Hum Genet (2003) 112 : 470–526
DOI 10.1007/s00439-002-0877-1

REVIEW ARTICLE

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The Finnish disease heritage III: the individual diseases

Received: 20 June 2002 / Accepted: 30 October 2002 / Published online: 8 March 2003

Abstract This article is the third and last in a series entitled The Finnish Disease Heritage I–III. All the 36 rare hereditary diseases belonging to this entity are described for clinical and molecular genetic purposes, based on the Finnish experience gathered over a period of half a century. In addition, five other diseases are mentioned. They may be included in the list of the "Finnish diseases" after adequate complementary studies.

Abbreviations *AFP* alpha-fetoprotein · *CT* computed tomography · *ECG* electrocardiography · *EEG* electroencephalography · *ENMG* electroneuromyography · *ERG* electroretinography · *HUCH* Helsinki University Central Hospital · *MBD* minimal brain dysfunction · *MIM* Mendelian Inheritance of Man (McKusick) · *MRI* magnetic resonance imaging · *OUH* Oulu University Hospital · *SEP* somatosensory evoked potential · *SPECT* single photon emission computed tomography · *TUH* Turku University Hospital · *VEP* visual evoked potential

Introduction

This article series will acquaint the international readership with the Finnish Disease Heritage, a collection of nearly 40 rare hereditary diseases over-represented in Finland. In the first article, investigations of the characteristics, causes and background of this phenomenon were reported. The second part dealt with the population prehistory and genetic roots of the Finns.

In this third article, the individual diseases are described so as to present the relevant details for practical purposes to medical geneticists and other physicians. Aspects of each disease are presented in sub-sections, facilitating the easy finding of desired details. While these descriptions must be limited to a certain extent, further detailed information is available from the selected articles given in the references section at the end, which is divided into separate sub-sections for each disease. In most cases, these articles are not separately referred to in the text. In choosing the references preference is given to the research based on the numerous patients and gathered experience in Finland. Also the "historical" development of the growing knowledge and the cornerstones of investigation are included. Most references in the Finnish language have been excluded. They are, however, mentioned in my book *Suomi-neidon geenit* (The Genes of Maiden Finland), Otava, Helsinki, 2000, upon which the presentations of this article are based. Those who can read Finnish texts may also have access to that book.

Out of the 36 diseases described, the most (32), are transmitted in an autosomal recessive manner. This has not been mentioned separately. The mode of inheritance of the two autosomal dominant and two X-linked disorders is *italicised* in the introduction of the disease.

The rare diseases have many — not to say too many — names. Among them, the name used mostly in Finland has been chosen as the first name. Unfortunately, no system prevails in this; practical circumstances and habit have often decided the name used. It can also be an abbreviation if the proper name is desperately long or otherwise complicated (e.g. AGU instead of aspartylglucosaminuria). Eponyms, though not recommended in general, may be handy in use (Herva disease instead of lethal congenital contracture syndrome). Important synonyms, practical abbreviations and old names are mentioned for clarity, but every possible name has not been included. As regards them, *McKusick´s (Online) Mendelian Inheritance in Man* is referred to.

The most important clinical features are presented to such an extent as to give an impression and preliminary diagnostic data for the disease. The pictures drawn by my colleague Dr. Mari Markkanen-Leppänen also serve to give an impression and memory aid. As concerns diagnostic investigations and prenatal diagnosis, the Finnish physicians are especially privileged in regard to gene di-

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Table 1 The diseases of the Finnish Disease Heritage in order of their incidence in Finland

