NARP syndrome and adult-onset generalised seizures

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ABSTRACT – The neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) syndrome is a maternally inherited disorder attributable to a heteroplasmic mtDNA point mutation. Catastrophic epilepsy may accompany severe, early onset forms of NARP, but seizures seem to be rare in cases with adolescent and adult onset. We describe a patient who developed clumsiness and visual problems in her teens. She had no clinical seizures but an EEG showed generalized spike and wave discharges. At this time the patient remained without a specific diagnosis. At the age of 21, the patient developed progressive ataxia and she also experienced a tonic-clonic status epilepticus. Further examinations revealed NARP syndrome. EEG abnormalities may precede adult onset seizures in the NARP syndrome.

Key words: NARP, mitochondrial disease, epilepsy, generalised, adult, retinitis pigmentosa

The neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) syndrome is a maternally inherited disorder with developmental delay, sensory neuropathy, ataxia, retinal pigmentary changes and proximal neurogenic muscle weakness. The syndrome, first described in 1992, is associated with a heteroplasmic mtDNA point mutation, a T→G change at nt 8993 of the mtDNA of the gene coding the subunit 6 of F1F0 ATP synthase (Holt et al. 1990, Mäkelä-Bengs et al. 1995). Since its original description, this mutation has been reported to result in a variety of clinical symptoms, including Leigh’s syndrome (Mäkelä-Bengs et al. 1995, Uziel et al. 1997).

Seizures, especially infantile spasms, have been described in patients with Leigh’s syndrome (Mäkelä-Bengs et al. 1995), but the incidence and type of epilepsy in other clinical forms of the NARP mutation are not well known. To date, only two NARP patients with onset of seizures during adulthood have been reported (Holt et al. 1990, Santorelli et al. 1997).

In this case report we describe a patient in whom adult-onset seizures led to the diagnosis of the NARP syndrome.

Case study

Our female patient was born to apparently healthy parents after a full-term pregnancy. Her only sister had severe mental retardation that was considered to be the result of asphyxia during delivery. The early childhood development of the patient was normal, but at the age of 14 she slowly developed slight clumsiness, difficulty in maintaining balance and problems with vision. She was examined by both an ophthalmologist and a pediatric neurologist. Her visual acuity was considerably impaired (0.4/0.6).
Pigmentation of the retina in the left eye was seen to be uneven, and some narrowing of the visual fields was detected. The neurological examination yielded results within normal limits and the clumsiness was thought to be due to the impaired vision. Results of computed tomography (CT) of the head and cerebrospinal fluid (CSF) parameters were normal, as well as the visual and auditory evoked potentials. The EEG showed, however, symmetric 3-4 Hz spike and wave discharges. The discharges were enhanced by both photostimulation and hyperventilation (figure 1A). The patient had experienced no epileptic seizures. Both the patient and her mother declined further investigations and thus no specific diagnosis of the disorder was arrived at that time. Subsequently, she was able to finish her primary education with minor difficulties and take up a profession as an assistant nurse.

At the age of 21, problems in maintaining balance rapidly progressed and the patient began to suffer falls. A primary health care physician noticed an ataxic gait and referred the patient for neurology ER. Upon examination, she was found to be very thin and her personality appeared immature and naïve. Ataxia of both lower and upper extremities was detected. The reflexes and brainstem functions seemed to be normal and there was no impairment in sensory functions or muscle strength. Brain CT revealed cerebellar atrophy. Both plasma (2.3 mmol/L, reference range 0.5-1.6 mmol/L) and CSF (4.1 mmol/L, normal < 2.7 mmol/L) lactate levels were elevated, this raising the suspicion of a possible mitochondrial disease.

