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Prenatal Diagnosis in Two Families with Fukuyama Type Congenital Muscular Dystrophy by Genetic Linkage

Oral Presentation

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With advances in positional cloning techniques, the Fukuyama-type congenital muscular dystrophy (FCMD) locus has been mapped to chromosome 9q31-33 as a first step in elucidating the genetic defect. Prenatal diagnoses of two FCMD families were carried out using genetic linkage analysis with polymorphic microsatellite markers flanking the FCMD locus.

There was no consanguinity in either family. The second child in family 1 and the third in family 2 were victims of FCMD, with psychomotor delay since early life, hyperCKaemia, cerebral dysgenesis on brain MRI and severe dystrophic changes in skeletal muscles. Prenatal diagnosis was performed for the third pregnancy in family 1 and the fourth in family 2. Amniocentesis was done at 15 weeks gestational age in family 1 and at 16 weeks in family 2. DNA was extracted from the lymphocytes of family members and fetal amniotic cells. Individuals were genotyped with flanking CA repeat markers, and both fetuses were analysed for risk calculation using the LIKAGE computer programme.

The fetus of family 1 had a 99 per cent probability of being a carrier, and the fetus of family 2 had a 86 per cent probability of FCMD homozygosity. The pregnancy in family 1 was maintained and resulted in a healthy baby, but the parents in family 2 opted for an artificial abortion at 20 weeks gestation. That fetus had vesicular nodules on the cerebral surface, suggesting the polymicrogyria typical for FCMD. Detailed neuropathological study is now under way. Thus, since the FCMD gene locus was identified, prenatal diagnosis has become feasible by linkage analysis with polymorphic markers.

Hereditary Motor and Sensory Neuropathies

Invited Lecture

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In a patient with chronic progressive motor and sensory neuropathy, the following investigations are required successively to diagnose one of the subtypes of hereditary motor and sensory neuropathy (HMSN) or Charcot-Marie-Tooth disease (CMT):

1. Detailed history and clinical examination is necessary to establish an isolated motor and sensory neuropathy without evidence of a more widespread neurological involvement. Metabolic disorders, infections, intoxication, immunological disorders, deficiencies or vasculitis have to be excluded. Electrophysiological testing usually allows distinction between demyelinating (HMSN I or CMT I), neuronal (HMSN II or CMT II) or intermediate (X-linked HMSN or CMTX) forms.

2. Investigation of parents and possibly affected family members is required to establish the mode of inheritance. A sporadic occurrence may be due to a de novo mutation, to an autosomal recessive form or to an acquired disorder.

3. DNA investigation is significant in the demyelinating and intermediate forms. At present, the following genes are known to be involved in hereditary motor and sensory neuropathies: (a) the peripheral myelin protein PMP-22 gene CMT1A (HMSN Ia) and hereditary neuropathy with liability to pressure palsies (HNPP), (b) the myelin protein P0 gene CMT1B (HMSN Ib) and (c) the gap junction protein connexin 32 gene CMTX (X-linked HMSN).

4. Sural nerve biopsy is indicated if the preceding investigations have not yielded a conclusive diagnosis.

The autosomal recessive demyelinating forms of HMSN (also categorized as CMT4) exhibit typical morphological features. One form is characterized by basal lamina onion bulbs, and the genetic defect of some of these families is linked to chromosome 8q. Another form is characterized by the abundant occurrence of focally folded myelin. However, this pathology is not specific:
it has also been found in some cases of CMT1B (P0). The pathology in autosomal recessive CMT2 is more severe than in autosomal dominant CMT2. The genetic defect in some autosomal dominant CMT2 families is linked to chromosome 1p36.

HETEROZYGOUS MUTATION IN SEVERE, INFANTILE, HYPERTROPHIC HEREDITARY MOTOR AND SENSORY NEUROPATHY

Oral Presentation

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Severe, early-onset cases of demyelinating hereditary motor and sensory neuropathy (HMSN) and hypomyelination in nerve biopsy are often designated as Dejerine-Sottas syndrome or HMSN type III; this entity was defined as an autosomal recessive disorder. Formerly, the authors have argued that the cases fulfilling this definition, but with mainly classical onion bulbs in nerve biopsy, are not autosomal recessive cases. Indeed, a few cases classified as Dejerine-Sottas syndrome or HMSN type III, but with classical onion bulbs, resulted from heterozygous mutations in the PMP-22 gene or the P0 gene. The authors present the genetic investigation of one of our patients with a severe, early-onset demyelinating neuropathy, high cerebrospinal fluid protein and hypomyelination with classical onion bulbs. DNA analysis revealed a heterozygous de novo mutation in the PMP-22 gene. This implies the existence of an autosomal dominant mutation in this patient.

SELF-MUTILATION IN HEREDITARY SENSORY NEUROPATHIES

Poster

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Self-mutilation (SM) in childhood is a complicated symptom with numerous aetiologies. Traditionally, severe mental retardation and/or profound psychiatric disorders are the main underlying conditions. The existence of SM in Tourette and Rett syndromes has only recently been recognised, while its mechanism in Lesch-Nyhan syndrome is still unclear. The authors have documented severe and disabling SM in familial dysautonomia and in hereditary insensitivity to pain with anhidrosis. (HASN types III and IV, respectively). Both conditions share a similar neuropathological picture consisting of selective loss of small myelinated fibres in peripheral nerves. This selective loss of pain-conducting fibres with preservation of larger fibres may be responsible for the hedonistic SM.

A FAMILY APPROACH TO THE APPLICATION OF COMPUTER GAMES FOR THE REHABILITATION OF CHILDREN WITH CEREBRAL PALSY

Poster

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The aim of this presentation is to provide an analysis of the application of computer games in the process of rehabilitation for disabled children. 150 children were examined aged between three and 15 years (78 boys, 72 girls) from families of differing social status and mostly with the spastic forms of cerebral palsy (two cases of familial cerebral palsy). 120 children have intellectual impairment. An IBM personal computer AT with different devices (joystick, mouse, keyboard, spatial hand manipulator created to order by the authors' centre which enables children with finger paresis to play computer games, and different software) was used. In two to three days the authors managed to teach a child (for whom the computer was a new experience) to correlate the actions