Name of disease	Clinical abbreviation*	Incidence in Finland	Patients known		Data known about the gene		
			in Finland	Elsewhere	Name	Locus	Character
Autosomal recessive							
Congenital nephrosis	CNF (NPHS1)	1:8,000	>300	<300	NPHS1	+	+
Infantile neuronal ceroid lipofuscinosis	*INCL* CLN1	1:14,000	>160	>200	CLN1 PPT1	+	+
Meckel syndrome		1:15,000	>100	Not very rare	MKS1 MES	+	–
Unverricht-Lundborg disease	*PME* PME-UL	1:17,000	~200	Not very rare	EPM1 CSTB	+	+
Aspartylglucosaminuria	*AGU*	1:18,000	>260	>30	AGA	+	+
Cartilage-hair hypoplasia	CHH	1:18,000	>170	>200	RMRP (CHH)	+	+
Spielmeyer-Sjögren disease	JNCL SS	1:19,000	~200	Not very rare	CLN3	+	+
Hydrolethalus syndrome		1:22,000	>80	~10		+	–
Diastrophic dysplasia	DD DTD	1:22,000	~200	>250	SLC26A2 (DTDST)	+	+
Autoimmune polyendocrinopathy — candidiasis — ectodermal dystrophy	*APECED* APS I	1:27,000	>90	~300	AIRE	+	+
Lethal congenital contracture syndrome (Herva)	LCCS	1:29,000	>40	Some	LCCS	+	–
Congenital chloride diarrhea	CCD? CLD?	1:33,000	>50	>200	DRA SLC26A3	+	+
Mulibrey nanism	MUL	1:37,000	>80	<20	TRIM37 (MUL)	+	+
Usher syndrome type 3	USH3	1:42,000	~100	Some	USH3	+	+
Salla disease		1:42,000	>100	>20	SLC17A5 (SIASD)	+	+
Cornea plana congenita	CPC CNA2	1:46,000	~90	>50	KERA	+	+
Congenital lactase deficiency	CLD	1:48,000	>40	<40	CLD?	+	–
Muscle-eye-brain disease	*MEB*	1:52,000	~30	>10	POMGnT1	+	+
Nonketotic hyperglycinemia	*NKH*	1:52,000	~50	~100	GCSP	+	+
Lethal arthrogryposis with anterior horn cell disease (Vuopala)	LAAHD	1:53,000?	~20	Some?		–	–
Jansky-Bielschowsky disease variant	$vLINCL_{Fin}$ CLN5 JB	1:59,000	>30	Some	CLN5	+	+
Hyperornithinemia with gyrate atrophy of choroid and retina	*HOGA* (GA)	1:63,000	>80	Not very rare	OAT	+	+
GRACILE syndrome (Fellman)		1:64,000?	>20	–	BCS1L	+	+
Selective malabsorption of vitamin B_{12}	SMB_{12} (MGA1)	1:68,000	~40	~150	CUBN MGA1	+	+
Nasu-Hakola disease	*PLO-SL*	1:71,000	>30	>120	TYROBP (DAP12)	+	+
Lysinuric protein intolerance	*LPI*	1:76,000	~50	>100	SLC7A7 (LPI)	+	+

Table 1 (continued)

Name of disease	Clinical abbreviation*	Incidence in Finland	Patients known		Data known about the gene		
			in Finland	Elsewhere	Name	Locus	Character
PEHO syndrome	*PEHO*	1:78,000	~30	~10		–	–
IOSCA syndrome	*IOSCA* (OHAHA)	1:90,000	>20	–	SCA8	+	–
Cohen syndrome		1:105,000	>30	>100	COH1 (CHS1)	+	–
Rapadilino syndrome		1:105,000	>10	Some?		–	–
Follicle stimulating hormone-resistant ovaries (Aittomäki)	*FSH-RO*	1:127,000	>20**	?	ODG1 FSHR	+	+
Northern epilepsy	CLN8	1:176,000	>20	–	EPMR CLN8	+	+
Autosomal dominant							
Meretoja disease	FAF	~1:6,000 (prevalence)	>400	9 kindreds	GSN	+	+
Tibial muscular dystrophy	TMD	3/year?	>300	6 kindreds	TTN	+	+
X-chromosomal							
Choroideremia		~2/year	>100	<400	CHM	+	+
Retinoschisis	RS	~1:17,000 (prevalence)	>300	Not very rare	XLRS1 (RS)	+	+

**Italicised* abbreviations are used as the practical name of the disease.
***Incidence figures include only the patients with a demonstrated gene mutation. In reality, the disease is much more common

agnosis; in general, diagnostic investigations that are useful in Finland are not necessarily suitable or reliable in other countries. For pathogenesis and molecular genetics, the biochemical and molecular genetic details are not presented here but can be found in the list of references. The same is true for the management. Of the historical aspects, the first descriptions of the disease in medical literature and in Finland are given. The Finnish researchers who have been active with their diseases recently are not mentioned, but the list of references will disclose them effectively. The sub-sections on epidemiology give data on the number of known patients in Finland and elsewhere. The map of Finland showing the birth places of patients' grandparents not only displays the geographical distribution of the genes of a particular disease, but it also visualises the different types of distributions dealt with in Part I (DOI s00439-002-0875-3). The naming of some Finnish experts gives the reader a possibility for solving problems that can be encountered with their individual patients. The experts can be contacted the easiest by e-mail. In case the e-mail address should fail — e.g. after some years — postal addresses of the institutions concerned given in the references may bring help. An expert on most of the gene tests is Dr. Irma Järvelä, HUCH (e-mail: irma.jarvela@hus.fi).

