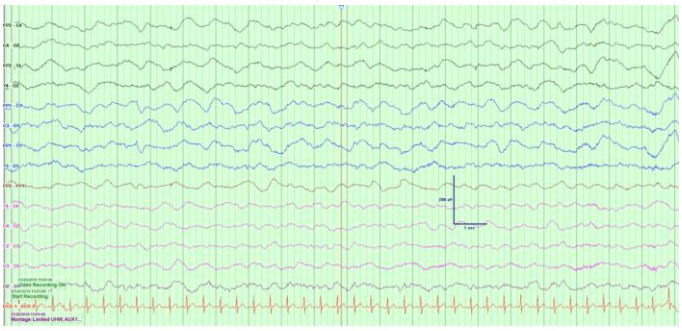

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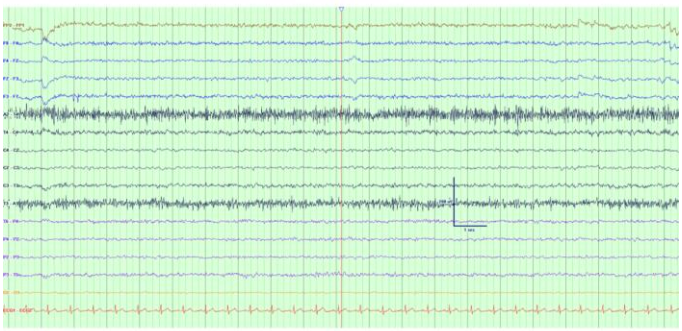
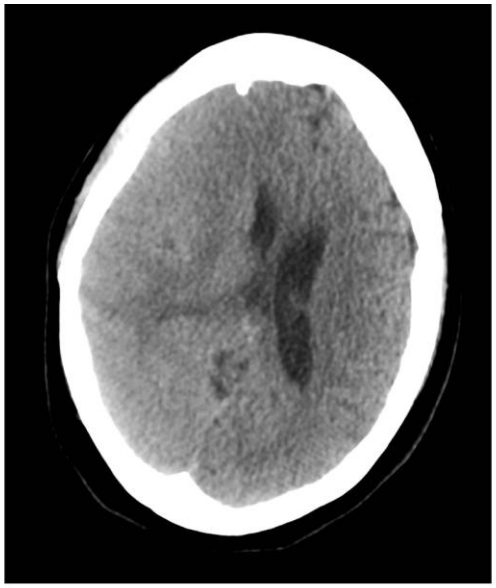


Figure 2

A



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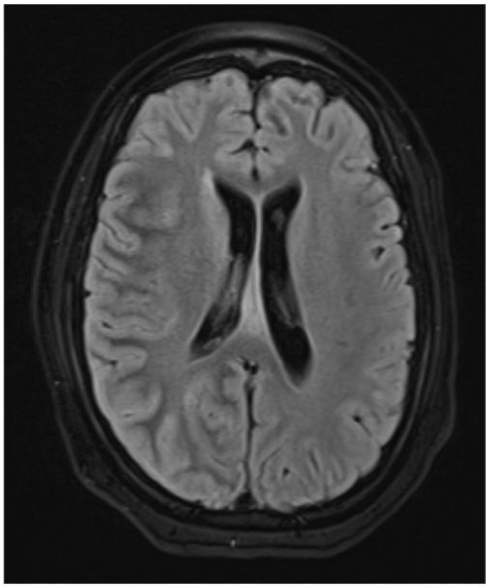

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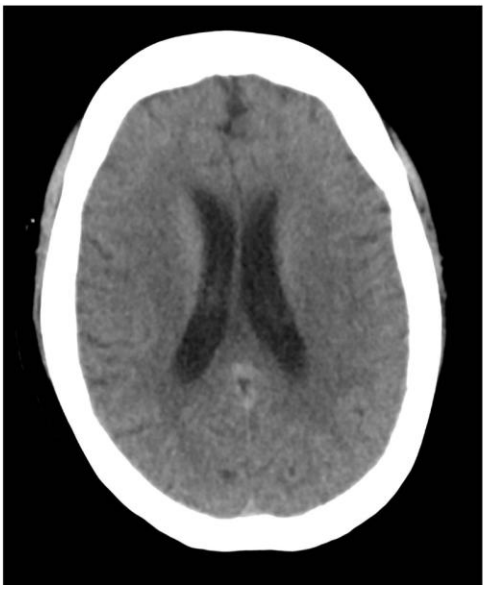

Figure 3