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Short clinical reports

Asystole in alternating hemiplegia with de novo *ATP1A3* mutation

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ABSTRACT

Alternating hemiplegia is a rare condition presenting with episodes of hemiplegia, epileptic seizures and, at times, dysautonomic attacks. De novo *ATP1A3* (Na^+/K^+ ATPase subunit) mutations were recently found to be the most common cause. We report a patient with alternating hemiplegia with de novo *ATP1A3* mutation who experienced new-onset episodes of collapse in early adulthood unrelated to seizures. An implantable cardiac loop recorder documented episodes of asystole up to 5 s long. Subsequently a permanent pacemaker was implanted. *ATP1A3* heart expression may be the explanation for the association of alternating hemiplegia and asystole episodes. Alternating hemiplegia has been associated with an increased risk of sudden death and lethal cardiac arrhythmias may be causative. Patients may need referral for appropriate cardiac investigations, especially if there is a change in symptoms. This case highlights the importance of clinical vigilance in patients with alternating hemiplegia.

1. Introduction

Alternating hemiplegia is a rare condition of unknown cause, whose incidence is estimated to be one in one million births. It presents with episodes of alternating hemiplegia of variable duration within the first 18 months of life. The episodes can also be bilateral, with dysphagia and, at times, co-incident dysautonomic (mostly respiratory) features. Patients may also often experience paroxysmal abnormal limb movements, epileptic seizures, and abnormal eye movements. Most patients have learning disabilities, and very often have interictal movement disorders (dystonia, chorea), spasticity or/and ataxia [Panagiotakaki et al., 2010]. Recently, de novo *ATP1A3* (Na^+/K^+ ATPase α3-subunit) mutations were found to be the cause in the majority of cases [Heinzen et al., 2012; Rosewich et al., 2012].

There is uncertainty about the long-term outcome of the disease [Bourgeois et al., 1993; Gordon, 1995]. Recently, a large European multicentre study [Panagiotakaki et al., 2010] found no evidence of deterioration in the frequency of the attacks or in the overall condition to age 52, but also showed an important risk of premature mortality, as 7 (4%) patients died before the age of 29, one (0.6%) during the two year prospective follow-up period, which accorded with a previous report [Sweney et al., 2009]. Most deaths occurred in relation to severe epileptic seizures or hemiplegic attacks. In one case, death occurred 'during an epileptic seizure complicated by cardiorespiratory arrest', and one other death was reported to be 'from cardiorespiratory failure' [Panagiotakaki et al., 2010].

We report on a patient with alternating hemiplegia and de novo *ATP1A3* mutation, who experienced prolonged syncopal attacks later in life and was found to have episodes of significant asystole.

2. Clinical report

This 23 year old female with alternating hemiplegia was referred to our clinic for investigation of episodes of loss of consciousness. She was born at term after a normal pregnancy, but suffered from foetal distress and required intubation briefly. She had delayed development, smiling at 4 months and walking independently at 6 years. There was no family history. At 3 months, she developed typical hemiplegic attacks, which occurred several times weekly; she also had bilateral episodes several times monthly. The diagnosis of alternating hemiplegia was formally considered at age 6. She also started having infrequent generalised tonic–clonic and simple partial motor seizures at age 12. The seizures remained drug-resistant despite several antiepileptic drugs including phenytoin, carbamazepine, phenobarbital, valproate, vigabatrin, and clonazepam. The frequency of her hemiplegic attacks improved only transiently with flunarizine and melatonin.

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At age 21, she started having, every two months on average, different episodes marked by sudden collapse, loss of consciousness, respiratory arrest and gradual cyanosis. The duration of these episodes was 30–90 s. These attacks were clinically distinct from both seizures and hemiplegic attacks. She continued concomitantly to have rare partial (simple motor) or generalised seizures (yearly) and almost daily hemiplegic (either unilateral or bilateral) attacks. 24 h ambulatory ECG recordings did not record any significant abnormality, but she did not experience a collapse during monitoring. At the age of 23, she was referred by her local neurologist because the new episodes continued to occur every two months. At this stage treatment consisted of carbamazepine, pizotifen and flunarizine. During hospital admission, no collapses were recorded; her interictal EEG showed rare bursts of anterior spike and waves. A three Tesla MRI scan showed right hippocampal sclerosis. Her routine 12-lead ECG was normal. An implantable cardiac loop recorder device (Medtronic Reveal) was then implanted. The default mode of this device was set to detect asystole longer than 3 s, as well as any tachycardias. Three episodes of asystole were recorded over four months, the longest lasting 5 s (Fig. 1). It was not possible to document a clear cut rhythm/symptom correlation with the available data. However, given the known risk of sudden death associated with the disease, it was decided to implant a dual chamber pacemaker (Medtronic Advisa DR MRI Surescan A3DR91 pulse generator with Medtronic 5086MRI pacing leads). This procedure was carried out after a best interest meeting and with the parents' assent. There have been no further collapses during the subsequent follow up of 26 months: interrogation of the pacemaker showed that it had been called upon to pace since implantation (e.g. 1.6% of the total time over the six months to the last interrogation, for example during episodes when the heart rate fell below 60 beats/minute).

She then underwent 94 h video-EEG telemetry showing slow background activity with bursts of anteriorly predominating generalised spike and slow wave activity. There were no ECG or EEG changes during several recorded hemiplegic episodes, no seizures were recorded.

The patient has a de novo mutation in *ATP1A3* (c.410C-T, [Heinzen et al., 2012]), resulting in amino acid substitution (Ser137Phe) in the second (M2) transmembrane domain of the protein.