Heterozygous manifestations are not mentioned under a separate subtitle in the descriptions of individual diseases, because their practical significance today is mostly small (see Vogel 1984, Clin Genet 25:381–415). Three diseases, however, deserve a special mention. Autosomal dominant tibial muscular dystrophy (TMD) is, in fact, a heterozygous manifestation of the gene of a severe limb girdle dystrophy. In X-linked recessive choroideremia, the heterozygous females have fundus changes resembling retinitis pigmentosa. This can lead to a tragic misdiagnosis. In congenital nephrotic syndrome of the Finnish type, heterozygous mid-trimester fetuses may show very high, but later decreasing, concentrations of alpha-fetoprotein in the amniotic fluid. Without a control amniocentesis, the consequence could be the abortion of a healthy fetus.

In the nationwide clinical investigations of ten diseases, heterozygous affections have been sought but the findings have been incidental and/or insignificant. Details can be found in the following references given in connection with the respective diseases: AGU, Autio (1972); APECED, Ahonen (1985); CNF, Norio (1966); INCL, Santavuori, personal comm.; LPI, Norio et al. (1971); Meckel, Salonen and Norio (1984); NKH, von Wendt et al. (1981); PLO-SL, Hakola (1972); PME, Norio and Koskiniemi (1979); rapadilino, Kääriäinen et al. (1989). In addition, obligate heterozygotes have shown intermediate values of enzymes or metabolites, respectively, in AGU (Aula et al. 1974, 1976; Mononen and Aronson 1997), HOGA (Takki and Simell 1974; Valle and Simell 2001), NKH (von Wendt et al. 1979), and Salla disease (Aula and Gahl 2001). AGU heterozygotes have shown proneness to chronic arthritis (Arvio et al. 2002). A statement of having demonstrated no heterozygous affections was found in the

investigations of 12 diseases. In 11 diseases, no mention of heterozygous manifestations could be found.

Before the disease descriptions, a compendium of the diseases in the order of their incidences in Finland is presented in Table 1. The incidences are based on lists of patients received from the expert doctors for each particular disorder. The birth incidence figures are calculated from the number of patients born in the decade when the number was the greatest. Most often this fell on the period when a doctor had made his or her nationwide thesis study on the disease. In many earlier texts, even widely differing estimates of the disease incidences have been presented. The incidence figures in Table 1 are calculated in the same way for all the diseases and are thus comparable. Over-estimations can hardly be obtained in this manner.

AGU

Aspartylglucosaminuria
MIM 208400

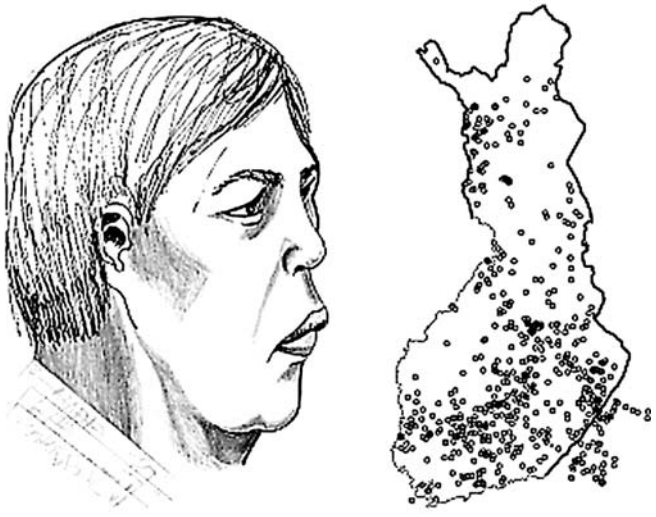

Fig. 1

AGU is a lysosomal storage disorder caused by defective activity of the enzyme aspartylglucosaminidase (glycoasparaginase) leading to progressive mental retardation.

