A Patient With 2 Different Repeat Expansion Mutations

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Background: Many inherited progressive encephalopathies have a poor outcome, and some are caused by repeat expansion mutations. How would the presence of 2 different expansion mutations affect the phenotype?

Objective: To describe a patient who has 2 distinct, rare genetic disorders: myotonic dystrophy (DM, OMIM 160900) and progressive myoclonus epilepsy of the Unverricht-Lundborg type (EPM1, OMIM 254800). Both conditions are caused by repeat expansion mutations. They affect the central nervous system causing mental retardation, but also produce a wide spectrum of disabilities in daily living.

Setting: Referral center.

Methods: Clinical description with accompanying photographs, electroencephalography and magnetic resonance imaging; DNA analysis of both of the mutations and chromosomal analysis with prometaphase spreads.

Results: The patient had clinical characteristics and findings of both myotonic dystrophy and progressive myoclonus epilepsy of the Unverricht-Lundborg type. Electroencephalographic recordings over a 3-year period showed typical findings for myoclonus epilepsy. The patient had no gross anomalies in brain magnetic resonance imaging. She had a normal karyotype, and both of the diagnoses were confirmed at the molecular level with the direct detection of the mutations.

Conclusions: Despite having 2 different progressive inherited disorders affecting the central nervous system, the patient, at age 28 years, showed only mild mental retardation with very slow progression. However, clear deterioration in activities of daily living has taken place during last 3 years.

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M yotonic dystrophy (DM) is an autosomal-dominant disorder, with an estimated incidence of 1 in 8000 in all human populations. It is therefore the most common progressive muscular dystrophy of adulthood. Myotonic dystrophy is characterized by (1) ptosis and weakness of other facial, jaw, and anterior neck muscles; (2) distal weakness of the limbs; and (3) myotonia. The clinical picture is very variable. In some cases a mild cataract may be the only sign of the disease, whereas the congenital form may be fatal. The underlying gene is located in 19q13.3 and codes for a protein named dystrophy myotonia protein kinase (DMPK). Recently, a gene located in the untranslated region of DMPK just downstream of its coding region was described. It seems that the expression of this gene, named DMAHP (DM locus associated homeodomain protein) is also affected by the repeat expansion mutation in DMPK, thus contributing to the phenotypic variation seen in patients with DM.

The [CTG]n repeat used in the diagnostics of DM is located in exon 15 of the DMPK gene. In the normal population this repeat is polymorphic, showing 5 to 35 copies of the CTG triplet. However, the triplet repeat is always expanded in patients with DM, and the number of copies (size) is even more variable, ranging from 50 to more than 2000. Increased size of the expansion correlates in general with increased severity of symptoms and with an earlier age of onset of the disease. The clinical diagnosis of DM is based on multiple classical features and positive electromyographic findings, which include polyphasic potentials and myotonic bursts. But in many cases, the diagnosis requires direct analysis of the triplet expansion mutation by DNA testing. Mo-
Progressive myoclonus epilepsy of the Unverricht-Lundborg type (EPM1) is an autosomal-recessive disorder that occurs with low frequency in many populations. It is most prevalent around the Baltic Sea, especially in Finland, where the incidence is 1 case per 20,000 births. It is also frequent in the western Mediterranean region. Progressive myoclonus epilepsy of the Unverricht-Lundborg type is characterized by onset at age 6 to 15 years, stimulus-sensitive myoclonus, tonic-clonic seizures, and progressive course. Typical electroencephalographic findings include symmetric, generalized and high-voltage spike-and-wave and polyspike-and-wave paroxysms. Sensitivity to photic stimulation is exceptionally high. With modern anticonvulsant therapy the symptoms are relatively well controlled, and the development of myoclonus is not always progressive throughout life. In adulthood, the symptoms usually become less severe, and epileptic seizure activity may cease. On average, the intelligence level of patients with EPM1 is normal, although a slow decline is often seen over time. Using a positional cloning strategy, loss of function mutations in the gene encoding cystatin B (CSTB), a cysteine protease inhibitor, were found to be responsible for EPM1. Later, an unstable expansion of a 12-mer (decamer) minisatellite repeat, located in the putative promoter region of the CSTB gene, was found to be the major cause of EPM1. It accounts for most (approximately 92%) of the disease chromosomes in patients with EPM1 worldwide. Previously, the diagnosis of EPM1 was based solely on careful clinical evaluation of the patients and exclusion of other types of progressive myoclonus epilepsy. Currently, specific mutation-based DNA testing is available to confirm the diagnosis.

