Sjögren-Larsson Syndrome in Sweden

An epidemiological, genetic, clinical and biochemical study

by

STEN JAGELL

Umeå 1981
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AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Rektorsämbetet vid Umeå universitet för avläggande av medicine doktorsexamen kommer att offentligen försvaras i Humanisthuset, hörsal G, fredagen den 29 maj 1981 kl. 9.15.

av

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med.lic.

UMEÅ 1981
ABSTRACT

SJÖGREN-LARSSON SYNDROME IN SWEDEN

An epidemiological, genetic, clinical and biochemical study

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The Sjögren-Larsson syndrome (SLS) is a genetically determined syndrome with autosomal recessive inheritance originally and comprehensively described from Sweden. It is characterized by the three cardinal signs congenital ichthyosis, spastic di- or tetraplegia and mental retardation.

The present investigation covers all 35 SLS patients alive in Sweden in 1978 and the genetic study all 58 SLS patients born in Sweden in 1886-1977. Forty-five of these were born in a restricted area in the northeast of Sweden and five more had ancestors from this area. This concentration is probably the result of a founder effect — transmission of the SLS gene mutation from early immigrants to this area — followed by little migration to and from this area. Ancestors of SLS patients have been traced back to an early immigrant to this area in the 14th century.

The mean yearly incidences of SLS per 100,000 newborn during the years 1901-1977 were 0.6 in the whole of Sweden, 10.2 in the county of Västerbotten and 2.7 in the county of Norrbotten. The corresponding prevalence figures for SLS on 31 December 1978 were 0.4, 8.3 and 2.6 per 100,000 in these areas, respectively.

The ichthyosis in the SLS was found to be congenital in the true sense of the word, as it was always seen at birth. The characteristic skin findings indicate that the use of replicas in ichthyotic patients may be a good complement to the clinical and histopathological examinations.

All SLS patients had mental retardation and spastic di- or tetraplegia. The first observation of these symptoms was made between the age of 4 and 30 months.

Small white glistening dots located in the ocular fundus were noted in all 30 SLS patients examined in this respect and seem to be pathognomonic for SLS.

The fatty acid patterns of plasma phospholipids, cholesteryl esters, triglycerides and free fatty acids in SLS patients were examined. The results suggest that SLS is possibly a disorder of fatty acid metabolism leading to an altered composition of polyunsaturated fatty acids due to a disturbance in the Δ6-desaturation of essential fatty acids.

Key words: Sjögren-Larsson syndrome, spastic diplegia, spastic tetraplegia, mental retardation, congenital ichthyosis, macular changes.
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Suspected faulty essential fatty acid metabolism in Sjögren-Larsson syndrome ................................................................. 235
This dissertation is based on the following papers

I. Jagell, S., K.H. Gustavson & G. Holmgren:

II. Jagell, S. & S. Lidén:
Ichthyosis in the Sjögren-Larsson syndrome.
Submitted to British Journal of Dermatology.

III. Hofer, P.Å. & S. Jagell:
A dermato-histopathological study.
Submitted to British Journal of Dermatology.

IV. Jagell, S. & P.Å. Hofer:
Sjögren-Larsson syndrome. Microscopic and scanning electron microscopic findings in replicas of the skin.
Submitted to British Journal of Dermatology.

V. Gustavson, K.H. & S. Jagell:
Dermatoglyphic patterns in the Sjögren-Larsson syndrome.

VI. Jagell, S. & J. Heijbel:
Sjögren-Larsson syndrome: physical and neurological features.
A survey of 35 patients.
Submitted to Neuropediatrics.
VII. Probst, F., S. Jagell & J. Heijbel:
Cranial CT in the Sjögren-Larsson syndrome.

VIII. Jagell, S., W. Polland & O. Sandgren:
Specific changes in the fundus typical for the Sjögren-Larsson syndrome. An ophthalmological study of 35 patients.

IX. Hernell, O., G. Holmgren, S. Jagell, S. Johnson & R.T. Holman:
Suspected faulty essential fatty acid metabolism in Sjögren-Larsson syndrome.
Pediatric Research, in press, 1981.

In the text these papers will be referred to by their Roman numerals.
GENERAL INTRODUCTION

The Sjögren-Larsson syndrome (SLS) is a syndrome characterized by mental retardation, spastic di- or tetraplegia and congenital ichthyosis, with an autosomal recessive mode of inheritance (Fig. 1 a-e). It is named after Torsten Sjögren, the late Professor of Psychiatry at the Karolinska Institute in Stockholm, and Tage Larsson, Ph.D. and honorary M.D., former Deputy Managing Director of the Skandia Life Insurance Company (Sjögren 1956, Sjögren & Larsson 1957). Sjögren observed some patients with the clinical picture of this syndrome, at institutions for the mentally retarded in northern Sweden when he visited them in 1955 as an inspector for the National Social Welfare Board in Sweden. These observations were the origin of his work on this disorder.

Independently of Sjögren and Larsson, the two paediatricians Professor Lars Söderhjelm and Associate Professor Herbert Enell reported SLS in three children earlier in the same year (1957) as Sjögren and Larsson published their extensive report (Söderhjelm & Enell 1957). During the following years several papers on SLS have been published (summarized by Richards 1972, Theile 1974 and Jagell et al. 1981).

Jagell et al. (1981) evaluated 88 earlier reports on 177 presumed SLS patients. These patients were classified according to the clinical picture as typical SLS patients (98 cases), atypical SLS patients (28 cases) and non-SLS patients (51 cases) (Table I). Besides the three cardinal signs (congenital ichthyosis, spastic di- or tetraplegia and mental retardation) there have been reports on degeneration in the macular region and glistening dots in the ocular fundus.
In addition to the cardinal symptoms, SLS individuals have been reported to have brain atrophy, speech defects, seizures, a small stature, retarded bone age, abnormal aminoaciduria, kyphosis of the spine, defective dental enamel, hypertelorism and abnormal dermatoglyphics (Theile 1974).

**Congenital ichthyosis**

Richards (1972), summarized information on 114 reported cases of SLS. He reported the ichthyosis in this syndrome to be of the kind known as non-bullous congenital ichthyosiform erythroderma with widespread hyperkeratosis and scaling. The skin is thickened and patterned and often has a fish-scale appearance. The face is usually mildly affected, more at the sides than in the front. The ichthyosis is most severe on the neck and lower abdomen and in the flexures. The brown colour of the most severely affected regions is striking. The skin is dry and the sweating ability tends to be reduced. The ichthyosis is present at birth or appears in the early months of life. It is stationary or may become slightly worse. Theile (1974), summarized 111 SLS cases, 89 of whom had also been reviewed by Richards (1972), and reported that the skin was rough and thick and showed thin furfuraceous scaling when scratched. The ichthyosis was reported to be generalized in most of these patients. It was seen in all patients on the extremities mainly in the neck and the joint flexures. In the literature survey by Jagell et al. (1981) 78 out of 81 typical SLS patients investigated, had the above characteristic dermatological picture, as against only four out of 28 atypical SLS patients (Table 1).

**Mental retardation**

Reduction of the level of intelligence has always been reported in SLS. According to Richards (1972), the degree of intelligence defect varies greatly, but is severe in about 70%. However, the physical handicap and
speech defect may lead to underestimation of the intelligence. Only eight patients have been reported to have a borderline IQ of about 70. Theile (1974) reported that all SLS individuals are mentally retarded and most of them severely retarded. In the literature survey by Jagell et al. (1981) 77 out of 81 typical SLS patients investigated were reported to be mentally retarded (IQ < 70). In four cases the information was insufficient (Table 1).

**Neurological symptoms**

The paralysis in SLS is a symmetrical spastic diplegia which is more pronounced in the lower than in the upper limbs. Most patients are unable to walk without assistance and most of them are confined to a wheel-chair. The spasticity of the muscles in the mouth is the cause of speech and feeding difficulties. Both the speech defect and epilepsy are regarded as frequent features of the disease (Richards 1972). Among the 111 SLS cases reviewed by Theile (1974), 64 were diplegic and 25 tetraplegic. In the review by Jagell et al. (1981), 78 out of 81 typical SLS patients investigated had spastic di- or tetraplegia (Table I). In three cases the neurological symptoms were atypical.

**Ocular symptoms**

Richards (1972) reported degeneration in the macular region in about 25% of patients with SLS. This condition was thought to be stationary, and did not appear to proceed to blindness. Theile (1974) found that among the total of 76 patients who were examined by an ophthalmologist, 38 had a normal fundus, 24 had degeneration of the macula and 15 showed glistening dots in the fundus. In the literature survey by Jagell et al. (1981) 27 out of 81 typical SLS patients investigated had or probably had glistening dots in the fundus of the eye and 34 were said to have no changes in the retina (Table I).
Other symptoms
Defective development of the dental enamel is a minor feature of the syndrome (Richards 1972). Findings at dermatoglyphic analyses have varied (Richards 1972). Out of 26 patients for whom information concerning the spine was available, there were six patients with kyphosis of the thoracic spine; one-third of 39 patients were reported to be short in stature (Theile 1974).

Pathological findings
Degeneration of neurones in the cortex and basal ganglia, and demyelination in the white matter were found in one patient by Sylvester (1969). Loss of Purkinje cells and small atrophic foci in the cerebellum were also noted. Hyperkeratosis, a thickened granular cell layer and acanthosis were found in skin sections (Sylvester 1969).