Clinical features

After an uneventful infancy the symptoms manifest at preschool age. Proneness to respiratory infections occurs. Speech development and learning abilities slow down. Restlessness, irritability, clumsiness and floppiness may cause suspicion of the so-called MBD syndrome. Attending normal school will not succeed. Attacks of agitation and confusion appear. By adult age, mental retardation is severe and speech is defective. Epileptic seizures are common.

The facial features become coarse with age, showing i.a. thick lips and big tongue. Facial angiofibromas as in tuberous sclerosis appear at adult age. Tendency to fractures is due to osteoporosis. Survival over 50 years is seldom, bacterial infections being the usual cause of death.

The growth has characteristic features. The height increases rapidly during the first year of life. The pubertal height spurt begins early but ends soon, resulting in a considerably low adult height. Menarche appears early, at about 11 years.

Diagnostic investigations

In the urine, aspartylglucosamine can be found. Vacuoles are seen in lymphocytes and monocytes. The deficiency of the AGA enzyme can be verified in fibroblasts or lymphocytes. Gene diagnosis is accurate and easy in Finland.

Pathogenesis

The activity of glycoprotein degrading enzyme aspartylglucosamine (N-aspartyl-β-D-glucosaminidase = AGA) is deficient. Aspartylglucosamine and other abnormal degradation products are stored in the lysosomes. This damages especially the brain cells.

Molecular genetics

The gene *AGA* is in chromosome 4q32-q33. Amongst the Finnish AGU genes, in 98% the point mutation AGU Fin major (488G>C) causes a change of cysteine into serine (C163S) in the AGA enzyme. Mutation AGU Fin minor, a 2-bp deletion in the second exon of the AGA gene (199–200delGA), is found as compound heterozygote in seven families. In AGU patients of the neighbouring countries of Finland, Sweden and Norway, the mutation AGU Fin major is found. In other countries different mutations occur in the same locus.

Management

There is no curative treatment. Adult patients often need institutional care. Carbamazepine is the first choice for epileptic seizures. Attempts at gene therapy are ongoing, also by aid of mouse models. Already, the AGA enzyme functions successfully in cultivated cells of the AGU patient.

Prenatal diagnosis

Prenatal diagnosis is possible by showing defective activity of AGA in cultivated amniotic cells or, in Finland, by a gene test.

Historical aspects

AGU was detected in 1967 as a by-product in Jorma Palo's investigation on the incidence of PKU in Finland.

He found an unknown amino acid spot in some of the tested urine samples. In the same year, Jenner and Pollitt described the same finding in two mentally retarded British siblings.

Epidemiology

In Finland, more than 260 patients are known from almost all over the country. From elsewhere, over 30 patients have been published.

Finnish experts

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Molecular genetics

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APECED

Autoimmune polyendocrinopathy — candidiasis — ectodermal dystrophy
Autoimmune polyglandular disease type I
APS I
MIM 240300

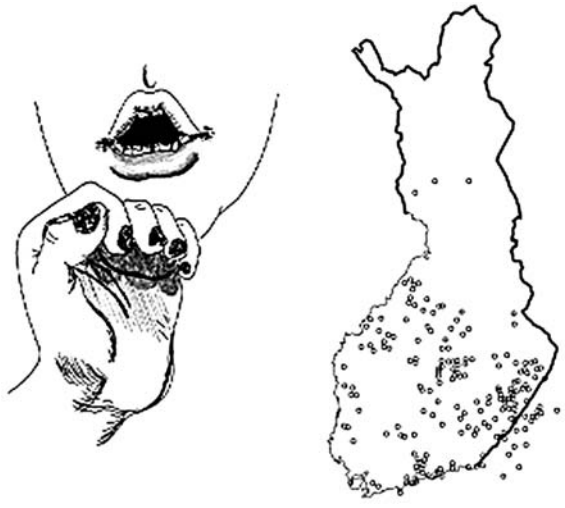

Fig. 2

APECED is a very polymorphic autoimmune disease, developing new manifestations over tens of years. Main findings are persistent candidial infections, chronic ectodermal alterations and many endocrinologic disturbances, one after another.

Clinical features

The long name of the disease describes the three groups of manifestations. The predilection for mucocutaneous candidial infections is the mouth. Cheilosis (rhagades at the corners of the mouth) is a typical finding. Other sites are nails, skin, esophagus, intestine, and genitals. Ectodermal lesions are enamel hypoplasia of the permanent teeth, punctate nail pits, corneal irritation and opacities, calcifications of eardrums, alopecia, and vitiligo. Different endocrinological defects appearing in childhood, and after that during subsequent decades, are hypoparathyroidism, adrenocortical insufficiency, atrophy of ovaries and testes, hypothyroidism, and diabetes mellitus. Also megaloblastic anemia, steatorrhea, and hepatitis may be autoimmune manifestations.

