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FRIEDREICH'S ATAXIA WITH EPILEPTIC SEIZURES

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Friedreich's ataxia is an autosomal recessively inherited neurodegenerative disorder caused by expansions of an unstable GAA trinucleotide repeat in the STM7/X25 gene on chromosome 9q. This disease can be associated with many abnormalities: cerebellar and sensory ataxia, heart disease – aproximately two third of the patients, musculoskeletal deformities – scoliosis being the most common, diabetes mellitus or impaired glucose tolerance. Epilepsy is seldom described as a clinical feature associated with Friedreich's ataxia, very few cases being presented in literature and the mechanisms of seizures are unclear. We present such a case of association of epilepsy with a genetically confirmed Friedreich disease. This is the case of an 18-year-old patient with history of Friedreich's ataxia and hypertrophic cardiomyopathy who was admitted in our clinic for a generalized seizure with chaotic movements of limbs (no proper tonic-clonic seizures) followed by minutes of altered level of consciousness, bite-inflicted tongue wound and postictal state with confusion. The particularity of the case consists in association of epileptic seizure and Dandy Walker malformation to Friedreich's ataxia, being known that epilepsy is rarely associated with this disease.

Keywords epilepsy, Friedreich's ataxia

INTRODUCTION

Friedreich's ataxia (FA) is an autosomal recessively inherited neurodegenerative disorder caused by expansions of an unstable GAA trinucleotide repeat in the first intron of the frataxin (STM7/X25) gene on chromosome 9q that reduces the gene function, hampering frataxin transcription[1]. As all the patients carry one or two copies of this expansion (the size of which varies greatly through generations), its identification constitutes the basis for the molecular diagnosis of FA[1]. The vast majority of patients (more than 95%) are homozygous for this genetic anomaly, while the rest are heterozygous, but still carry an aberrant allele (due to point mutations) on the chromosome lacking the triplet expansion[2]. pointing out that the X25 gene copies on both 9q chromosomes must malfunction for the disease phenotype to arise.

The triplet repeat is pathological not by its quality (as up to 35 to 40 GAA triplets may occur in normal chromosomes), but by its quantity: The lower limit for the disease-inducing genotype is at around 70 GAA triplets, while the upper is beyond 1000[3]. Moreover, the larger the GAA repeat sequence, the more serious its repercussions on both frataxin expression and disease severity, at least up to a threshold of ~500 repeats, beyond which the gene function is too heavily impacted (i.e. the expression of frataxin is too depressed) for further increases in the number of repeats to have any noticeable supplementary consequence on the clinical presentation[1]. It has been posited that, for all practical purposes, such extreme length (GAA)n blocks (of more than 500 repeats) completely abolish hnRNA (heterogenous nuclear RNA) processing into mature mRNA (messenger RNA) for frataxin[4]. Therefore larger blocks (of 600, 700 or even more than 1000) are as clinically deleterious as those of 500 repeats[4]. By contrast, shorter repeat sequences have more nuanced consequences, probably due to lesser degrees of X25 gene dysfunction, correlated with some residual frataxin RNA processing and frataxin expression (grossly inversely proportional to the number of GAA repeats)[2]. Consequently in patients with repeat blocks of less than 500 GAA units the block length is correlated with the severity of the disease, in terms of both progression rate and precocity of onset of disease itself and of various symptoms (such as dysarthria and motor deficit)[2,5]. Furthermore, in homozygous patients, the length of both alleles should be taken into account, the smaller one being correlated with the age of onset, while the length of both is involved in determining the age at which the patient can no longer leave the wheelchair[6].