Prognosis
Sjögren and Larsson (1957) found that the mean expectation of life for SLS patients was 44 per cent of that for the Swedish rural population as a whole. Intercurrent infections played a major role in the causes of death (Theile 1974). The mental retardation and ichthyosis appear to be stationary but for some patients deteriorating gait has been reported (Sjögren & Larsson 1957).
Table I. Re-evaluation by the present author of the diagnoses in patients reported by other authors to have SLS (Jagell et al. 1981). (Number of patients diagnosed catamnestically within brackets)

<table>
<thead>
<tr>
<th>Congenital ichthyosis</th>
<th>Typical</th>
<th>Atypical</th>
<th>Insufficient</th>
<th>No ichthyosis</th>
<th>No information</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical SLS&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>78 (4)</td>
<td>2</td>
<td>1 (13)</td>
<td>0</td>
<td>0</td>
<td>81 (17)</td>
</tr>
<tr>
<td>Atypical SLS</td>
<td>4</td>
<td>15</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Non-SLS</td>
<td>0</td>
<td>41 (4)</td>
<td>1 (3)</td>
<td>2</td>
<td>0</td>
<td>44 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>82 (4)</td>
<td>58 (4)</td>
<td>11 (16)</td>
<td>2</td>
<td>0</td>
<td>153 (24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological symptoms</th>
<th>Spastic di- or tetra-plegia</th>
<th>Other neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical SLS</td>
<td>78 (9)</td>
<td>3</td>
</tr>
<tr>
<td>Atypical SLS</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Non-SLS</td>
<td>32 (4)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>131 (13)</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mental retardation</th>
<th>Mentally retarded</th>
<th>Not mentally retarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical SLS</td>
<td>77 (14)</td>
<td>4</td>
</tr>
<tr>
<td>Atypical SLS</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Non-SLS</td>
<td>40 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>143 (18)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optic fundus</th>
<th>Glistening dots</th>
<th>Other fundic changes</th>
<th>No changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical SLS</td>
<td>27</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Atypical SLS</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Non-SLS</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>1)</sup>Evaluation by the present author in typical SLS, atypical SLS and non-SLS.

Atypical SLS = SLS diagnoses uncertain because of atypical clinical picture or insufficient information.
Fig. 1 a) Case 67, aged four and b) case 30, aged 42 years, with congenital ichthyosis, spastic diplegia and mental retardation (Sjögren-Larsson syndrome). c) The left axilla with hyperkeratosis in a seven-year-old boy with the Sjögren-Larsson syndrome. d) The right wrist with characteristic increased skin markings and scales on the forearm in a 28-year-old female Sjögren-Larsson patient. e) The left knee with hyperkeratosis in a 21-year-old man with the Sjögren-Larsson syndrome.
The aim of this investigation was to make a uniform study of a systematically collected material of SLS patients in order to elucidate the following aspects of the syndrome.

1. The incidence and prevalence in the whole of Sweden and in a few sub-areas of the country (I).
2. The mode of inheritance of the syndrome (I).
3. The clinical dermatological (II), histopathological and morphometric (III), skin surface (IV) and dermatoglyphic features (V).
4. The neurological features (VI, VII).
5. The ophthalmological features (VIII).
6. The fatty acid pattern of the plasma lipids, in an attempt to find out whether SLS could be due to a disturbance of polyunsaturated fatty acid metabolism (IX).

MATERIAL AND METHODS
A short summary of the materials studied and the methods used is given below. More detailed descriptions are presented in the following papers (I-IX).

The epidemiological and genetic study (I)
Inquiries concerning patients with SLS were sent to centres for child rehabilitation, all paediatric clinics, and authorities for the mentally retarded in all counties of Sweden, and to departments of dermatology and district nurses in the two northernmost counties of Sweden. All the 41 families with 58 SLS individuals, 28 males and 30 females, born in Sweden between 1886 and 1978, and their genealogy were studied.

Genealogic and family data were obtained by interviews, a search of archives, and from hospital records. The family material was tested for inheritance of SLS by the a-priori method (Emery 1976). The difference between the number of observed and expected individuals was also tested by the Chi-square method (Rao 1967). Further, the material was tested by the maximum likelihood method, the singles method and Weinberg's proband method (Emery 1976).
The clinical dermatological study (II)

All SLS patients, 20 males and 15 females, alive in Sweden in 1978, and one further male patient born in 1980, were examined with special attention to the ichthyosis. The ichthyosis was described with regard to the age at onset, subsequent development, anatomical distribution and severity. Multiple colour photographs were taken of all parts of the body in each patient. The DNA synthesis of the epidermis was studied in skin biopsies taken from the same site in all individuals. Eight patients and eight healthy controls matched according to sex and age were examined. The biopsies were transferred to a culture medium containing tritiated thymidine for labelling of the DNA-synthesizing epidermal cells. The labelled cells were visualized autoradiographically and counted at a magnification of 400 times. The transit time of the stratum corneum was determined in six patients and six healthy controls by use of dansyl chloride fluorescence (Jansen, Hojyo-Tomoko & Krigman, 1974). The dansyl chloride was applied by means of an occlusive patch test technique and the fluorescence was visualized by a UVA source (Wood's light): The day of disappearance of the fluorescence was determined. The number of cell layers in the stratum corneum was counted in skin biopsies taken about one week after interruption of the dansyl chloride application. The replacement rate for stratum corneum was calculated as number of cell layers in stratum corneum divided by the transit time measured by the duration in days of dansyl chloride fluorescence.

Histopathological examinations, morphometric and replications studies (III, IV)

Histopathological studies were performed on skin biopsies taken from the right forearm just below the elbow in all 35 SLS patients alive in 1978 and one further male patient born in 1980. Morphometrical studies were carried out with the aid of a semiautomatic image analysis system (Leitz A.S.M.). Replica series prepared with silicone rubber impression material reflecting the skin surface pattern in SLS patients and controls were studied.
Dermatoglyphic examinations (V)

Finger and palm prints were obtained from all 35 SLS patients alive in 1978, by means of the Faurot inkless method (Walker 1957). The dermatoglyphic patterns and flexion creases in the palms and digits were classified as described by Beckman et al. (1962) and compared with a normal material.

Neurological studies and physical examinations (VI)

The histories and hospital records were scrutinized with special reference to perinatal complications, psychomotor development, intelligence testing, previous examinations - especially neuroradiological ones - and orthopaedic operations.

Neurological and physical examinations were performed in all 35 SLS patients alive. Electromyography was performed in 14 patients and examinations of the motor and sensory nerve conduction velocity in 13.

Cranial computer tomography (VII)

Cranial computer tomography with a Mark I EMI scanner was undertaken in five SLS patients aged 6, 14, 14, 22 and 40 years and five sex and age matched controls. Attenuation values of white cerebral matter were compared between SLS individuals and controls.

Ophthalmological studies (VIII)

Ocular examinations, which were performed in all 35 SLS patients alive in 1978, included ophthalmoscopy in 35, slit lamp examination in 22, photography of the ocular fundus in 11 and electrooculography in two patients.

Biochemical studies (IX)

The fatty acid patterns in plasma phospholipids, cholesteryl esters, triglycerides and free fatty acids were analysed by gas-liquid chromatography in 11 SLS patients, 15 mentally retarded controls and 18 healthy controls. The individual proportions of 23 fatty acids were calculated and compared.
RESULTS AND COMMENTS

Genetic and epidemiological investigation (I)

All the 35 SLS patients studied showed the full syndrome, characterized by the cardinal signs congenital ichthyosis, spastic di/tetraplegia and mental retardation, already during the first years of life. The mean yearly incidences of SLS per 100,000 newborn during the years 1901-1977 were 0.6 in the whole of Sweden, 10.2 in the county of Västerbotten and 2.7 in the county of Norrbotten. The corresponding prevalence figures for SLS on 31st December 1978 were estimated to be 0.4, 8.3 and 2.6 per 100,000 persons in these three areas, respectively.

Ancestors of most patients from the SLS area were traced back to the late 17th century without a common ancestor being found. This is not surprising if the gene was well distributed in the population, which seems probable. Most SLS individuals were related to other patients with SLS. Parental consanguinity was noted in one-fourth of the SLS families, but the parents relationship was usually distant. They all came from a small area and their ancestors were often known ten generations back from this area. The consanguinity was not always the most probable reason for their SLS gene heritage, as sometimes they were closely related to other SLS patients.

Autosomal recessive inheritance was supposed on the basis of a sex ratio (male: female) close to one, healthy parents, and consanguinity in and blood relationship between many of the SLS families. Out of the 58 identified Swedish SLS patients, 45 were born in a restricted area in the northeast of Sweden where the frequency of heterozygotes of the SLS gene was calculated to be 2.6 % of the population. The frequency of carriers was calculated to be 2 % in the county of Västerbotten, 1 % in the county of Norrbotten and only 0.2 % in the whole of Sweden with the exception of these two counties.
Dermatological investigations (II-V)

All clinical symptoms; congenital ichthyosis, mental retardation, spastic di/tetraplegia and glistening dots in the ocular fundus occurred in all affected patients but only the skin changes were noted at birth.

The ichthyosis in the Sjögren-Larsson syndrome was found to be congenital in the true sense of the word, as it was always seen at birth. The ichthyosis was generalized already at birth, with a hyperkeratosis which was less pronounced in the face. Collodion-like membranes were never seen at birth. The ichthyosis developed to its full extent during the first year of life. It showed furfuraceous, lamellar and non-scaly hyperkeratosis, as a rule in various combinations. The ichthyosis was generalized, affecting most of the skin moderately but only slightly affecting the face, palms and soles. It occurred preferentially on the sides and back of the neck, flexures and lower abdomen. These areas were the ones which most frequently had dark scales. The non-scaly hyperkeratosis produced characteristic easily visible skin markings. Erythema was found only rarely in adults. The hair and nails were clinically normal, as was seemingly in most cases the ability to sweat. The rate of DNA synthesis of the epidermis and the production of the horny layer were increased.