Diagnostic investigations

Laboratory investigations are needed, depending on the suspected manifestations. Autoimmune antibodies against different target organs may be detectable. A diagnostic gene test is in use in Finland, but its limitations must be taken into consideration as concerns uncommon mutations.

Pathogenesis

The immune defence mechanisms have gone astray, destroying the tissues of the organism. The details are unknown, as are the interconnections of ectodermal and autoimmune phenomena.

Molecular genetics

The gene, *AIRE* (autoimmune regulator), is in chromosome 21q22.3. In nearly 90% of the Finnish disease genes the mutation is 889C>T = R257X. Over 40 different mutations have been detected in the same locus in different populations. The predicted structure of the proline-rich AIRE protein includes two zinc finger motifs. It is a DNA-binding protein and probably participates in the regulation of transcription. A mouse model exists.

Management

No treatment is available to stop the autoimmune process. Supplementary hormone therapy and accurate follow-up are essential for the endocrine deficiencies. Alertness for new endocrinopathies is important, but it must not be allowed to invalidate the daily life of the patient too much. A permanent endocrinologist is of utmost importance to the patient. Support for the mental health of the patient should not be forgotten.

Candidial infections must be treated often with systemic fungicides like ketoconazole, because continuous candida infection may expose the oral mucosa to malig-

nant transformation. Effective local treatment is important for corneal symptoms. Cosmetic nail, skin and hair problems demand both sympathy and concrete means.

Prenatal diagnosis

A gene test gives possibilities for prenatal diagnosis in risk families, at least in Finland, although the diagnosis of the first affected sib often comes too late for that.

Historical aspects

The disease was described by Thorpe and Handley of the USA as early as 1929. Many names have been given to the disease. In Finland, Visakorpi and Gerber published the first description in 1963.

Epidemiology

In Finland, over 90 patients are known; elsewhere about 300. The incidence in Finland is about 1:25,000, but in Sardinia 1:15,000 and in an Iranian Jewish population greater than 1:10,000.

Finnish experts

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Cartilage-hair hypoplasia

Metaphyseal chondrodysplasia, type McKusick
CHH
MIM 250250

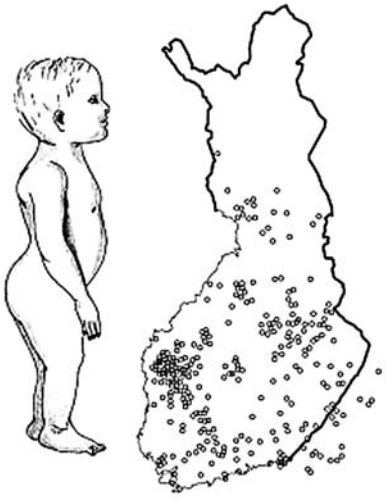

Fig. 3

Cartilage-hair hypoplasia is a short stature syndrome combined with sparse growth of hair and immunodeficiency.

Clinical features

Dwarfism is of intrauterine onset. The femora and humeri are particularly short. The fingers are short and hypermobile. The laxity of articular ligaments, limited extension at the elbows, bow legs, and accentuated lumbar lordosis are the usual findings. The structure and function of joints is nearly normal. The adult height is 100–140 cm.

The hair, beard, eyebrows, eyelashes, etc. are sparse and thin. In some patients, banal infections may be overwhelming, even life-threatening, due to immunodeficiency. Childhood anemia may be frequent and even severe. Colonic aganglionosis and impairment of spermatogenesis are often associated with CHH. Disposition for malignancies, particularly for lymphomas, is increased.

Diagnostic investigations

The metaphyses of the long bones of the extremities show splaying and irregular growth plates in X-ray during childhood. Laboratory investigations for detecting cell-mediated immunodeficiency are needed. A gene test is available for the majority of patients.

Pathogenesis

The pathogenetic mechanism is unknown. Some kind of disturbance in cell proliferation would explain many affections of the disease.