Until now the researchers failed to unravel the precise function of *frataxin*, but it is certain that this iron-binding protein resides in mitochondria, where it plays a crucial role in the iron metabolism[7]. *Frataxin* may sense iron, or store it, or accompany it in the iron-sulphur clusters or in the hem biosynthesis. It may also function as some kind

of 'metabolic switch'[8].
It also seems to be involved in the control of oxidative stress as a ROS (reactive oxygen species) scavenger[8]. It is clear that frataxin deficiency results in increased oxidative damage but it is uncertain whether this is the consequence of faulty protection (as evidence is gathering about its involvement in the detoxification of reactive oxygen species) or of heightened ROS generation (which may be the result of defective respiratory chain leading to electrons spilling out of the mitochondria)[8]. No direct proof has emerged as yet for a link between frataxin and ROS production, so the evidence is rather circumstantial: patients lacking frataxin (which are essentialy those with FA) have (in blood, urine, and lymphoblasts) increased markers of oxidative stress (such as hydrogen peroxide and oxidized glutathione), while their fibroblasts and lymphoblasts are excessively sensitive to oxidative stress[8].
Frataxin deficiency mai provoke iron build-up and oxidative aggression, which may lead to inflammation and, through it, to neural degeneration[8].
Indeed, this seems to be the case in the heart of FA patients: there are inflammatory changes in the myocardium accompanied by infiltrating leukocytes, which may play a role in the progression of cardiomyopathy[9].
Similarly, Schwann cells lacking frataxin are subjected to inflammatory injury and finally succumb to it[8]. As they are in close proximity to DRG neurons, their death may result in loss of myelin and axonal degeneration[8].
The role of inflammation in the demise of frataxin-deprived Schwann cells is corroborated by the ability of anti-inflammatory therapy to revive the dying cells (antiapoptotic medication may have a similar effect)[10].
Although the lack of frataxin induces inflammation that affects Schwann cells but not oligodendrocytes, it prevents the proliferation of both cell types. However DRG (dorsal root ganglia) neurons are exempt from this effect[11].
The inflammatory reaction may be spurred by the pro-inflammatory cytokines released by the Schwann cells themselves (as these cells may be partially responsible for the immune response in the CNS (central nervous system), alongside with microglia) and is associated with altered iron metabolism secondary to frataxin absence (which is the most outstanding feature of FA)[8].
It is unclear why this inflammation-driven neurodegeneration affects prominently the cerebellum, particularly the dentate nucleus. There is physiologically a high iron concentration in the dentate nucleus, but this also holds for other regions of the CNS which seem to be spared in FA[8].
Although is tempting to attribute some of the detrimental consequences of frataxin deficiency to iron accumulation (and to the resultant neuronal degeneration) in the dentate nucleus, X-ray fluorescence studies performed in FA patients failed to demonstrate an unequivocal increase (or decrease) in iron content compared to normal tissues. Even worse, large amounts of other metals (copper, zinc) have been shown to be present in the very CNS territories where iron is abundant. However there is no definite evidence for the participation of these oligoelements in the destruction of the neurons in the dentate nucleus, despite attempts made to prove this by tissue staining for superoxide dismutase (SOD) and ATPase α-peptide[8].
The degeneration of the large sensory neurons in the dorsal root ganglia and spinocerebellar tracts explains the neurological symptoms of FA, which generally start in the early teens. They consist primarily in cerebellar symptoms such as progressive gait and limb ataxia and diminished vibration sense, but also include muscular weakness and extensor plantar reflex[8].
The motor impairment progresses until finally the patient can no longer manage whithout a wheelchair[8]. Despite the severity of the motor disability, the most deadly manifestations of the disease are the cardiac ones (with a life expectancy of about four decades), primarily hypertrophic cardiomyopathy and arrhythmias[8].
Iron accumulation (in the mitochondria with autophagy and degenerative changes in the myocardium) is the culprit, as it is for the pancreatic injury resulting in a high incidence of diabetes[8].
This disease can be associated with many abnormalities: cerebellar and sensory ataxia, heart disease – aproximately two third of the patients, musculoskeletal deformities – scoliosis being the most common, diabetes mellitus or impaired glucose tolerance[8]. Epilepsy is seldom described as a clinical feature associated with Friedreich's ataxia, very few cases being presented in literature and the mechanisms of seizures are unclear[12,13]. We present such a case of association of epilepsy with a genetically confirmed Friedreich disease.