All epidermal layers in all the 35 SLS patients were increased in thickness compared with those in normal subjects. The stratum corneum was, according to the morphometric measurements, about four times thicker than the normal. There was often a small number of parakeratotic cells but patchy parakeratosis was exceptional. In biopsies taken from the right cubital fossa the stratum granulosum was mostly three cell layers thick, compared with no more than two cell layers in healthy controls. The keratohyalin granules in the stratum granulosum were more pronounced than in normal biopsies. The stratum spinosum was acanthotic and its height was about twice the normal according to the morphometric measurements. In almost all biopsy specimens there was also some papillomatosis.
The characteristics of the ridges, furrows and scales were helpful in distinguishing SLS patients from other cases of ichthyosis with a histopathological picture similar to that of SLS. Thus, the replication method was a valuable complement in discriminating different ichthyoses, as the skin surface patterns may differ without any differences in the histopathology.

The dermatoglyphic patterns in the SLS patients differed from those in the normal material. There was an increase of whorls on digits I–III, a decrease of radial loops on digit II, and a lower pattern frequency in the interdigital area III on the right hand and in area IV on both hands in the SLS patients. There was an increased frequency of the transitional type I four-finger line and a larger variation in the atd angles in SLS.

The variations in the frequencies of dermatoglyphic patterns in the SLS patients compared with a normal material indicate an early prenatal pathological influence on the formation of dermatoglyphics in SLS. The dermatoglyphic alterations were, however, not sufficiently pronounced to be of diagnostic value in the individual case.

Neurological, neurophysiological and other somatic investigations (VI)

About half of the 35 SLS patients were born preterm with a weight and length within the normal for their gestational age. The prematurity did not have any prognostic importance.

According to medical records the first observation of pathological reflexes, muscular hypertonus and paresis in the legs, as well as of mental retardation, was made between the age of 4 and 30 months. Neurological symptoms were noticed earlier in those who later turned out to be severely motor-handicapped. All patients were diagnosed as
having spastic diplegia in their childhood but two patients later became functionally totally handicapped in all four extremities and were therefore diagnosed as tetraplegics. Their spasticity was not different from that of the others. They represent the lower end on the functional scale. Only one patient (case 38) differed inexplicably from the others, as her leg muscles became hypotonic in her early teens.

In some SLS patients the functional motor handicap in the legs became more pronounced during prepuberty and puberty, probably owing to a combination of increasing inactivity and increasing imbalance between muscular strength, body weight and height. Their arm function and their intelligence did not deteriorate. There were no signs of neurological progression except in case 38. The motor handicap did not increase with age after puberty in the other SLS patients as judged by function, contractures, and the proportion of patients confined to a wheel-chair did not increase. There was no elimination of more handicapped SLS patients in higher age groups that might have obscured a progression of the neurological symptoms with age.

Sensory and motor conduction velocity and EMG did not reveal any dysfunction of the sensory system or of the peripheral motor neurones except in two of 14 examined SLS patients.

Most patients were operated on several times by orthopaedic surgeons to improve the function of the legs and feet, but longterm observation revealed only slight improvement of their function.

Height was reduced as a result of shortness of the legs, kyphosis, scoliosis and contractures in hip and knee joints.

Mental retardation was noted in all SLS patients and was severe (IQ below 50) in two-thirds of them. There were no observations of progression of the mental retardation.

Enamel hypoplasia was not observed in the primary teeth. In the permanent dentition, however, generalized enamel hypoplasia occurred in four out of 12 clinically examined SLS patients. Thus, SLS patients
seem to have an increased frequency of enamel hypoplasia, indicating an ectodermal tooth defect (Forsberg, Jagell & Reuterving).

Cranial computer tomography (VII)
No specific morphological abnormalities of the brain or atrophic changes were found in our five SLS patients examined by cranial computer tomography (CT). This is in contrast to several reports of some types of congenital cerebral anomalies as well as cerebral atrophy seen at pneumoencephalography (PEG). Varying examination routines, unspecific standards of assessment and the phenomenon of gas distension of the ventricles and subarachnoid spaces at PEG may explain most of these findings. The attenuation values in the central white matter were somewhat lower in our SLS group than in the controls. The difference between the groups was not statistically significant (p > 0.05), which may have been due to the smallness of the material. An approximate 95% confidence interval for the population attenuation difference is given by the interval between -0.7 and 3.9. The values for individuals within the SLS group, as well as for those within the control group, differed significantly, with higher values with increasing age. The paired difference between SLS and control patients was not constant. These observations could be explained by lower attenuation values in some SLS patients and higher values due to age in both groups. The lower values might be due to the fact that SLS might be a chronic progressive, heredodegenerative disorder of the brain and spinal cord with a generalized breakdown of the neural substance and a higher water content in the white cerebral matter of the brain (Sylvester 1969).

Ophthalmological investigations (VIII)
Reduced visual acuity was found in the 12 patients who could be examined in this respect. This reduction could be secondary to changes in the
cornea or macula or the finding might be explained by insufficient co-operation due to mental retardation. Blepharitis, conjunctivitis and hyperaemic conjunctiva were found in most of the patients and were probably due to the ichthyosis on the margins of the eyelids. Corneal changes in the outer epithelium which were mostly visible only by slit lamp examination, were found in 16 of 35 patients. The defective fragile epithelium of the cornea (keratitis punctata) was thought to explain photophobia, as they occurred together.

In the retina there were small white glistening dots located in the macular region and arranged in a circle. These glistening dots, which were noted in the fundus of all 30 SLS patients examined in this respect, are not known from other disorders and seem to be pathognomonic for SLS. The dots varied in number from about 5 to 50, with about the same number in both eyes in any one person. It is not known at what age the dots first become visible, but in the present study the youngest patient with glistening dots was only 12 months old. An increasing number or size of these dots with age may be expected if the disease has a progressive course. We have not followed individual patients to see whether this number or size increases with age. In the whole group of SLS patients, no correlation was found between the number of glistening dots and either age or the severity of spasticity, mental retardation or ichthyosis.

Biochemical investigations (IX)
The fatty acid patterns of plasma phospholipids, cholesteryl esters, triglycerides and free fatty acids in SLS patients were examined. Mainly in plasma phospholipids but to a lesser degree also in the cholesteryl esters, triglycerides and free fatty acids the relative concentrations of metabolites derived from linoleic acid by Δ6 desaturation were found to be significantly lower than in controls,
suggesting a metabolic defect. The results suggest that in SLS there may be a defect in polyunsaturated fatty acid (PUFA) metabolism. The defect appears to lie in the Δ6 desaturation of PUFA metabolism, since the relative concentrations of plasma long-chain ω 6 acids derived from linoleic acid were lower than in controls.

A metabolic study of urinary samples from 35 SLS patients was performed by means of a series of chemical tests and by analysis of the amino acid pattern by high-voltage paper electrophoresis. Organic acids were analysed by gas chromatography-mass spectrometry and qualitative analyses for mono- and disaccharides were performed by thin-layer chromatography on cellulose. These analyses revealed no error in metabolism of amino acids, organic acids or carbohydrates (Holmgren et al. 1981).

Serum zinc and serum copper levels were examined in 18 individuals with SLS and no indications of disturbed zinc or copper metabolism were found (Jagell et al. 1981 b).

GENERAL DISCUSSION AND CONCLUSION

The genetic analyses strongly supported an autosomal recessive inheritance of the syndrome, with full penetrance. The cardinal signs were congenital ichthyosis, spastic di/tetraplegia, mental retardation and glistening dots in the ocular fundus.

The mean yearly incidence of SLS in the county of Västerbotten, 10/100,000, will probably remain at this relatively high level in the future until further migration of people to and from this county lowers the SLS gene frequency. On the other hand, the very low incidence of SLS in southern and central Sweden (1 per million), due to the low frequency of the SLS gene, will remain low but show local variations influenced by chance.

In 1957 the mean expectancy of life for persons with SLS was about half that of the general population (Sjögren&Larsson 1957). Most deceased SLS individuals died from respiratory diseases at a young age. Another
probable reason for the low mean life expectancy was poor living conditions. Nowadays, this group of patients are not more susceptible to infections than the general population and the mortality rate due to infections is low in SLS. The life expectancy and the prevalence of SLS have increased considerably during the last two decades and will probably increase further in the next thirty years as a result of a decreased mortality rate.

The concentration of SLS patients to a restricted area in northeastern Sweden is probably the result of a founder effect - transmission of a SLS gene mutation from early immigrants to this area followed by little migration to or from the area. The founder effect hypothesis is supported by the following observation: Only six families with SLS children are known where one or both parents were born outside the two northern counties in Sweden. Three of these six families originate from a small area in Medelpad from which Nils Fartegnson's family is known as far back as the 11th century. It is possible that this family or its fellow immigrants from Medelpad were carriers of the SLS gene mutation responsible for the three SLS patients in the county of Medelpad and for the 51 patients with parents born in the northern counties.

It cannot be decided whether the SLS patients in the remaining three families with parents of SLS children born in southern and central Sweden originate from the same SLS gene mutation as in the other 38 SLS families. This is plausible, however, as the mutation frequency of the SLS gene is very low in southern and central Sweden.

A correct delineation and diagnosis of SLS are of fundamental importance for genetic and epidemiological investigations as well as for pathogenetic studies and evaluation of the effect of treatment. SLS should be suspected in a child with slight or moderate congenital ichthyosis at birth. The ichthyosis never has a 'collodion-membrane' appearance at birth. The SLS diagnosis is confirmed when signs of spastic diplegia and mental retarda-
tion develop which were noted in the Swedish patients between six and 30 months of age. Glistening dots in the ocular fundus might be an obligatory finding. The spastic diplegia and the mental retardation are often pronounced in SLS.

