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Identical mutation associated with distinct clinical phenotypes of Friedreich's ataxia: case report

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Friedreich's ataxia is an autosomal recessive disease and the most frequent inherited ataxia. The disease is characterized by expression of the unstable GAA trinucleotide repeat expansion located in the first intron of the FXN gene on chromosome 9. Clinically, it is presented by progressive gait and limb ataxia, absent reflexes with positive Babinski, and cardiomyopathy with no difference regarding race and gender. Our patients are teenage siblings in whom analysis of DNA confirmed both alleles with full mutation in the FXN gene that codes for frataxin. Even though both siblings have full mutation and are both in the same age group, their clinical presentation and course of the disease are rather different. The sister has almost all typical neurologic signs of Friedreich's ataxia with progressive course despite supportive therapy. The brother shows only hypertrophic cardiomyopathy with no neurologic or skeletal disturbances so far. It is possible that other factors may also play an important role in the clinical presentation and course of Friedreich's ataxia. The cases of our patients prove that it is not advisable to foresee the clinical course based solely on the number of repeats.

Keywords: Friedreich's ataxia; siblings; mutation

INTRODUCTION

Friedreich's ataxia (FA or FRDA) is an autosomal recessive spinocerebellar disorder that has a slow, degenerative course. It affects one *per* 50 000 people and is the most frequent inherited ataxia. Friedreich's ataxia is characterized by progressive gait and limb ataxia, with no difference regarding race and gender. Genetically, it is identified by expression of the unstable guanidine adenine adenine trinucleotide (GAA) repeat expansion in the first intron of the *FXN* gene on chromosome 9. Most patients are homozygous for the expansion of GAA triplet repeat within the *FXN* gene. A great majority of patients with FA (about 94%) are homozygous for the GAA trinucleotide, while only a small percentage (about 6%) are compound heterozygotes for GAA expansion and frataxin point mutation responsible for the formation of abnormal protein as a possible source of different clinical presentation (1). The expanded GAA repeat is thought to result in frataxin deficiency by interfering with transcription of the gene by adopting an unstable helical structure. The larger the number of repeats, the more profound is the reduction in frataxin expression (2). The age at disease onset, severity, progression speed, and neurologic involvement vary with the number of repetitive GAA sequences (3). The broad clinical spectrum includes late-onset FA (LOFA) and FA with retained reflexes (FARR).

There are many issues regarding frataxin. Studies have shown that frataxin is a mitochondrial protein important for normal production of cellular energy. Defect in frataxin results in abnormal accumulation of iron in mitochondria, hence leading to excess production of free radicals. As body

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cells and tissues have different sensitivity to frataxin deficiency, cells normally requiring and producing greater amounts of frataxin tend to be most affected by FA. Some of those are sensory neurons in the dorsal root ganglion, which highly express the frataxin gene, as well as myocardial muscle fibers which also require larger amounts of frataxin than other tissues. Studies in patients with FA have shown mitochondrial iron-like deposits in heart muscle not present in healthy hearts. Along with histology in approximately 65% of patients with FA there are abnormal electrocardiography (ECG) findings, mostly T wave inversions and concentric ventricular hypertrophy (4). In over 90% of patients, there will be absent sensory nerve action potentials, while nerve conduction velocity studies might be only mildly reduced. Expected are abnormal findings in brainstem auditory and visual evoked potentials in about 75% of patients with FA. Unfortunately, chronic progression of the disease will cause patients to lose the ability to walk about 15 years of the onset of symptoms. In patients with predominant heart disease, especially if coupled with diabetes (as in 10% of patients), death tends to occur earlier than expected.

Considering clinical diagnosis, progressive limb and gait ataxia developing before the age of 25 is highly indicative of FA. Children with delayed ability to walk, difficulty in standing steadily, and in running should be examined further. In FA, in addition to typical cerebellar ataxia, there is also a loss of joint position sense, hence children tend to assume a wide-based stance. Affected children will almost always have diminished or absent patellar and ankle reflexes. Sometimes, these symptoms become more pronounced after an immune episode such as febrile illness. Initially it may be possible to notice fine hand tremor or problems in drawing and writing in a young child, as hands tend to be affected earlier than legs. Dysarthric speech may be attributable to young age or other issues and overlooked as an important early symptom.