3. Discussion

We report a patient with alternating hemiplegia who developed new, prolonged collapses in her early adulthood which contrasts with the general observation that the spectrum of paroxysmal events remains stable after their onset [Panagiotakaki et al., 2010]. The patient fulfilled the major diagnostic criteria for the condition [Neville and Ninan, 2007], although she had atypical features such as foetal distress at birth and hippocampal sclerosis, both probably not directly related to the condition. Indeed hippocampal sclerosis can be consequence of brain insults or seizures [Jellinger and Attems, 2012; Scott et al., 2003]; it does not per se define temporal lobe epilepsy without characteristic clinical and neurophysiological features [Wieser, 2004]; prolonged EEG recording in our patient showed generalised epileptic activity, with no focal component. Episodes of asystole were found on implantable cardiac loop recorder monitoring; no further episodes occurred after a pacemaker was implanted.

We assume that these episodes of asystole are linked with the alternating hemiplegia due to *ATP1A3* mutation, but there are several confounders that need to be considered. The patient had concomitant drug-resistant epilepsy and hippocampal sclerosis was found as a structural abnormality. Seizures involving temporal structures can at times induce significant bradycardia or asystole [Winesett et al., 2009], seizures preceding asystole can be subtle [Novy et al., 2009]. Despite the hippocampal structural abnormality, seizures in our patient were not suggestive of temporal involvement either clinically (partial motor seizures previously described in alternating hemiplegia [Neville and Ninan, 2007]) or electrophysiologically (showing generalised epileptic activity without focal component). The episodes of collapse were, moreover, clearly distinct in content, tempo, and timing from the patient's habitual seizures and ceased after the pacemaker implantation. Hippocampal sclerosis is not associated per se with cardiac arrhythmia [Ansakorpi et al., 2004]. Carbamazepine can rarely be associated with cardiac conduction defects, mostly atrio-ventricular block [Kennebäck et al., 1992]; our patient's clinical cardiological evaluation and routine interictal 12-lead ECG was normal. The patient had been on long-term treatment with carbamazepine for years before onset of the episodes.

ATP1A3 is highly expressed in cardiomyocytes and atrioventricular node cells (http://www.genecards.org/cgi-bin/carddisp.pl?gene=ATP1A3&search=atp1a3). *ATP1A3* mutations are known to cause rapid onset dystonia–parkinsonism (DYT12), in which condition seizures, but not cardiac arrhythmias, are occasionally described [Brashear et al., 2007]. While in both conditions activity of the protein is reduced, in rapid onset dystonia–parkinsonism, expression of the protein is markedly reduced [de Carvalho Aguiar et al., 2004] whereas in alternating hemiplegia, the function of the protein seems altered [Heinzen et al., 2012]. Toxic inhibition of the Na^+/K^+ ATPase (e.g. by ouabain) is well known to induce a wide range of arrhythmias (including nodal arrest), although they are usually not paroxysmal [Vassalle et al., 1963]. Alternating hemiplegia

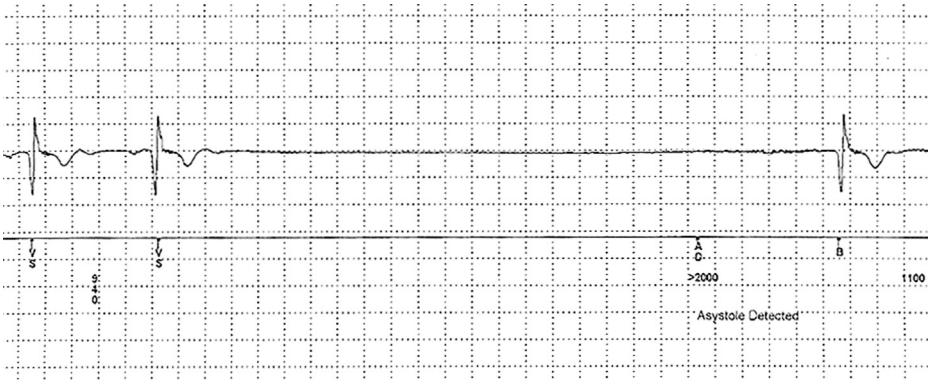

Fig. 1. Five seconds asystole episode recorded by the loop recorder device.

and asystolic episodes may thus both be paroxysmal symptoms of a single genetic defect.

Identifying episodes of asystole is important given the risk of sudden death in alternating hemiplegia. Epilepsy is also well known to be associated with premature mortality [Surges and Sander, 2012], but in alternating hemiplegia premature mortality has been shown not to be exclusively linked with seizures as some of the reported deaths were said to be due to cardiorespiratory arrest also in isolation or following hemiplegic episodes [Panagiotakaki et al., 2010; Sweney et al., 2009]. To our knowledge, there are no published post mortem examination data in premature death in alternating hemiplegia, cardiac abnormalities have never been reported in alternating hemiplegia before death. Additional studies are required. Cardiac monitoring should be considered in patients with alternating hemiplegia, if they experience suggestive episodes. Cardiac monitoring duration should be adapted to the frequency of the episodes (Holter, R-Test-one week recording or implantable loop recorder in case infrequent episodes). In people without associated medical conditions, ventricular pauses longer than 3 s are variably associated with symptoms and appear not to significantly increase premature mortality [Saba et al., 2005], but in alternating hemiplegia, where sudden deaths have repeatedly been reported, they should be considered seriously. Implantation of a pacemaker could be lifesaving.

4. Conclusions

This case shows that isolated potentially life-threatening cardiac arrhythmia can develop later in the course of alternating hemiplegia. Episodes in this condition may have various causes (cerebral and cardiac), in line with a widespread consequence of the genetic defect. In the presence of suggestive symptoms, arrhythmia should be actively sought as it may be preventable.

Conflict of interest

The authors declare no conflict of interest.

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