One characteristic of SLS is congenital ichthyosis. At present ichthyosis may be classified into the following four groups: 1) ichthyosis vulgaris, 2) X-linked ichthyosis, 3) autosomal recessive types of nonbullous congenital ichthyosiform erythroderma, or lamellar ichthyosis, and finally 4) autosomal dominant bullous congenital ichthyosiform erythroderma or epidermolytic hyperkeratosis. The third group is clinically heterogeneous and includes different entities of ichthyosis with recessive inheritance. SLS is included in this group, since the inheritance is recessive, the histopathological picture rather conforms with other entities under this heading and at least some SLS individuals have erythema.

Generalized, dry, slight or moderately hyperkeratotic skin, sometimes with erythema but never with a collodion appearance, is always seen already at birth in SLS patients. The appearance of the skin at birth gives the diagnosis congenital ichthyosis. Congenital ichthyosis is a very rare condition and is usually not associated with other abnormalities. An autosomal recessively inherited form of congenital ichthyosis, also called 'lamellar ichthyosis', must be suspected if the parents themselves do not have ichthyosis. Some rare syndromes with congenital ichthyosis are known however, of which SLS is the most common. The SLS diagnosis is supported by typical but not pathognomonic histopathological features of a skin biopsy.

SLS is characterized by a disturbed function of the central nervous system causing mental retardation and moderate or pronounced spastic paresis, mainly affecting the lower extremities more than the upper. Our findings concerning the neurological symptoms do not differ from those previously reported in SLS or in spastic di- or tetraplegia with mental retardation of other origins. The degree of motor handicap is parallel
to the severity of mental retardation. None of our clinical observations supported the concept of Sylvester (1969) of a progressive course of the disease. A slight progression of the motor handicap may, however, be masked by the positive effect of physiotherapy or of orthopaedic corrective operations, or it may be so slight that it is not observable with present examination techniques.

All 30 Swedish SLS patients examined ophthalmoscopically in the present study, the youngest one year old, displayed glistening dots in the ocular fundus. It is not yet possible to state when these signs are first visible. The reason why other examiners have not reported glistening dots in all their SLS patients is probably that the changes are often so slight that they are easily overlooked or their significance has not been realised. The measured visual acuity was reduced probably secondarily to macular changes; the finding may also have resulted partly from poor co-operation due to mental retardation.

SLS is often discussed together with 'Rud's syndrome', which according to Ewing (1979) should be called the 'oligophrenia, epilepsy and ichthyosis syndrome', with the diagnosis based upon the presence of all these clinical findings. The few patients reported to have this latter syndrome certainly do not represent one single entity and there is at present some controversy regarding the criteria for its diagnosis. Spasticity is not a sign of 'Rud's syndrome' and the ichthyosis is not congenital but rather of the ichthyosis vulgaris type (Lever and Schaumburg-Lever 1975). Ewing (1979) found that about half of the reported patients with 'Rud's syndrome' had sexual infantilism, which was never found in the Swedish SLS population.

'Xeroderma and mental retardation', also named De Sanctis-Cacchione syndrome (De Sanctis & Cacchione 1932), is characterized by xeroderma pigmentosum, microcephaly and dwarfism, symptoms which are quite different from those in SLS; Refsum's disease, a 'phytanic acid storage disease'
which is also called 'heredopathia atactica polyneuritiformis', has retinitis pigmentosa, night blindness, peripheral polyneuropathy, cerebellar ataxia and ichthyosis as its major clinical components (Steinberg 1979). The phytanic acid is increased in plasma and tissues. Refsum's disease is most likely due to a deficiency in phytanic acid α-hydroxylase activity (Steinberg 1979). The ichthyosis in the same disease is clinically different from that in SLS, with large scales and vacuoles at the dermo-epidermal junction on microscopic examination (Davies et al. 1978).

There are no other known syndromes which may be mistaken for SLS when spasticity and mental retardation have become obvious.

The pathological manifestations in SLS involve tissues of ectodermal origin. Both the skin and the nervous system, including the retina as well as the cornea and the dental enamel are abnormal in SLS. The pathogenesis of the ichthyosis in SLS is unknown besides the heredity. Scaliness had been reported following deficiency of arachidonic acid (Prottey 1978). The SLS patients in the present study had, however, normal plasma levels of arachidonic acid (IX). A low relative concentration of γ-linolenic acid was found in our SLS patients as compared with controls. This was most likely due to a defect of Δ6 desaturation of linoleic acid. Δ6 desaturase activity is probably dependent on zinc (Cunnanae & Horrobin 1980). There were no indications of zinc deficiency in the SLS patients of the present material, however, and oral intake of zinc sulphate did not influence the skin (Jagell et al. 1981 b). It has been suggested that prostaglandins derived from fatty acids regulate the epidermal turnover and that reduced prostaglandin synthesis may be a cause of scaliness (Protty 1978). Inhibition of prostaglandin synthesis may be induced by a deficiency of essential fatty acids (Ziboh et al. 1974). The present investigation revealed normal linoleic and arachidonic acids, but low γ-linolenic acid (IX).
The dermatoglyphic alterations in SLS are probably not directly related to the SLS gene in homozygous form but are more likely secondary to skin changes in the early development of the hands.

The pathogenetic significance of the glistening dots in SLS is unknown. They occur in the area of the macula where the ganglion cells are numerous. These white dots may be a sign of ganglion degeneration or fatty degeneration of microglial cells (Daicker 1972). This presumed degeneration may be the cause of the reduced visual acuity. It might also be present in other parts of the central nervous system in SLS patients and be related to the motor handicap and the mental retardation.

Blepharo-conjunctivitis and punctate keratitis and other corneal defects are regarded as symptoms of ectodermal disease.

It is not yet known whether the neurological disorder in SLS is progressive or not. A prenatal non-progressive impairment of the central nervous system may be the result of an early developmental defect. This hypothesis is supported by the apparently non-progressive course of SLS and the non-progressive congenital ectodermal defects involving the skin and cornea.

The hypothesis that SLS is a progressive metabolic disorder involving the central nervous system is supported by the autopsy finding in a SLS patient of histopathological signs of demyelination in the central nervous system (Sylvestre 1969). The low nerve conduction velocity in the peripheral motor and sensory nerves in one SLS patient of the present series was probably due to demyelination.

The present study has shown that in SLS Δ6-desaturation may be defective. It is tempting to speculate that an abnormal composition of polyunsaturated fatty acids (PUFA) might influence myelination and the composition and function of microsomal, mitochondrial and extracellular membranes.
Sjögren-Larsson syndrome (SLS), originally described in Sweden, has been studied in a countrywide survey. A total of 58 SLS patients in 41 families were traced, 35 of them still alive in 1978. Thirty patients, 23 alive and seven deceased, have not been reported earlier. SLS is an autosomal recessively inherited disorder. All SLS patients developed the full syndrome, characterized by the cardinal signs congenital ichthyosis, spastic di/tetraplegia, mental retardation and glistening dots in the macular region of the ocular fundus. The mean incidences per 100,000 in the years 1901 - 1977 were 0.6 in the whole of Sweden, 10.2 in the county of Västerbotten and 2.7 in the county of Norrbotten. In the above-mentioned areas, the prevalence figures for SLS on 31st December 1978 were estimated to be 0.4, 8.3 and 2.6 per 100,000 persons, the frequencies of SLS gene carriers 0.5, 2.0 and 1.0 %, and the gene frequencies 0.002, 0.010 and 0.005, respectively. Of the 58 identified Swedish SLS patients, 45 were born in a restricted area in the northeast of Sweden.

The ichthyosis in SLS patients was always present at birth in a slight or, most often, moderate degree. Collodion skin was never seen at birth. The parents who are heterozygotes for the SLS gene had normal skin. The ichthyosis was congenital in the true sense of the word. The ichthyosis developed to its full extent during the first year of life. It was most often moderate and showed furfuraceous, lamellar and most often non-scaly hyperkeratosis, as a rule in various combinations in the same individual. It was generalized, with a predilection for flexures, the sides and back of the neck, and the lower abdomen. These areas were the ones which most frequently had dark scales. Erythema was only rarely found. The hair and nails were clinically normal, as was probably in most cases the ability to sweat. The DNA synthesis in the epidermis was increased, as well as the production of keratin. The ichthyosis in
SLS belongs to the rather heterogeneous group of hyperkinetic ichthyosis named 'lamellar' ichthyosis, recessive congenital ichthyosis or non-bullous ichthyosiform erythroderma.

The histopathological picture of the skin in SLS was characterized by a thick stratum corneum with slight parakeratosis, a thickened stratum granulosum, acanthosis and papillomatosis.

The finger and palm dermal-ridge patterns showed variations from a normal material. Replica studies revealed papillomatosis and longitudinal and transverse furrows in the skin surface.

Disturbed mineralization of the permanent teeth was a common finding. The neurological features of SLS were mental retardation combined with a moderate or pronounced non-progressive spastic muscular hypertonus which mainly affected the legs more than the arms. The onset of neurological symptoms and signs of mental retardation was observed between four and 30 months of age. The degree of motor handicap was parallel to the severity of the mental retardation. Epileptic seizures were reported in every third of the SLS patients - the same frequency as was found in an unselected series of cases with severe mental retardation (Gustavson et al. 1977). The neurological symptoms were thus uncharacteristic and could not be distinguished from spastic di- or tetraplegia with mental retardation of other origin. Cranial computer tomography revealed no signs of cerebral atrophy. All the Swedish SLS patients had clinical signs of a central nervous disease. However, the possibility of peripheral nerve involvement in SLS was not excluded and two SLS patients displayed signs of peripheral neuropathy.

