HEREDITARY MYOPATHY, OLIGOPHRENIA, CATARACT, SKELETAL ABNORMALITIES AND HYPERGONADOTROPIC HYPOGONADISM: A NEW SYNDROME

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A new syndrome in three siblings, a man and two women, now aged 33-45 years, is described. The syndrome consists of the following symptoms:
1. Oligophrenia (IQ about 30, Terman-Merrill test) with harmonic infantilism.
2. Dense cataract with onset in childhood.
3. Myopathy, mainly affecting proximal muscles but also facial, masticatory, and external ocular muscles. The myopathy probably had its onset at puberty and progressed, in 2 of the 3 siblings until they were confined to a wheel chair.
4. Signs of pyramidal tract involvement and slight ataxia, probably congenital and nonprogressive.
5. Deficient speech development.
6. Skeletal changes including thoracic deformity, scoliosis, pes planovalgus, shortening of the fourth toe, and osseous dystrophy especially in the hands and feet.
7. Hypergonadotropic hypogonadism with primary amenorrhea in one of the sisters, very early menopause in the other and pronounced testicular atrophy in the brother. There were no signs of other endocrine insufficiency and the secondary sex characters, body hair distribution and libido were normal. The karyotype was normal in all three siblings. The heredity was considered to be probably autosomal recessive. Since, therefore, a number of independent organs were affected, the syndrome has been assumed to be caused by a penetrating metabolic defect the nature of which is unknown.

The combination of oligophrenia and progressive muscular dystrophy is rare. These symptoms as well as some others, probably constituting an hitherto undescribed syndrome, were observed in three siblings, two sisters now aged 33 and 43 and a brother 45 years old.

The three siblings were numbers 4, 5, and 9 in a sibship of 9 among whom 6 were girls. No other cases with the same symptoms are know in the family which has been traced back 5 generations without any evidence of consanguinity beeing revealed. The family has been living in Sweden as long as is known.

The mental retardation was moderatly severe (IQ 30 in the Terman-Merrill test) and there has been no evidence of progression. All three siblings were friendly, happy and easy to obtain contact with — they exhibited true harmonic infantilism. They have all been at different institutions for the mentally retarded since the age of about 4.

The patients underwent operation for bilateral, dense cataract at 9, 9, and 4 years of age. The cataract was probably not congenital but instead developed rather acute in childhood.

The motor development was also delayed in all three children. At the age of 4 they could not walk or even stand and they were only able to speak single words. They were found to have spastic

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paresis in the legs with brisk tendon reflexes and a positive Babinski sign. At that age they were given the diagnosis of Little's disease. However, during the years, the signs of pyramidal tract damage slowly disappeared and at puberty the two older siblings could walk without difficulty.

After puberty there was a rapid deterioration of motor function progressing to disablement leading to confinement to a wheel chair in two of the sisters at 25-30 years of age. At 45 years of age the brother could still walk with two sticks. Atrophy and paresis mainly of the proximal muscle groups were found. However, there was also some engagement of the distal muscle groups. The sternocleidomastoid and brachioradial muscles were the muscles most strongly affected. The extraocular muscles were involved but there was no ptosis. The facial muscles were clearly affected especially in the younger sister who had a pouting, loose underlip. There was no hypertrophy of the muscles nor any evidence of myotonia.

The distribution of the muscle weakness and atrophy strongly suggested a myogenic myopathy as cause of the disablement. This was confirmed by electromyography that indicated a distinct myopathic pattern. Single fibre EMG showed a picture well corresponding with that usually seen in proximal myopathies (Stålberg and Ekstedt 1973). A muscle biopsy from the biceps muscle of the arm of the youngest sister was examined histologically (K.G. Henriksson). There was a marked variation of muscle fibre diameter. The endomysial and perimysial connective tissue was increased. A considerable increase of adipose tissue was seen in the preparation. The sarcolemmic nuclei were in many fibres located centrally and rows of sarcolemmic nuclei containing distinct nucleoli were found. No infiltration of inflammatory cells was observed but hyalin degeneration was seen in several fibres. Histochemical examination with myosine ATPase, NADH-diaphorase, phosphorylase, and examination with Gomori's trichrome stain on frozen sections showed normal conditions. There was a normal distribution of type I and type II fibres. These findings are thus well in agreement with the diagnosis of myogenic myopathy.

At the age of 35 to 45 the tendon reflexes had gradually weakened. The most severely afflicted sibling, the younger sister, had total areflexia. Apart from slight signs of ataxia, the neurological examination did not reveal pathological findings. Motor conduction velocity in the peripheral nerves and EGG were normal.

It is thus probable that the patients had two types of motor impairment, first a rather mild congenital and nonprogressive spastic paresis, which the children were trained to overcome, and secondly a rapidly progressing myopathy starting at puberty.

The siblings had a very characteristic speech disturbance. They had, all their life, talked like small children. Their speech was unclear, certain consonants were missing, double consonants were difficult to manage and their vocabulary was infantile.

A number of skeletal changes were observed in the patients. The thorax was strongly developed in relation to the trunk, and the pelvis was small. One of the sisters had a funnel chest and marked thoracic scoliosis. All had relatively short extremities, the hands were gracile but the feet were heavy and short with pronounced pes planovalgus. The fourth toe was unproportionally short. The bones of the fingers and toes showed reduced mineralization; and the metacarpals, metatarsals, and phalanges were very thin on X-ray. The older sister had a history of three serious fractures.

The younger of the sisters had primary amenorrhea, and the older of them had only had a few sparse menstrual periods between the ages of 18 and 21. Both of them had essentially normal body-hair distribution and normally developed breast. The man had also abundant body hair and well-developed external genitalia, but soft testes with a volume of only 1 ml bilaterally. All siblings had normal karyotypes. X-ray of the sella turcica was normal and there were no clinical or laboratory signs of adrenocortical or thyroid insufficiency. The serum FSH and LH values were high and the response to intravenous infusion of LH-Releasing Hormone was very strong. These laboratory findings are similar to what is found in women after a normal menopause (Lundberg 1973*a*) and in men with the Klinefelter syndrome (Lundberg and Wide 1973).

The three siblings were all clearly below the mean height — the man 165 cm and the women 147 and 149 cm respectively. The younger sister had probably a cardiomyopathy.

Oligophrenia, cataract, delayed motor development caused by pyramidal tract lesion and slight ataxia, progressive myopathy, infantile speech, skeletal growth disturbances, and hypergonadotropic hypogonadism, were thus present in all three siblings. This hereditary syndrome does not seem to have been described previously. An autosomal recessive hereditary trait seems probable. A metabolic defect is assumed as the pathogenetic mechanism. However, a broad-based biochemical screening has so far failed to reveal any significant findings. A full description of this syndrome as well as a discussion of differential diagnostic problems will be given elsewhere (Lundberg 1973*b*).

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