As always, not only neurologic symptoms lead to diagnosis, and upon physical examination it may be possible to find pes cavus and kyphoscoliosis. Some of the children complain of tiredness and loss of weight, as swallowing becomes affected with weakening of facial muscles. A rather unspecific but often present symptom is peripheral cyanosis of lower limbs, as well as horizontal nystagmus. A very serious and mostly lethal symptom is concentric hypertrophic cardiomyopathy including myocarditis, tachycardia, and hypertension (5). Emotional lability may be expected, especially with progression of the disease course. For assessing the course of ataxia, it is recommended to use the International Cooperative Ataxia Rating Scale (ICARS).

So far, no medication altered the progressive course of the disease, even though the search for experimental drugs increasing the amount of frataxin is very active. Prior to starting FA treatment, the level of vitamin E needs to be evaluated as its deficiency caused by mutation on chromosome 8 creates a very similar clinical picture and can be treated. Considering the formation of free radicals by excess mitochondrial iron, coenzyme Q is recommended as an antioxidant with the possible effect on heart dysfunction. Furthermore, studies have shown some improvement of neurologic and cardiac function with idebenone, which is recommended in conjunction with physical therapy.

CASE REPORT

Our first patient was a 15-year-old girl. Her family and personal history are rather uneventful. Her psychomotor development has been normal, and she did not suffer from any serious illness. She was admitted for diagnostic evaluation of clumsiness and transitory tremor of hands, which became more visible after a short febrile illness. On initial physical examination, she had scoliosis (and wore thoracic orthosis), *pes cavus*, and wide based stance. She had heart murmur II/VI. Cardiac examination and tests (ECG and ultrasonography) confirmed concentric hypertrophic cardiomyopathy with hypertension. Neurological examination showed mild ataxia, horizontal nystagmus and mild tremor of the hands. Electromyoneurography (EMNG) indicated full loss of nerve conduction potentials with signs of demyelination and borderline velocities on lower extremities. Genetic analysis of DNA for FA confirmed our clinical suspicion of FA, as she has full mutation with 1095/1095 continuous GAA triplets. Her therapy included the angiotensin-converting enzyme (ACE) inhibitor, idebenone and coenzyme Q with physical therapy. Due to the progression of scoliosis, she had corrective spine surgery, which allowed her to walk more easily. Despite all supportive therapy administered for three years of the diagnosis, the score on ICARS is increasing (6). Her walking capacity from being widely based has now become impossible without support of the wall for a 10-meter test or aid of another person when turning. Her gait speed has now become markedly reduced and spastic. She has lost the capacity to stand with feet together, but is able to stand in natural position without support, with moderate sway. The spread of her feet in standing position with eyes open increased from 25 cm to 35 cm. In the finger to nose test, she now has segmented movements and moderate dysmetria with intention tremor. Her speech from having mild modification of fluency is now considerably slow and dysarthric with slurring, but most words are still understandable.

Her younger brother, now aged 14, has never had any similar clinical or neurologic symptoms. On outpatient cardiol-

ogy examination, there was hypertension and concentric hypertrophic cardiomyopathy with inversion of T waves on ECG. His *FXN* genotype has full mutation with 669/669 GAA repeats. His neurologic status and EMNG have been unremarkable for two years now. However, repeated cardiologist's examinations revealed progression of cardiomyopathy as well as of hypertension. He is now also receiving ACE inhibitor, coenzyme Q and idebenone therapy.