CLINICAL HISTORY

Our patient was 28 years old when assessed. Her birth and perinatal period were uneventful, and motor milestones were passed uneventfully. The first signs of EPM1 occurred at age 8 years, when nightly myoclonic jerks appeared. Her first generalized seizure occurred at age 14 years. During the same year, the clinical diagnosis of EPM1 was made on the basis of electroencephalographic findings and clinical history. Her first symptoms of DM emerged during the second decade of life. At that time her main symptom was muscular weakness, which was most evident in her lower limbs. By age 13 years, her electromyographic findings were compatible with DM. Slow deterioration of basic mental capacity began at age eight years, but she managed to pass normal school. By age 16 years she had developed a scoliosis of 65°, which was surgically corrected, and had had 5 atrial fibrillation attacks requiring electric cardioversion. At age 21 years, she underwent a thorough cardiologic examination, including both echocardiography and a 24-hour electrocardiography registration, which were both normal. The results of neuropsychological tests (Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Benton, Luria, Poppelreuter, Raven, and Stroop) taken at age 22 years showed dyscalculia, poor short-term memory, and difficulties in visuo-spatial thinking, but the overall level of cognitive capacity was considered within the normal range. At age 23 years she was institutionalized because of behavioral problems and poor seizure control. Before her current valproate-lamotrigine-clonazepam combination therapy, she had several incidents of epileptic status together with numerous generalized seizures. On 2 occasions, her condition was life-threatening, requiring general anaesthesia (latest at age 23 years) with subsequent intensive care treatments, prolonged recovery from a comatose state (longer than 1 week), and episodes of pneumonia. Figure 1 shows the pedigree, and Figure 2, photographs of our patient.

CURRENT STATUS

The last electromyographic study results were positive, but there was no clinical myotonia (no convincing percussion myotonia of the thenar musculature or the tongue). At age 23 years, our patient had no lens opacities. She now has mild tremor in her hands and head. She has mild ptosis and atrophy of the anterior neck muscles. Her speech is affected by the weakness of her cheeks; she cannot whistle or retain air in her cheeks. Distal limb weakness is evident as well as atrophy of the hand muscles. She is unable to walk alone but can stand up and to some extent move with a wheelchair. Both hand and leg movements are ataxic, and she is occasionally unable to feed herself. She cannot straighten her legs properly to full length while standing, and she has a residual scoliosis of 35°. Cardiac arrhythmia, which she experienced during the second decade of her life, has not been a recent clinical problem. She has not had any seizures since she was 25 years old. During the last 4 years, there has been only 1 incident that was regarded as a pseudoseizure. Our patient is now being treated with sodium valproate (2200 mg/d), lamotrigine (50 mg/d), clonazepam (2 mg/d), and fluoxetine (10 mg/d).
Her mental status has slowly deteriorated, and by age 25 years she had mild mental retardation (IQ class 50-69). Reevaluation at age 27 years (Wechsler Adult Intelligence Scale plus an interview) showed that her overall cognitive capacity was unchanged. She could follow television programs and generally recalled events well from the past week. During the last few years, her interest in contemporary world events as reported in the media has declined, and her ability to read and to understand written text has deteriorated.

**ELECTROENCEPHALOGRAPHIC AND MAGNETIC RESONANCE IMAGE FINDINGS**

Her interictal electroencephalographic recordings have been typical for EMP1 with background slowing and generalized spike-and-wave or polyspike discharges and myoclonias on photic stimulation. No progression has occurred in control registrations over a 3-year period. Brain magnetic resonance imaging has shown no focal pathologic changes in the brain parenchyma. Subarachnoid spaces are rather large in all areas (cortical, central, and cerebellar), especially frontally, where the sulci are bilaterally deep. Also, the sylvian fissure seems rather wide. In addition, the bony structure of the skull is thick (Figure 3).

**DNA AND CHROMOSOMAL ANALYSIS**

Our patient’s diagnoses of both DM and EPM1 were confirmed by DNA analysis. Figure 4 shows a Southern blot analysis with BglI digest hybridized with probe p5B1.4,26 where an extra allele is clearly visible. Figure 5 illustrates the structure of the DMPK gene with special reference to DNA fragments created by different restriction enzymes. In normal cases, BglI creates only a 3.4-kilobase fragment. The diagnosis of EPM1 was confirmed by Southern blot analysis of PstI-digested DNA hybridized with a cystatin B complementary DNA probe (Figure 6).16,21 The transmission of the expanded alleles is shown by arrows. Figure 7 shows the localization of the 12-mer expansion in the putative promoter region of the CSTB and the short distance from the first exon of this gene. In prometaphase spreads, the patient had normal karyotype 46,XX.