The height was reduced as a result of shortness of the legs, kyphosis, scoliosis and contractures in the hip and knee joints.
All examined SLS patients had small white glistening dots in the macular region from early childhood. Changes in the outer epithelium of the cornea were common. Reduced visual acuity, blepharitis, conjunctivitis and hyperaemic conjunctiva were also common in SLS.

SLS is possibly, at least in part, a disorder of fatty acid metabolism leading to an altered composition of polyunsaturated fatty acids due to a disturbance in the Δ 6-desaturation of essential fatty acids. It might be speculated that the observed relative deficiency of γ-linolenic acid could have an influence on myelination in these patients. This hypothesis remains to be proved, however.
ACKNOWLEDGEMENTS

I wish to thank all those who have helped to make this thesis possible, in particular the following:

My main supervisors Professor Karl-Henrik Gustavson, former head of the Department of Paediatrics, University Hospital, Umeå where the main part of this work was carried out, and Associate Professor Gösta Holmgren, for their guidance, constant support and advice throughout the investigations. Without their great knowledge, enthusiasm and readiness to help, this work would not have been possible;

Associate Professor Per-Åke Hofer for his penetrating criticism and co-operation during this work;

My co-authors Jan Heijbel, M.D., who also accompanied me on interesting travels throughout Sweden in the search for SLS patients, Professor Sture Lidén, Associate Professor Olle Hernell, Associate Professor Frans Probst, Ola Sandgren, M.D., Werner Polland, M.D., Professor Ralph T. Holman and Susanne Johnson, Ph.D., for invaluable guidance in their fields of knowledge;

Bo Zetterlund, M.D., Department of Neurophysiology, University Hospital, Umeå, for performing electromyography and nerve conduction velocity tests and for experienced advice;

Professors Lars Söderhjelm, Ulf Halldén, Bengt Hagberg, Lars Beckman, Ingrid Gams torp, Herbert Helander and Lisa Welander and Associate Professors Sigfrid Blom, Gunhild Beckman and Hans Kollberg for valuable discussions;
Tage Larsson, Ph.D., M.D. for his stimulating interest in this work; I am grateful to him and to the late Professor Torsten Sjögren (1896-1974) and his wife, Göta Sjögren for their extensive study on SLS which formed a valuable basis for my investigations;

Maud Marsden for her interest and for skilful revision of the English text;

Jayanti Chotai, Ph.D. for statistical work and advice;

Birgitta Nordin, Margaretha Rönnbäck, Eva Sundqvist and Lolomai Örnehult for patiently and competently typing the manuscripts;

Yvonne Andersson for drawing the figures beautifully;

Rolf Lind, Rolf Eklund, Barbro Jakobson, Bengt Carfors and Per Olov Karlsson for photographic assistance;

Astrid Lundgren and Ewa Wikman for technical assistance;

Barbara Steele, Ph.D. for valuable librarian work;

The vicars and other officials of the parishes and provincial archives concerned, for their willingness to assist in the genealogical research;

Jonas Bure (1575-1655), Custos Archivi, for his excellent genealogical work which made it possible to trace the ancestors of SLS patients back to the Middle Ages;

All my patients and their families with no exception, for their positive and helpful collaboration and willingness to participate in the whole study;

The staff in charge of the patients, for careful assistance and for their loyal support of this work;
Colleagues in different hospitals for allowing access to the hospital records of their patients and for permitting me to include these patients in my study;

All other friends and colleagues for their interest and support;

And finally, Stefan, Mattias, Anna and Kristina, who have contributed more than I can possibly express.

This study was supported by grants from the Swedish Medical Research Council (Proj. No. 19X-05445), The Sävstaholm Society, The Eir Fiftieth Anniversary Foundation, The Finsen Foundation, The Karl-Oskar Hansson Foundation, The Medical Faculty of the University of Umeå, The Samaritan Foundation, The H. Hierta Foundation, The Edvard Welander Foundation and 'Förenade Liv' Mutual group Life Insurance Company, Stockholm, Sweden.
CASE REPORTS

Case 1, KF, family I (1 Ca in ref. 21). A male, born in 1886, brother of cases 2 and 5. Mental retardation, generalized congenital ichthyosis and paralysis of the legs from birth. Unable to walk. He died in 1926 of a heart disorder. No autopsy was performed.

Case 2, JF, family I (1 Cb in ref. 21). A female, born in 1891, sister of cases 1 and 5. A history of mental retardation, congenital ichthyosis and inability to walk. She died in 1894. Cause of death unknown according to pastoral records. No autopsy was performed.

Case 3, LW, family II (1 a in ref. 21). A female, born in 1894, sister of cases 6 and 14. Congenital ichthyosis. Psychomotor retardation noticed at an early age. She could walk slowly with support. Her gait had deteriorated gradually since school age. Physical examination in 1955 at 61 years of age (Sjögren): Height 151 cm, weight 57 kg. Slight tremor in the orbicular muscle of her mouth and in her tongue and left arm. Contractures in the knee and hip joints. Muscular hypertonus in the legs and arms - less pronounced in the arms. Bilateral ankle clonus. Able to walk with support, dragging her feet. Electromyography showed no signs of peripheral motor neuron lesion. Ophthalmological examination in 1955: In the macular region there were five or six round and oval, smoothly delimited pale atrophic areas in the pigmented epithelium. IQ 42 (Terman-Merrill). She died of pneumonia in 1963. No autopsy performed.

Case 4, VJ, family III (new case). A female, born in 1894. She was a sister of the grandfather of case 56. Congenital ichthyosis, spastic diplegia and psychomotor retardation from infancy. Never able to walk. Admitted to an institution for the mentally retarded. She died in 1962 of cardiolsclerosis. No autopsy was performed.
Case 5, PF, family I (1 Cc in ref. 21). A male, born in 1899, brother of cases 1 and 2. Congenital ichthyosis, psychomotor retardation and paralysis of the legs from birth. Never able to walk. He died in 1909, of unknown cause according to pastoral records. No autopsy was performed.

Case 6, MW, family II (1 b in ref. 21). A female, born in 1900, sister of cases 3 and 14. Congenital ichthyosis. She died of pneumonia in 1901. No autopsy was performed.

Case 7, AA, family IV (1 Aa in ref. 21). A female, born in 1901 with an uneventful delivery, sister of case 11. Mental retardation and congenital ichthyosis from birth. Never able to walk. Physical examination in 1919, paralysed legs, congenital ichthyosis, severe mental retardation. She could not speak or hear. Short stature. Had lived in an institution for the mentally retarded since 1919. Physical examination in 1949: She sat at a table the whole day doing nothing. 'Dry skin' over almost the whole body. She was able to dress and feed herself but was not able to walk. Severe contractures in the knee joints. Physical examination in 1955 (Sjögren): Height 154 cm, extensive ichthyosis, severe mental retardation, unable to speak, diplegia, reduced muscular power in her hands. Hyper-tonus in the legs and arms - more pronounced in the legs. Flexion contractures in the hip, knee and foot joints. She was unable to walk. Parkinsonism 1958. She died in 1958 of carcinoma of the stomach. No autopsy was performed.

Case 8, EV, family V (1 Ba in ref. 21). A female, born in 1901, sister of cases 10, 12 and 15. Mental retardation and ichthyosis from birth. Paralysis of the legs, never able to walk. She died in 1915 of whooping cough. No autopsy was performed.

Case 9, EF, family VI (new case). A female, born in 1906, sister of case 13. Congenital ichthyosis. Spastic diplegia and mental retardation from a young age. Seizures from the age of one year. Unable to walk. Has
spoken a few words since the age of four years. No school education. Physical examination in 1922: Appeared short owing to shortness of the paralysed legs. Could not walk without support. Obese. Unable to speak. She lived for many years in an institution for the mentally retarded. She died of pulmonary tuberculosis in 1937. No autopsy was performed.

Case 10, PV, family V (1 Bb in ref. 21). A male, born in 1906, brother of cases 8, 12 and 15. Mental retardation and ichthyosis from birth. Paralysis of the legs, never able to walk. He died in 1915 of unknown cause according to pastoral records. No autopsy was performed.

Case 11, IA, family IV (1 Ab in ref. 21). A female, born in 1907, sister of case 7. Uneventful delivery. Congenital ichthyosis. Tried to walk and speak from the age of six years. Physical examination in 1918 revealed spastic paresis and congenital ichthyosis. She was able to stand with support, and answered questions with simple words. She had lived in an institution for the mentally retarded since 1919. Physical examination in 1949: Paralysed legs. Could not walk but was able to stand with support. Generalized ichthyosis, less expressed in her face. Her speech was blurred but she spoke a few words and short sentences. Dressed and undressed herself. She was able to eat without help. Terman-Merrill test was not possible. Physical examination in 1955 (Sjögren): Congenital ichthyosis over large areas of the body. Diplegia of the legs. Some paresis of the arms. Marked hypertonus in the arms and legs. Flexion contractures in the hip and knee joints. Leg muscles moderately atrophied. Exaggerated tendon reflexes. Unable to walk. In 1967 increasing stiffness of the joints. In 1969 she was able to move herself from her wheel-chair to the toilet and back. Gradual motoric impairment and deterioration of mental abilities during recent years. Cataract developed in 1971. In 1973 she could move herself from the wheel-chair to the bed. Could not walk without support. Able to speak a few words. Slight right-sided scoliosis. Severe contractures in her legs. Severe congenital ichthyosis.
In 1978 thyroid and hepatic tests were normal. In 1978 a large ovarian cyst containing 6 litres of fluids was extirpated.