DISCUSSION

We present our patients, teenage siblings with FA, whose number of GAA (1095/1095 and 669/669) classifies them into the same category of disease severity, i.e. full mutation (66-1700 GAA). The sister has almost typical clinical development and presentation of the disease with the physical signs of scoliosis, *pes cavus* and cardiomyopathy, and neurologic signs of tremor, nystagmus and ataxia. On the other hand, her brother had only worsening of cardiomyopathy and hypertension, with normal neurologic status. Such different clinical presentations would be expected in compound heterozygotes or in homozygotes with premutation alleles, which is not the case in our patients (2, 7). Our concern with the brother is the possibility of sudden cardiac death in childhood, as it may be difficult to control the progression of cardiac involvement (8). Since the sister has lost patellar reflexes, it could be arguable that the brother has FARR variant (with retained deep tendon reflexes), while she has the classic variant of the disease. This only supports the idea that FARR is just a phenotype variability of the same genetic disease (9). It may also be that the sister as the more severely affected sibling is harboring larger expansions in spinal cord and other affected tissues (10). Variable clinical expressions have been described in siblings in whom the disease onset occurred as late as 60-70 years. However, these cases are an excellent proof that small homozygous expansions with approximately 120-130 GAA repeats, which were interrupted either with GAAGAG, GAAGGA or GAAGAAAA sequences, will have differential phenotype display (2). Profound cytoskeleton anomalies in patients with FA such as marked spinal scoliosis with progressive course requiring spinal surgery in the sister may also be explained by gene silencing which spreads in cis over the *PIP5K1B* gene in cells of FRDA patients correlating with expanded GAA repeat size (11).

CONCLUSION

Phenotypic diversity of FA is expanding, but the progressive course is a constant. So far, no gender differences have been described in the literature. The age at onset and the structure of GAA repeat expansion play an important role in determining clinical features and differential diagnosis of FA, but other factors such as somatic mosaicism, repeat interruptions, modifying mutations and environmental factors must also be considered (7). Therefore, in familial FA, the disease course in relatives should not be predicted solely from the repeat length.

Abrreviations:

GAA - guanidine adenine adenine
FA or FRDA - Friedreich's ataxia
LOFA - late-onset FA
FARR - FA with retained reflexes
ICARS - International Cooperative Ataxia Rating Scale
EMNG - Electromyoneurography
ACE inhibitor - angiotensin-converting-inhibitor

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Malenica M., Kukuruzović M., Bitanga S. – praćenje bolesnika, pisanje rada/*patient monitoring, writing paper*
Cvitanović-Šojat Lj., Krakar G. – analiza i tumačenje podataka, pisanje rada/*data analysis and interpretation, writing paper*
Valent B. – prikupljanje podataka, pisanje rada/*data collection, writing paper*

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SAŽETAK

Identična mutacija povezana s različitim fenotipom Friedreichove ataksije

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Friedreichova ataksija je autosomno recesivna bolest koja je najčešća među nasljednim ataksijama. Bolest je karakterizirana ekspresijom nestabilne ponavljajuće GAA sekvence trinukleotida koja se nalazi u prvom intronu gena FXN na 9. kromosomu. Klinički se najčešće prikazuje progresivnom ataksijom, arefleksijom uz pozitivan Babinski te kardiomiopatijom, bez obzira na rasu i spol. Naši su bolesnici tinejdžeri brat i sestra, kod kojih je analiza DNA potvrdila oba alela s punom mutacijom u genu FXN koji kodira frataksin. Iako oboje imaju punu mutaciju i oboje su u istoj dobnoj skupini, njihov klinički izražaj i tijek bolesti su vrlo različiti. Sestra ima gotovo sve tipične neurološke znakove Friedreichove ataksije, uz progresivan tijek unatoč potpornoj terapiji. Brat zasad pokazuje isključivo hipertrofičnu kardiomiopatiju bez neuroloških ili koštanih poremećaja. Moguće je da i drugi čimbenici imaju važnu ulogu u kliničkoj prezentaciji i tijeku Friedreichove ataksije. Primjer naših bolesnika potvrđuje da nije preporučljivo predviđati klinički tijek isključivo na broju ponavljajućih sekvencija.

Ključne riječi: Friedreichova ataksija; blizanci; mutacija