The patient was admitted to the neurological ward for further investigations. Brain MRI was carried out and it confirmed the finding of cerebellar atrophy, but revealed no additional pathologies. As the patient was in good health she was shortly discharged and further investigations were planned at the outpatient clinic. The patient was however brought back to the ER a few days later due to tonic-conic status epilepticus. Upon arrival of the paramedics, the patient was given 5 mg diazepam i.v. and the convulsions abated. At the ER, the patient quite rapidly regained consciousness and the results of neurological examination were unchanged from previous findings. In further investigations, an interictal EEG (figure 1B) showed spike and slow wave discharges. The electroneuromyography (ENMG) revealed mixed-type polyneuropathy mainly in the lower extremities, affecting both sensory and motor fibers, even though there were no clinical signs or symptoms of neuropathy. In the ophthalmological evaluation the pigmentation of the retina was seen to be uneven, but there was still no typical retinis pigmentosa found. Visual acuity was 0.4/0.4 and the bilateral concentric visual field narrowing as before. Mutation analysis of the mitochondrial DNA test revealed a T8993G mutation. Subsequently, the patient’s sister, mother and maternal grandmother all tested positive for NARP.

The patient was started on lamotrigine and, following a rash reaction, was switched to valproate. She has since remained seizure-free.

Discussion

In agreement with previously reported cases (Holt et al. 1990, Puddu et al. 1993, Uziel et al. 1997, Santorelli et al. 1997), our patient harbored typical features of the NARP syndrome, e.g., ataxia, visual symptoms due to retinal pigmented changes, and mild mental retardation. Also neuropathy was present, yet without clinical symptoms and verified only by ENMG.

The clinical symptomatology of the NARP mutation is variable, and three or four types of disease can be differentiated. The most severe form appears in infancy or in early childhood as Leigh’s syndrome with psychomotor regression, brain stem dysfunction, ataxia and optic atrophy, and often with a lethal course (Tatuch et al. 1992, Ciafaloni et al. 1993, Mäkelä-Bengs et al. 1995, Santorelli et al. 1997, Uziel et al. 1997). An intermediate clinical presentation during infancy manifests with seizures, apnoic spells, feeding problems, cerebellar dysfunction and visual impairment due to retinitis pigmentosa (Mäkelä-Bengs et al. 1995, Santorelli et al. 1997, Uziel et al. 1997). Symptomatology starting in later childhood, adolescence or during adulthood seems to run the most benign course. These patients present with visual symptoms, ataxia, mild mental deterioration and hearing loss (Holt et al. 1990, Ciafaloni et al. 1993, Ortiz et al. 1993, Mäkelä-Bengs et al. 1995, Santorelli et al. 1997, Uziel et al. 1997). Some subjects with the NARP-mutation may only have migraine or may even be completely asymptomatic (Tatuch et al. 1992, Ortiz et al. 1993, Mäkelä-Bengs et al. 1995). Disease severity is determined by the degree of heteroplasmcy (the mutant load), i.e., the higher the degree of heteroplasmcy the more severe is the clinical presentation (Holt et al. 1990, Mäkelä-Bengs et al. 1995, Santorelli et al. 1997).

Most of the reported cases of the NARP mutation associated with epileptic seizures have had Leigh’s syndrome or some other severe clinical presentation of infancy or early childhood (Holt et al. 1990, Ortiz et al. 1993, Fryer et al. 1994, Mäkelä-Bengs et al. 1995, Santorelli et al. 1997, Uziel et al. 1997, Parfait et al. 1999, Desguerre et al. 2003). In these patients, both partial seizures and infantile spasms may appear. NARP patients with the onset of symptoms after infancy have been reported to have both myoclonic, tonic-clonic and possibly atypical absence seizures (Fryer et al. 1994, Tatuch et al. 1994, Parfait et al. 1999). Only two cases with adult (age 24 and 26 years) onset tonic-clonic seizures in NARP have previously been described (Holt et al. 1990; Santorelli et al. 1997).

In our patient, EEG displayed generalized spike and wave discharges whereas previous studies noted only non-
Figure 1. Interictal EEG showing spike and wave discharges.
epileptic EEG changes (Holt et al. 1990, Santorelli et al. 1997). Thus, epileptiform EEG abnormalities can appear in the absence of clinical seizures or may precede the onset of epilepsy by several years. We did not observe any progression of the EEG abnormalities with time. On the basis of our case report, we propose that symptomatic generalized epilepsy may accompany the NARP syndrome, and that epileptiform EEG changes may precede clinical seizures by several years.

References