Last examination: At 73 years of age she was nursed in an institution for mentally retarded. She was in fairly good health. She was able to eat with a spoon but not to move herself about in a wheel-chair.

Case 12, PW, family V (1 Bc in ref. 21). A male, born in 1910, brother cases 8, 10 and 15. Uneventful delivery. Congenital ichthyosis. Mental retardation and spastic diplegia were noted before the age of one year. Physical examination in 1927: His legs were short and there were contractures in the knees and feet. Unable to walk. Crawled on his paralysed legs or shuffled forwards in the sitting position. Needed help for meals. Could not speak. The skull and face appeared enlarged. Congenital ichthyosis. He died in 1936 of pulmonary tuberculosis. No autopsy was performed.

Case 13, RF, family VI (new case). A female, born in 1912. Sister of case 9. Uneventful delivery. Congenital ichthyosis. Spastic diplegia and mental retardation from an early age. Medical examination in 1922: Able to stand on her feet with support. Crawled on her knees. Contractures in the knees. Moderate congenital ichthyosis. Dysarthria. Severe mental retardation, IQ 35 (Binet and Simon). She could speak a few words. Managed to eat with some support. Recognized relatives. Legs paralysed, poor stability in the rest of the body. She lived in an institution for the mentally retarded with her sister (case 9) from the age of ten years until she died of pulmonary tuberculosis in 1936. No autopsy was performed.

Dragged her toes. Marked hypertonus in her legs - more in the right leg - and some in the arms. IQ 44 (Terman-Merrill). Electroencephalography normal. Electromyography revealed no peripheral motor neuron lesion.

Ophthalmological examination in 1955: 'Outside the actual macular area four or five circular areas of atrophy of the retinal pigment of about the same size'. She died in 1972 of influenza and pneumonia. No autopsy was performed.

Case 15, BW, family V (1 Bd in ref. 21). A female, born in 1912, sister of cases 8, 10 and 12. Mental retardation and ichthyosis from birth. Never able to walk. She died in 1916, of unknown cause according to pastoral records. No autopsy was performed.

Case 16, BL, family VII (5 a in ref. 21). A female born in 1912, sister of cases 19 and 20. Mental retardation and ichthyosis from birth. Legs paralysed. Medical examination in 1917. Considered to have Little's disease and oligophrenia. She died of pneumonia in 1921. No autopsy was performed.

Case 17, BL, family VIII (new case). A male, born in 1915. First cousin of the mother of case 29. Congenital ichthyosis. Spastic diplegia since childhood. Never able to walk. Crawled on his paralysed legs until old age. Able to walk with immobilized legs with crutches or move in a wheelchair. Not able to stand without support. Attended a school for the mentally retarded for some time but did not learn to read or write. Able to manage most ADL functions. In 1970 radiotherapy for basal cell carcinoma in the nose. In 1975 Bell's palsy. Mental retardation, dysarthria, congenital ichthyosis. He could move himself between his bed and wheelchair in 1977. Was able to eat without help, dress himself and wash the upper half of his body. Some reduction of strength in his arms and spastic pareses in his legs, with severe contractures in his legs. In 1978 extraction of cataract, right eye. Macula corneae in both eyes. Enlarged prostate. Several orthopaedic operations performed on the legs. He lived
with his mother until 1975 and later in a longterm hospital because of his handicap. Terman-Merrill test was not possible.

Last examination: At 63 years of age he was in good health. He was able to eat with a fork and move himself about in a wheel-chair.

Case 18, GS, family IX (new case). A female, born in 1915, sister of case 23. Congenital ichthyosis. Mental retardation and spastic diplegia from infancy. Unable to walk and moved about by crawling. Attended a school for the mentally retarded. She died of a heart disorder in 1937. No autopsy was performed.

Case 19, AL, family VII (5 b in ref. 21). A male, born in 1915. Brother of cases 16 and 20. Congenital ichthyosis. He died in 1916 of pneumonia and whooping cough. No autopsy was performed.

Case 20, BL, family VII (5 c in ref. 21). A male, born in 1919, brother of cases 16 and 19. Congenital ichthyosis and diplegia from birth. Medical examination in 1924: Mental retardation, congenital ichthyosis, spastic diplegia. Unable to walk. Arms normal. Medical examination in 1932: Marked spasticity in his legs. Pronounced talipes valgus. Mental retardation. He could read a few words. Seizures for some time. He died in 1941 of pulmonary tuberculosis. No autopsy was performed.

Case 21, GB, family X (new case). A male, born in 1920. Congenital ichthyosis and spastic diplegia since birth. Lived with his mother until 1977 and later in a home for the mentally retarded. Medical examination in 1929: Severe mental retardation. He could speak a few words. Followed simple instructions. Skin very dry and scaly. Thick dark hyperkeratosis in some places. Strong rigidity of the lower extremities. Never able to walk on his feet - moved about on his knees or in a wheel-chair. He had attacks of seizures a few times monthly. Medical examination in 1974: Dry scaly skin over the whole body. Muscular atrophy in the legs. Contractures in the knees and ankles. Parkinsonism had just developed in his right arm.
Terman-Merrill test was not possible.

Last examination: At 60 years of age he was nursed in a long-term ward as he was no longer able to feed himself without help and could no longer use his wheel-chair.

Case 22, EN, family XI (3 a in ref. 21). A female, born in 1921. Sister of cases 26 and 27. Pregnancy and delivery were uneventful. Congenital ichthyosis. Mental retardation evident from the age of three years. A few seizures occurred in infancy. Had seizures from 13 to 17 years of age. Menarche at 14 years. Tried to walk with support from the age of 3 years. Medical examination in 1955 (Sjögren): Height 150 cm. Pronounced ichthyosis over the whole body. Severe mental retardation. Able to speak a few words. Considerable paresis in the legs, less in the arms. Marked hypertonus in the legs, less in the arms. Moderate flexion contractures in her knee and foot joints. Slight muscular atrophy in the lower legs. Could only walk with support. Medical examination in 1969: The hips and knees were in a markedly flexed position. Pronounced left-sided equinovarus. Kyphosis. She has had several orthopaedic operations. She is still alive in 1981, living with her sisters. IQ 30 in 1965 (Terman-Merrill).

Last examination: When she was 58 years old she was able to eat with a fork and walk with support.


Case 24, TG, family XII (new case). A male, born in 1924. Uncle of case 49. Congenital ichthyosis. Spastic diplegia and mental retardation since infancy. Never learnt to speak. He died of pneumonia in 1930. No autopsy was performed.
Case 25, IB, family XIII (new case). A female, born in 1924. Sister of case 28. Congenital ichthyosis. Spastic diplegia and mental retardation from infancy. Seizures. Medical examination in 1928: Unable to walk, sit or crawl. Thin hair, poor teeth. Blepharitis. She stared into space and rested on her back without giving any contact. She died of pneumonia in a hospital in 1928. No autopsy was performed.

Case 26, AN, family XI (3 b in ref. 21). A female, born in 1927, sister of cases 22 and 27. Pregnancy and delivery uneventful. Congenital ichthyosis. Mental retardation and spastic diplegia noted from the age of about three years. No school education. In 1965 her visual acuity was 0.4. Glasses were of no help. Pronounced spastic paresis in her legs, slight in her arms. She can walk with difficulty without support. Ankle clonus. Able to dress and wash herself. Speaks short sentences fairly well. Lives with relatives. Has had several orthopaedic operations on the legs. IQ 30 in 1965 (Terman-Merrill).

Last examination: At 52 years of age she was able to eat with a fork and walk with difficulty without support.

Case 27, LN, family XI (3 c in ref. 21). A female, born in 1928, sister of cases 22 and 26. Whooping cough at the age of a few weeks. Congenital ichthyosis. Mental retardation and spastic diplegia from infancy. Unable to walk and move about by crawling. She had the stature of a 10-year-old child when she was 20. She often had seizures during childhood. No menarche. She died in 1950 of influenza. No autopsy was performed.

Case 28, IB, family XIII (new case). A female born in 1929, sister of case 25. Congenital ichthyosis. Uneventful delivery. Spastic diplegia and mental retardation from infancy. She learnt to speak a few words at the age of two years. She could eat without help from the age of four years. No school education. She learnt to count to five. In 1952 her IQ was 20. There were severe flexion contractures in the hips and knees. She sat in a wheel-chair and was unable to stand. Could say a few words. Able to feed
herself with some help. She had bronchial asthma. In 1962 pronounced kyphoscoliosis. She has undergone several orthopaedic operations on the legs.

Last examination: At 49 years of age she was able to eat with a knife and fork and she was able to move about in a wheel-chair.

Case 29, EE, family XIV (new case). A male, born in 1933. Pregnancy and delivery uneventful. Birth weight 4 kg. His mother is first cousin to case 17. He started to walk on tiptoes when three years old, with support. Spastic diplegia and mental retardation from infancy. Psychomotor retardation noted at 7 months. Crawled without the support of his legs. Confined to a wheel-chair from the age of 26 years. Lived at home until 1978, when he moved to an institution for the mentally retarded. Could not walk without support. He learnt to write his name but not to read or count. Kyphosis.

Last examination: At 45 years of age he was able to eat with a fork and move about in a wheel-chair.


Last examination: At 44 years of age he was able to eat with a fork and walk with help. His speech was fairly good.
Case 31, SN, family XV (new case). A female, born in 1938. The pregnancy was uneventful. Born pre-term in an uncomplicated breech delivery. Birth weight 3,200 g. Ichthyosis, spastic diplegia and mental retardation noted from the age of about one year. Born at home and not examined by any doctor during her first year of life. In 1942 she could walk a few steps with support on her tiptoes with strong adduction spasticity. No school education. She could not read, write or count. Pronounced kyphosis. Difficulties in speaking sentences. IQ 45 in 1947. Confined to a wheel-chair in 1965. Up to that date she shuffled her feet when walking with trestles. Severe contractures in the legs. X-ray revealed luxation of both hip joints in 1977. Orthopaedic operations on the legs.