CASE REPORT

This is the case of an 18-year-old patient with history of Friedreich's ataxia and hypertrophic cardiomyopathy who was admitted in our clinic for a generalized seizure with chaotic movements of limbs (no proper tonic-clonic seizures) followed by minutes of altered level of consciousness, bite-inflicted tongue wound and postictal state with confusion. During the last three months the patient repeated at least three such episodes.
Clinical examination fulfilled the Harding's diagnosis criteria: pes cavus, kyphoscoliosis, foot deformities including high plantar arches and hammertoes of both feet (figure 1); no cardiac or vascular murmurs on the cardiovascular examination; generalized muscle hypotrophy, motor weakness of the lower extremities, extensor plantar responses in spite of areflexia, limb ataxia (figure 2), severe gait ataxia of sensory and cerebellar type, difficulty in standing without support, dysarthria, slurred speach, loss of vibratory and position sense in both upper and lower limbs, mild cognitive impairement (IQ 55).

Figure 1 Foot deformities (high plantar arches and hammertoes of both feet) and muscle hypotrophy.

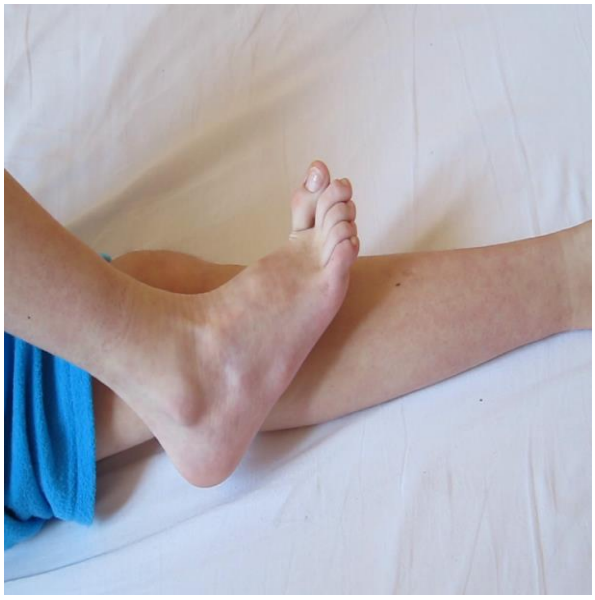

Figure 2. Heel-knee-shin tests demonstrate severe limb ataxia.

International Cooperative Ataxia Rating Scale (ICARS): (1) Posture and gait score (static score) 28/34; (2) Kinetic score (limb coordination) 43/52; (3) Dysarthria score 5/8; (4) Oculomotor movement score 1/6; (5) Total ataxia score 77/100

The *ECG (electrocardiography)* revealed sinus rhythm, HR 62 bpm, with negative T waves in DI, DIII, V3-V6.

The *electroencephalography (EEG)* (interictal examination) was wihout interictal epileptiform activity, while *cerebral magnetic resonance imaging* (MRI) revealed a large communicating fourth ventricle (Dandy Walker type malformation), inferior vermian hypoplasia, without hydrocephalus or cortical dysplasia (figure 3).

