LETTERS TO THE EDITOR

Homozgyosity for Asn86Ser mutation in the CuZn-superoxide dismutase gene produces a severe clinical phenotype in a juvenile onset case of familial amyotrophic lateral sclerosis

A 13 year 9 month old girl, the daughter of consanguineous (first cousin) Pakistani parents, presented with pain in her right calf of two months duration and increasing weakness in her right leg with an inability to bear weight. Neurological deficit was initially confined to the right lower limb. Examination showed an asymmetrical lower motor neuron pattern with distal hypotonia and weakness, wasting in the right quadriceps and peroneal muscles, and absent reflexes and flaccid plantar responses. After one week of inpatient observation muscle weakness progressed and lower amplitude compound muscle potentials were also seen in the upper limb, confirming an ascending picture of disease progression. The muscle weakness extended to involve facial muscles with definite weakness distally in the right upper limb and profound weakness in the lower limbs. Further progression led to reduced expiratory air flow and pneumonia with respiratory failure and death 14 weeks after presentation.

The predominant clinical features in this patient were progressive asymmetrical lower motor neuron weakness and wasting with more marked involvement of lower limbs and distal musculature, together with bulbar involvement. A paternal uncle had also recently died, aged 34, following an 11 month illness with rapidly progressive motor neuron disease with initial spastic features and later a flaccid symmetrical pattern. These observations suggested a diagnosis of familial motor neuron disease of the progressive muscular atrophy type.

Blood samples were collected from this patient, her parents, her paternal grandmother, and a paternal aunt and uncle. Genomic DNA was isolated and screened for mutations in the superoxide dismutase (SOD1) gene by PCR amplification, single strand conformation polymorphism analysis, and DNA sequencing. An aberrant band shift was identified in amplified DNA in exon 4 of the SOD1 gene. The amplified DNA was sequenced and a single base change was identified (nucleotide 257A→G) causing an amino acid change of asparagine (Asn) to serine (Ser) (AGT) at codon 86. The mother was homogygous for this mutation, both of her parents (III.1, III.2) (fig 1), and her paternal uncle (III.7) were heterozygous, while her aunt (III.4) and grandmother (II.4) were homozygous for the normal allele.

In order to check that this sequence change was not a harmless polymorphism, 67 Scottish amyotrophic lateral sclerosis (ALS) patients, 60 anonymous Scottish controls, and 84 anonymous healthy Pakistani controls were also analysed using allele specific oligonucleotides and dot blot hybridisation. All were homozygous for the normal allele at codon 86. This codon is extremely well conserved throughout the animal and plant kingdom, specifying Asn in 54 different species in the EMBL-SWISS-PROT alignment database. This finding alone implies that this amino acid is functionally important.

The family described here is extensive with many first cousin marriages and potentially many heterozygotes or homozygotes for this mutation. To date two people have died of ALS. The proband was homozygous for the mutation Asn86Ser, while her paternal uncle was probably heterozygous (fig 1). The other heterozygotes in this family appear to be clinically healthy. Therefore, at present, it is not possible to predict the ALS risk factor associated with heterozygosity of Asn86Ser. Recently, a Japanese family with two affected members heterozygous for the Asn86Ser mutation has been reported.1 The clinical phenotypes of these two subjects were very different. The father died of respiratory failure at the age of 56 years, four years after onset of symptoms but with only upper body involvement. His daughter, diagnosed at the age of 36 years with lower limb weakness and slow progression of the disease to a general muscular atrophy nine years after onset of the first symptoms, survived for more than 11 years.

There has only been one previous report of homozygosity for a SOD1 mutation in ALS. An autosomal recessive form of FALS in a Swedish/Finnish population has been described in nine families.11 Homozygosity for the Asp90Ala mutation caused ALS in 30/37 subjects identified. There have been no reports of heterozygosity for the mutation associated with ALS in this population. However, the heterozygous form of the same mutation identified in Belgian subjects has led to the development of ALS.12 The clinical phenotype associated with a given mutation in the SOD1 gene is clearly not only dependent on the mutation itself, but may also be influenced by the genetic background of the patient, and possibly by environmental factors. The Asn86Ser mutation has only been identified in a small number of people as yet. In our Pakistani family there were two patients with ALS. The female proband was homozygous for Asn86Ser and had a more severe form of disease than her uncle, who was probably heterozygous. Along with the possible complication of variable penetrance, the true relationship between this mutation and ALS may not be discovered for some time.

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RP11 is the second most common locus for dominant retinitis pigmentosa

Autosomal dominant retinitis pigmentosa (ADRP), an inherited retinal degeneration, is caused by mutations in two known genes, rhodopsin and peripherin/RDS, and seven unidentified by linkage analysis, on chromosomes 1cen, 7p, 7q, 8q, 17p, 17q, and 19q. This high level of locus heterogeneity
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