Last examination: When she was 40 years old she was able to eat with a fork and move about with difficulty with support.

Case 32, AR, family XVI (7 a in ref. 21). A female born in 1939. Pregnancy and delivery uncomplicated. Congenital ichthyosis. Mental retardation and spastic diplegia from infancy. Walked at four years of age without support but dragged her left foot. Able to speak a few words when six years old. Admitted to an institution for the mentally retarded in 1950. Waddling gait, able to walk by dragging left foot behind her. She did not elevate the feet when walking but moved them in a half-circle outwards. Congenital ichthyosis all over the trunk and the extremities (Sjögren). Physical examination in 1956: Short stature. Somewhat infantile sexual development. Walked with difficulty without lateral differences. Skin coarse, leathery, somewhat scaling. Severe caries and almost no teeth left. Could not speak. Good muscular power in her arms. No school education. Talipes equinus. Moderate muscular hypertonus in the arms, less in the legs. Foot clonus bilaterally. Walked with difficulty without support. Gait spastic, dragged her toes, more so on the left foot. Marked circumduction. Ophthalmological examination revealed small aggregates of pigment and choroidal atrophy in her right macula. She died in 1957 from streptococcal angina. No autopsy
was performed. Intelligence test was not possible.

Case 33, NH, family XVIII (2 a in ref. 21). A male, born in 1939. Pregnancy and delivery uncomplicated. Born pre-term. Congenital ichthyosis. Physical examination in 1950: Unable to stand without support, atrophy in both legs, both legs were adducted. Congenital ichthyosis. Able to speak a few words. Could feed himself but not dress himself. He had diurnal enuresis. Terman-Merrill test not possible. In 1964, crawled or moved about in a wheel-chair. In 1969 he was able to dress himself with some support. He has lived in an institution for the mentally retarded since 1950. In 1978 kyphoscoliosis and pronounced lordosis.

Last examination: At 41 years of age he was able to eat with a fork and move about in a wheel-chair.

Case 34, UB, family XIX (10 a in ref. 21). A female, born in 1945. Pregnancy and delivery uneventful, born pre-term with a birth weight of 2,150 g. Congenital ichthyosis. Spastic diplegia and mental retardation since infancy. She was able to sit without support at 2-3 years of age. Physical examination in 1954: General ichthyosis, spoke in isolated phrases. Tendon reflexes were increased bilaterally. Babinski positive bilaterally. Able to walk with bent knees, shuffling, with support. In 1955 she could read and write simple words with block letters. In 1963 she was able to read fairly well but could not write all block letters. She could eat without help and dress herself with some help. She had good articulation. Was able to count from 1-10. Could walk with support. Severe myopia. In 1964 she had seizures. In 1965 total left-sided paresis suddenly developed, but she had no unconsciousness or seizures. Five months later she could walk again with walking aids. In 1973 scoliosis was observed. In 1976 she had diurnal enuresis. IQ 48 in 1954 and 47 in 1965 (Terman-Merrill). Orthopaedic operations were performed on the legs. She lives with her parents.

Last examination: At 33 years she was able to eat with a fork and move about in a wheel-chair.
Case 35, KN, family X (9 a in ref. 21 and case 1 in ref. 24). A female, born in 1947. Born pre-term in an uneventful delivery. Birth weight 2,000 g and weight 12 days of age 1,980 g. At 11 months her head circumference was 47.5 cm. She had poor head stability. The head circumference was 50 cm at two years of age. At that time she had no spasticity but was not able to sit without support. She could not turn around in bed. She showed no tendency to walk. Pneumoencephalography at two years of age was not quite successful but showed wide sulci. Physical examination in 1955: Pronounced spasticity in the legs. Unable to walk. Able to stand with difficulty with support. Could answer questions correctly. Able to write her name. She had generalized hyperkeratosis, except in her face. She could raise herself from the supine to the sitting position with difficulty. Clonus in the feet and knees. Pronounced planovalgus. Crossed her legs when sitting. In 1956 she could stand with support but was unable to walk. In 1957 she could walk with support, but unsteadily. Scissor gait. Pronounced spasticity in the adductor muscles. No contractures. Pronounced spasticity in the legs. Walked with crutches with contracted legs, or crawled on her knees. IQ 45 in 1960 and 40 in 1964 (Terman-Merrill). In 1965 she managed ADL. In 1972 she was confined to a wheel-chair. Several orthopaedic operations were performed on her legs and feet.

Last examination: At 31 years she was able to eat with a fork and knife and walk with support. She could speak well but slowly.

Case 36, EH, family XXI (4 a in ref. 21 and case 2 in ref. 24). A female, born in 1950. Parents are second cousins. Uneventful pregnancy and delivery at home. Birth weight 3,450 g. Congenital ichthyosis. Walked from the age of 1 1/2 years with support. Spasticity in the legs from 1-2 years of age. In 1961 spasticity was more pronounced in her legs than in her arms. Talipes equinovarus. Ankle clonus in her left foot in 1955. Able to speak and read fairly well. Repeated orthopaedic operations on her legs and feet.

Last examination: At 30 years of age she was able to eat with a fork
and walk with difficulty without support. Her speech was good.

Case 37, BM, family XXI (11 a in ref. 21 and case 3 in ref. 24). A male, born in 1952. His mother's first cousins are cases 8, 10, 12 and 15. Pregnancy and delivery were uneventful. His birth weight was 3,020 g. Congenital ichthyosis was seen at birth. Spastic diplegia was noted at 2 years 10 months. He could walk with support and speak a few words at that age. At six years of age he could speak fairly well and walk with difficulty without support. Several orthopaedic operations were performed on the legs. He learnt to ride a three-wheel bicycle, read simple books, write words with block letters and to play an electric organ and accordion so well that he could join a Salvation Army orchestra. His IQ (Terman-Merrill) was 66 in 1961 and 61 in 1967.

Last examination: At 28 years of age he was able to eat with a fork and walk with difficulty without support. His speech was good.

Case 38, EL, family XXII (new case). A female, born in 1956. The pregnancy and delivery were uneventful. Her birth weight was 3,040 g. Ichthyosis was seen at birth. Her psychomotor development was normal during the first months of life, according to her parents. Seizures occurred at the age of seven months. Brisk reflexes in her legs were noted at 13 months and foot clonus was observed at 1 year 8 months. At that age the muscular tonus in her legs had decreased. She could not sit without support. She had some ability to grasp objects but not to use them. Mental retardation was obvious at that time. At 12 years of age she had daily generalized tonic-clonic seizures. She managed to eat with a spoon. She could stand on her feet and walk a few metres with two-hand support and move from the floor into her wheel-chair and back again when 12 years old. She had clonus in the patellar and achilles reflexes and pronounced spasticity in her legs. She was now in her best condition. After the age of 12 years her physical status deteriorated. At 13 years she had pronounced muscular hypotonus in both legs. She lost her ability to walk and move. At 15 years
of age her patellar and achilles reflexes were lost. She had a right
scoliosis at that time from vertebra T1 down to L4, which became worse
during the following years. No other signs of progression of the clinical
picture were found.

Last examination: At 24 years she was able to eat with a spoon but not
with a fork and able to move about slightly in a wheel-chair. Her speech
was poor.

Case 39, TJ, family XXIV (1 in ref. 2 and case 4 in ref.10). A male, born
in 1957. Born pre-term. Pregnancy and delivery were uneventful. His birth
weight was 2,950 g. He had congenital ichthyosis at birth and slow motor
activity from birth onwards. He never learnt to speak or to chew food.
Exaggerated tendon reflexes were observed in his legs at 14 months and
diplegia was diagnosed at 18 months. For some years he was still able to
remain in a sitting position with slight support for a short while, but
he could never sit without support. He was able to stand with much support
between the ages of five and 13 years. At five years epilepsy, with gene-
ralized tonic-clonic seizures, began. An increasing kyphoscoliosis was
noted from that time. He was never interested in motor activity and he
never achieved a motor development more advanced than that of an 8-month
baby, although he received a maximum of stimulation and physical training.
His decline into a totally helpless individual could be fully explained
by his poor interest in co-operation, severe tetraplegia and muscular atrophy
due to inactivity.

Last examination: At 23 years of age he was totally helpless, with no
speech or any functional movements in the arms or legs.

Case 40, AL, family XXV (new case). A male, born in 1957, brother of case
50. Born full-term. Pregnancy and delivery were uncomplicated. His birth
weight was 3,400 g. He had congenital ichthyosis and slight erythema at
birth. Spastic diplegia and mental retardation were noted at two years of
age. He learnt to walk fairly well with crutches and learnt to speak and
read well. Orthopaedic operations were performed on his legs.

Last examination: At 22 years he was able to eat with a fork and walk with difficulty without support. His speech was good.

Case 41, CH, family XXVI (new case). A female, born in 1957. The parents were first cousins. Born pre-term in an uncomplicated delivery. Her birth weight was 2,540 g. Congenital ichthyosis was noted in the birth records but was first seen at three months of age by the parents. Spasticity and mental retardation were observed at about 15 months of age. She learnt to walk with difficulty and with support. Her speech was difficult to understand. Her IQ was 50 in 1962 and 1964 (Terman-Merrill).

Last examination: At 22 years of age she was able to eat with a fork and walk with support.