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**Figure 2.** Patient photographs. Note the high hair line, ptosis, and otherwise characteristic facial features of myotonic dystrophy. Wasting of the anterior neck muscles is evident in the side view. Mild residual scoliosis can also be seen.

**Figure 3.** Magnetic resonance images of our patient. Left, T1-weighted coronal section, where basal ganglia and surrounding structures (asterisk) appear normal. Center, T2-weighted coronal section, where normal cerebellar structures are seen. Right, T1-weighted axial section showing normal basal ganglia (asterisk). Arrow indicates a large frontal sinus in clearly thickened frontal bone. In all images, the relatively enlarged subarachnoid spaces are apparent.
Our patient shows the clinical symptoms and signs of 2 inherited disorders: DM and EPM1. Her case history and all the electrophysiological and imaging findings are consistent with both of these diagnoses. Moreover, findings of direct DNA analyses reveal the pathognomonic mutations for both disorders. The probability for this combination of genetic disorders occurring concomitantly by chance is well over 1 in 160 million, and in this respect her condition can be regarded as unique (8000 for DM and EPM1, respectively, for the later incidence in Finland; EPM1 is more rare than this in global perspective). Quite remarkably, both of these syndromes are caused by unstable expansion mutations, and both of them also affect the central nervous system. Given the progressive nature of these syndromes, one could expect severe mental deterioration with marked additional disabilities by the end of third decade of life. However, our patient has only mild mental retardation with relatively late deterioration of activities of daily living. The clinical symptoms produced by these 2 mutations are manifold. In our patient, loss of distal muscle strength has been considerable, but clinical myotonia has not been a feature. Our patient had a relatively late deterioration of activities of daily living. An expected arrhythmic tendency and epileptic activity have ceased. The clinical history demonstrates that with the present treatment, cognition is relatively spared during the disease processes. The clinical symptoms of EPM1 progress insidi-

**COMMENT**

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**Figure 4.** Southern blot analysis of our patient's myotonic dystrophy shows an expanded Bgl1 fragment indicating an expansion larger than 150 copies of the CTG motif. The lanes of interest (starred) contain DNA samples of different concentrations. A reduction in the copy number has taken place because the patient's father has an expanded Bgl1 allele of 5 to 6 kilobases (kb) in size (data not shown).

**Figure 5.** The human myotonic dystrophy (DM) protein kinase gene and the localization of the probe p5B1.4 used in the detection of the DM mutation. The top of the figure shows the reduction of the target fragments on various restriction enzyme digests (E, EcoRI; B, BamH1; Bg, Bgl1). Exon 15 contains the [CTG]n motif expanded in patients with DM, shown as a black box.3,7,9,27-31

**Figure 6.** Southern blot analysis showing enlarged restriction fragments in patients with progressive myoclonus epilepsy of the Unverricht-Lundborg type (EPM1). The DNA has been digested with restriction enzyme PstI, and the blot has been hybridized with the cystatin B complementary DNA as a probe. Control individuals show the normal 2.6-kilobase (kb) restriction fragment. Lanes marked EPM1+ contain DNA from patients for whom the enlarged fragment size has been determined: the normal-sized fragment is absent, and abnormally enlarged restriction fragments occur instead. The transmission of enlarged alleles from the father and mother of our patient is indicated with arrows on the blot. A faint constant fragment (C) occurs in all individuals.

**Figure 7.** Illustration of the structure of the cystatin B (CSTB) gene and an enlarged view of the putative promoter region of the gene showing the location and sequence of the normally polymorphic (2 or 3 copies) 12-mer (dodecamer) repeat. H indicates HindIII; E, EcoRI; and P, PstI.
ous and in general become prominent in the teenage years. Previously, the symptoms were progressive throughout life, and the shortening of lifespan was associated with the use of phenytoin. The drug treatment of choice is now sodium valproate, which has increased the life expectancy and the functional capacity of patients. As add-on therapy, clonazepam and lamotrigine may be used. With current effective polytherapy, patients now live to their 60s.

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