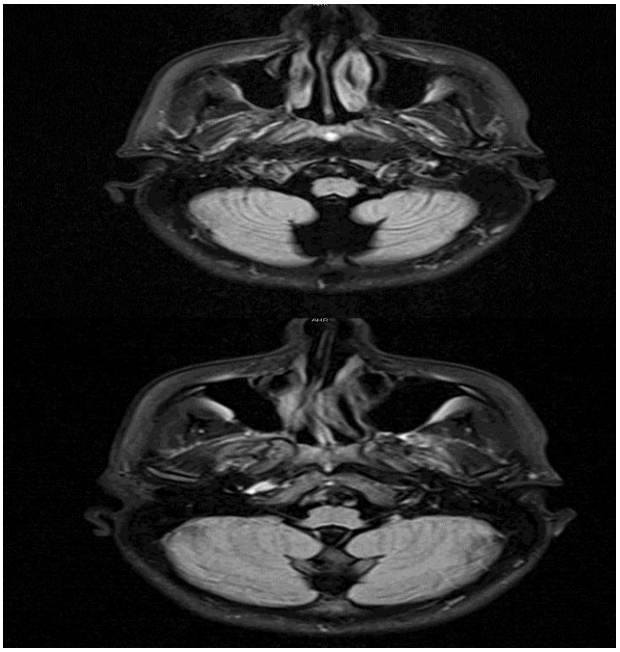

Figure 3. large communicating 4th ventricle (Dandy Walker type malformation), prominent cerebellar folia, and inferior vermian atrophy.

RESULTS AND DISSCUSIONS

The clinical syptoms point to a diagnosis of epileptic seizures associated with Friedreich's ataxia. There are no other detected MRI cortical lesions to explain seizures.

During hospitalization no epileptic seizure ocurred. Despite the fact that EEG examination revealed no paroxistic irritative rythm or cortical lesion on cerebral magnetic resonance imaging which could provoke seizures. In this case, the patient presented 3 clinical episodes of generalized seizure consisting in chaotic limb movements (suggestive of frontal lobe epilepsy), tongue bite, and alteration of the consciousness level, followed by several minutes of postictal confusion. We decided to initiate antiepileptic therapy with sodium valproate. For the last 6 months, under antiepileptic medication, the patient has had no epileptic seizures.

There are nevertheless reports of epilepsy in patients with FA, such as a case of generalized epilepsy in childhood where MRI examination revealed subependymal gray matter heterotopia[13] and a case of myoclonic epilepsia partialis continua[14].

Electroencephalographic studies usually yield normal results or only mild changes (abnormal slow or irregular background rhythm, intermittent paroxysmal rhythm) in patients with Friedreich's ataxia[12]. Nevertheless some of these patients develop seizures. The duration and severity of the disease do not correlate with the EEG alterations, but in cases where diencephalic and brain stem structures are affected, so that the inhibitory mechanisms are interfered with, a higher incidence of seizures was noticed[12]. The inflammation triggered by the immune activity of the Schwann cells may provide an

explanation for the epileptic seizures that may occur, albeit rarely, in FA patients. This supposition is endorsed by the mounting evidence suggesting a role for inflammation in epileptogenesis[15,16,17].

Indeed, in seizures-prone brains glial cell activation may result in the excessive expression of glycine transporter 1 (which is also expressed in neurons). Furthermore astrogliosis has been linked to various models of epilepsy, such as the tetanic stimulation model (associated with exuberant astrogliosis in the hippocampus) or the intrahippocampal KA model[18].

Another possible mechanisms of seizures could be related to phenotype variation of Friedreich's ataxia (partially) determined by the size of (GAA)n expansions[3]. Their repeat length influences age at onset, onset of dysarthria, onset of motor skill impairment and progression rate but also other clinical features[8]. At neuronal level, the decrease in frataxin expression, as seen in Friedreich's ataxia, markedly alters neuronal and mitochondrial iron metabolism in both the mitochondrion and the cell. The resulting dysregulation of iron trafficking damages tissues leading to neuro- and cardio-degeneration, with possible lesions of neuronal cortical circuits with epileptogenesis.

CONCLUSION

The particularity of the case consists in association of epileptic seizures and Dandy Walker malformation to Friedreich's ataxia, being known that epilepsy is rarely associated with this disease.