Case 42, KV, family XXVI (new case). A male, born in 1958. Born full-term in an uncomplicated delivery with a birth weight of 2,110 g. He had congenital ichthyosis with scaling, mostly on the abdomen. Spasticity was noted at 12 months and mental retardation from early childhood. He learned to walk with difficulty, with support, but was later confined to a wheelchair. He could read and speak fairly well. He had simple part-time in a factory at 20 years of age. Repeated orthopaedic operations were performed on his legs.

Last examination: At 20 years of age he was able to eat with a fork and move about in a wheelchair.

Case 43, AA, family XXVIII (case 3 in ref.10). A male, born in 1960. Born full-term in an uncomplicated delivery. His birth weight was 3,320 g. Congenital ichthyosis. Mental retardation was noted at 11 months and spasticity at 12 months. Several orthopaedic operations were performed on his legs and he had a considerable amount of physiotherapy but did not learn to walk on account of severe spastic diplegia. His arm function was fairly good. His speech was poor.

Last examination: At 20 years he was able to eat with a fork and move
about in a wheel-chair. His speech was inarticulate.

Case 44, UV, family XXIX (case 2 in ref.10). A male, born in 1960. Uneventful pregnancy and delivery at term. His birth weight was 2,750 g. He had congenital ichthyosis and appeared at birth to have a large skin costume. Pronounced erythema and intense scaling were noted on the trunk on the second day of life. Neonatal icterus occurred but there were no indications for blood exchange transfusions. He had feeding difficulties initially and on discharge from the paediatric ward at the age of 16 days his weight was 2,450 g. He had slow motor activity from birth onwards. At one year of age he had pronounced psychomotor retardation with diplegia. He started to grasp with his hands at two and a half years of age. Seizures began when he was seven years old. On examination at eight years he was able to raise his head a little when lying prone, and could grasp objects with difficulty but not use them. At that time he had pronounced tetraplegia with generalized muscular atrophy and contractures in the hip and knee joints. He could balance his head for only a short time when being held in the sitting position. He did not speak. His psychomotor development was now at its maximum, equivalent to that of a five-month baby. He gradually lost most of his abilities during the following years. Finally he could only swallow with difficulty, follow an object with his eyes, move slightly without any modulation and move his right hand slightly with no useful function.

Last examination: At 20 years of age he was totally helpless with no speech or any functional movements in the arms or legs.

Case 45, SL, family XXX (new case). A male, born in 1960. He was born full-term in an uncomplicated delivery. His birth weight was 2,650 g. Congenital ichthyosis and slight erythema were noted at the age of five days. Mental retardation was observed at 10 months and spastic diplegia at 16 months. He learnt to walk with support but was later confined to a wheel-chair. Seizures started from one year of age. Orthopaedic operations
were performed on the legs. His speech was poor.

Last examination: At 18 years of age he was able to eat with a fork and move about in a wheel-chair.

Case 46, BL, family XXXI (new case). A male, born in 1960. He was born pre-term in an uncomplicated delivery. His birth weight was 3,600 g. He had congenital ichthyosis. Spastic diplegia was noted at 10 months and mental retardation a few months later. He could walk with support. He had seizures for some years, which later ceased. Orthopaedic operations were performed on the legs.

Last examination: At 18 years of age he was able to eat with a fork and walk with support.

Case 47, CF, family XXXII (new case). A male, born in 1961. Born pre-term. in an uncomplicated delivery. His birth weight was 2,550 g. Congenital ichthyosis. Spasticity in the legs and mental retardation were noted at about 13 months of age. He never learnt to walk.

Last examination: At 19 years of age he was able to eat with a fork and move about in a wheel-chair or crawl functionally.

Case 48, BG, family XXXIII (new case). A male, born in 1963. The parents were second cousins. He was born pre-term in an uncomplicated delivery. His birth weight was 2,500 g. Congenital ichthyosis and erythema were noted at birth. His mother observed abductor spasticity when he was only three months old. Spastic diplegia and mental retardation were present from early childhood onwards. Several orthopaedic operations were performed on his legs. He learnt to walk with crutches. His speech was fairly good. Seizures began in his teens.

Last examination: At 16 years of age he was able to eat with a fork and walk with support. His speech was fairly good.

Case 49, IG, family XXXIV (case 1 in ref.10). A female, born in 1963. Case 24 was her uncle. She was born full-term in an uneventful delivery.
Her birth weight was 3,510 g. She had congenital ichthyosis and slight erythema at birth. Mental retardation, spastic diplegia and luxation of her right hip were noted at 11 months of age. She was severely handicapped already as a child and never learnt to walk with support in spite of energetic physiotherapy and orthopaedic operations. A pronounced scoliosis developed in her teens.

Last examination: At 17 years she was able to eat with a fork but she could not move about functionally in a wheel-chair. Her speech was rather good.

Case 50, AL, family XXV (new case). A female, born in 1964. Sister of case 40. She was born pre-term in an uneventful delivery. Her birth weight was 2,740 g. Congenital ichthyosis was noted at birth and spasticity in her legs at four months of age. Mental retardation was recorded at two years of age. She learnt to walk poorly with support and was mainly confined to a wheel-chair in spite of energetic physiotherapy and orthopaedic operations.

Last examination: At 16 years of age she was able to eat with a fork but she could not move about functionally in a wheel-chair and her speech was slight.

Case 51, AU, family XXXV (new case). A male, born in 1965. He was born pre-term in an uneventful delivery. Birth weight 3,000 g. He had congenital ichthyosis. Muscular hypertonus was noted in his legs at 15 months of age. Mental retardation was recorded at about two and a half years. He learnt to walk easily with crutches, throwing his paretic legs forwards, but could only take a few steps without support. Pneumoencephalography and gas myelography at the age of two years were normal. He was treated with anticonvulsive drugs because of epileptic seizures. Orthopaedic operations were performed on his legs.

Last examination: At 14 years of age he was able to eat with a knife and fork, and walk a few metres without support but six km with crutches.
He could read the text on television.

**Case 52, KL, family XXXVI (new case).** A male, born in 1969. He was born full-term in an uneventful delivery. Birth weight 3,360 g. Congenital ichthyosis with scaling and some erythema were seen at birth. Pylorotomy was performed at the age of six weeks. Mental retardation was noted at nine months and spasticity in the legs at 18 months. He learnt to walk well with support. His speech was inarticulate. Orthopaedic operations performed on the legs.

Last examination: At ten years he was able to eat with a fork and walk well with support but his speech was inarticulate.

**Case 53, AJ, family XXXVI (new case).** A female, born in 1969. She is a sister of case 54. She was born full-term in an uneventful delivery. Her birth weight was 3,390 g. Congenital ichthyosis was noted at birth and she had slight erythema on her sixth day of life. Spastic diplegia was observed at 13 months and mental retardation at one year five months. She learnt to walk with support. Orthopaedic operations were performed on her legs.

Last examination: At nine years of age she was able to eat with a fork; she could walk with support and speak rather well.

**Case 54, EJ, family XXXVI (new case).** A male, born in 1971. He is a brother of case 53. He was born full-term in an uneventful delivery. Birth weight 3,920 g. Congenital ichthyosis at birth. His skin costume appeared to be too large and oedematous. Mental retardation was noted at six months and spastic diplegia at 14 months. Seizures began at six years of age. He crawls forwards with the help of his arms. Orthopaedic operations were performed on the legs with no improvement of walking.

Last examination: At seven years he was not able to feed himself without help. He could move about by sliding on the floor and speak a few words.
Case 55, MJ, family XXXVII (new case). A male, born in 1973. He was born full-term in an uncomplicated delivery, with a birth weight of 3,530 g. He had congenital ichthyosis and his skin costume appeared wrinkled at birth. Mental retardation and spastic diplegia were noted at two and a half years. He learnt to speak well and walked without support with a diplegic gait. Orthopaedic operations were performed on his legs.

Last examination: At seven years of age he was able to walk with difficulty without support, eat with a fork and speak slowly but well.

Case 56, MJ, family XXIX (new case). A female, born in 1973. She was born full-term with a birth weight of 2,690 g. She was born in the breech position and had slight asphyxia during delivery with Apgar scores of 2, 7 and 8 after one, five and ten minutes. She had some twitchings for five minutes at the age of about 12 hours. She had congenital hip dislocation bilaterally and congenital ichthyosis and her skin appeared wrinkled. Mental retardation and spastic diplegia were noted at two years of age. Elongation of the Achilles tendon was performed to relieve a tiptoe position of one of her feet.

Last examination: At seven years she was able to walk slowly without support, eat with a fork and speak rather well.

Case 57, LN, family XL (new case). A female, born in 1974. She was born pre-term in the breech position with slight asphyxia, with Apgar scores of 4, 8 and 9 after one, five and ten minutes. Her birth weight was 2,510 g. Hyperbilirubinaemia necessitated blood exchange transfusions. She had congenital ichthyosis at birth and her skin costume appeared to be too large. She had erythema on the second day of life. Mental retardation and spastic diplegia were noted at one year seven months. She learnt to walk with support. Orthopaedic operations were performed on the legs. Conduction velocity tests revealed a low conduction velocity in both upper and lower motor and sensory neurons.

Last examination: At six years of age she was able to walk with support,
eat with a fork and speak fairly well.

Case 58, MP, family XLI (new case). A male, born in 1977. He was born full-term in an uneventful delivery. His birth weight was 3,000 g. He had congenital ichthyosis at birth with a pasty consistency of the skin, which was also somewhat erythematous. Mental retardation was noted at one year of age and spastic diplegia at one year nine months.

Last examination: At three years of age he could stand with support, eat with a spoon and drink from a glass.
REFERENCES