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REFERENCES

1. McDaniel D.O., Keats B., Vedanarayanan V.V., Subramony S.H., Sequence Variation in GAA Repeat Expansions May Cause Differential Penotype Display in Friedreich's Ataxia, Movement Disorders, 2001, 16, 1153–1158.
2. Schols L., Amoiridis G., Przuntek H., Frank G., Epplen J., Epplen C., Friedreich's ataxia Revision of the phenotype according to molecular genetics, Brain, 1997, 120, 2131–2140.
3. Pandolfo M, Friedreich ataxia: Detection of GAA repeat expansions and frataxin point mutations. Methods Mol Med., 2006, 126, 197-216.
4. Campuzano V., Montermini L., Molto M.D., Pianese L., Cosse ´e M, Cavalcanti F., et al., Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion, Science, 1996, 271, 1423–1427.
5. McDaniel D.O., Keats B., Vedanarayanan V.V., Subramony S.H., Sequence Variation in GAA Repeat Expansions May Cause Differential Phenotype Display in Friedreich's Ataxia, Movement Disorders, 2001, 16, 1153–1158.
6. McCabe D.J., Ryan F., Moore D.P., McQuaid S., King M.D., Kelly A., Daly K., Barton D.E., Murphy R.P., Typical Friedreich's ataxia without GAA expansions and GAA expansion without typical Friedreich's ataxia, J Neurol., 2000, 247(5), 346-55.
7. Holley A.K., Bakthavatchalu V., Velez-Roman J.M., St. Clair D.K., Manganese superoxide dismutase: guardian of the powerhouse. Int J Mol Sci., 2011, 12, 7114–7162.
8. Anzovino A., Lane D.J.R., Huang M.L.H., Richardson D.R., Fixing frataxin: 'ironing out' the metabolic defect in Friedreich's ataxia, British Journal of Pharmacology, 2013, DOI:10.1111/bph.12470.
9. Huang M.L., Sivagurunathan S., Ting S., Jansson P.J., Austin C.J., Kelly M. et al., Molecular and functional alterations in a mouse cardiac model of Friedreich ataxia: activation of the integrated stress response, eif2alpha phosphorylation, and the induction of downstream targets, Am J Pathol., 2013, 183, 745–757.
10. Lu C., Schoenfeld R., Shan Y., Tsai H.J., Hammock B., Cortopassi G., Frataxin deficiency induces schwann cell inflammation and death, Biochim Biophys Acta, 2009, 1792, 1052–1061.
11. Koeppen A.H., Morral J.A., Davis A.N., Qian J., Petrocine S.V., Knutson M.D. et al, The dorsal root ganglion in Friedreich's ataxia, Acta Neuropathol., 2009, 118, 763–776.
12. Remillard G., Andermann F., Blitzer L., Andermann E., Electroencephalographic findings in Friedreich's ataxia, Can J Neurol Sci., 1976, 3(4), 309-312.
13. Golomb M.R., Illner A., Christensen C.K., Walsh L.E., A child with Friedreich's ataxia and epilepsy. J Child Neurol., 2005, 20(3), 248-250.
14. Ziegler D.K., Van Speybroech N.W., Seitz E.F., Myoclonic epilepsia partialis continua and Friedreich Ataxia, Arch Neurol., 1974, 31(5), 308-311.
15. Walker L., Sills G., Inflammation and Epilepsy: The Foundations for a New Therapeutic Approach in Epilepsy? Epilepsy Curr., 2012, 12(1), 8–12.
16. Vezzani A., Epilepsy and Inflammation in the Brain: Overview and Pathophysiology, Epilepsy Curr., 2014, 14, 3–7.
17. Devinskyemail O., Vezzani A., Najjar S., De Lanerolle C., Rogawski A., Glia and epilepsy: excitability and inflammation, Trend in Neurosciences, 2013, 36(3), 174–184.
18. Shen H., van Vliet E., Bright K.A., Hanthorn M, Lytle N., Gorter J., Aronica E., Bosion D., Glycine transporter 1 is a target for the treatment of epilepsy, Neuropharmacology, 2015, 99, 554-565.