Molecular genetics

The gene (*RMRP*, formerly *CHH*) is in chromosome 9p13. Instead of a protein, it encodes an RNA molecule that combines with several proteins to form a complex functioning as an endoribonuclease. The most common mutation is 70A>G, found in 92% of the Finnish, 40% of other European and in all Amish patients investigated so far. About 40 other mutations have been found in the *RMRP* gene. The details of the disturbance caused by the mutated gene are not known.

Management

With the exception of short stature, other skeletal problems are few, at least if being overweight can be avoided and physical exercise is not forgotten. Possible orthopedic problems must be treated symptomatically. Growth cannot be enhanced by medication. Inconveniences due to shortness can be alleviated by structural amendments in the dwelling surroundings.

Severe hypoplastic anemia may require repeated blood transfusions. Precautions for a fulminant course of infections should be taken. Alleviation for varicella can be tried at the detection of the first vesicles by antiviral medication such as acyclovir. Vaccinations with live or attenuated viral vaccines should be avoided.

Prenatal diagnosis

Intrauterine ultrasound investigation of shortlimbedness is uncertain. A gene test gives the diagnosis in a majority of at risk families.

Historical aspects

Victor McKusick described CHH from the Amish community in the USA in 1964. Jaakko Perheentupa identified CHH as belonging to the Finnish Disease Heritage in 1972.

Epidemiology

In Finland over 170 patients are known; in the Amish community about as many. Some dozens of cases are known elsewhere.

Finnish experts

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Choroideremia

MIM 303100

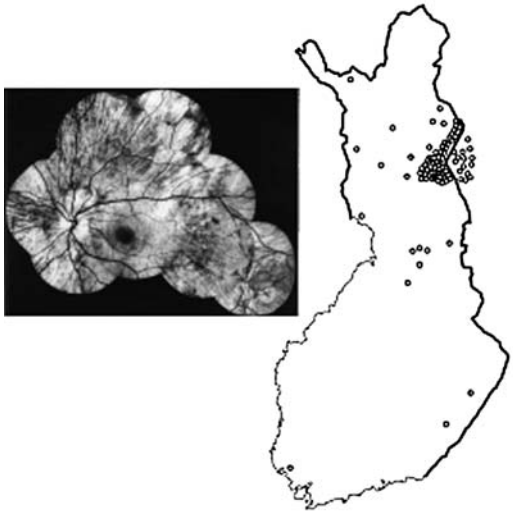

Fig. 4

Choroideremia is an *X-linked* dystrophy of ocular choroidea and retina, which leads to visual handicap at adult age.

Clinical features

The features of choroideremia resemble those of retinitis pigmentosa, with symptoms such as night blindness and narrowing of visual fields. Visual acuity decreases slowly. Macular visus is maintained for a long time; reading ability may be preserved beyond the age of normal retirement. The severity varies greatly, also intrafamilially.

Diagnostic investigations

The eye fundi show whitish, slowly increasing atrophy of the retinal pigment epithelium and choriocapillaris. It resembles that seen in *HOGA* , but is not sharply demarcated. ERG will be abolished. The pedigree is compatible with X-linked transmission.

Also carrier females are recognizable through slowly progressive pigmentary fundus changes resembling retinitis pigmentosa. They, however, cause no or only insignificant symptoms. It is a tragic mistake if the doctor, without knowing the exact diagnosis, frightens the carrier female with a proclamation of blindness.

Pathogenesis

The disease process is linked in a complicated way to the so-called rab escort protein (REP1), which regulates the transport of proteins. Many theories of the details have been proposed.

Molecular genetics

The gene, *CHM,* is in the X chromosome at q21.1. Dozens of point mutations and several deletions are known. The main mutation in Finland, splice mutation CHM*SAL (1639+2insT), has not been found elsewhere. Contrary to expectations, there are three different mutations in Northern Finland, and three different deletions have been found in three kindreds in Southern Finland.

Management

The degeneration process cannot be corrected nor delayed. The visual handicap can be aided by several rehabilitative procedures and auxiliary devices. The prognosis is often much better than could be predicted from the ocular fundi. Accurate genetic counselling is important.

Prenatal diagnosis

Prenatal diagnosis has been possible for a long time by a gene test, but its requirement and ethical principles are unclear. The carriers can be detected by the ophthalmoscopy.

Historical aspects

The first published description is that of Mauthner of Austria in 1872. In Finland, extensive investigations have

been done by Forsius and his collaborators since the 1960s. The first Finnish publication is by Takki in 1974.

Epidemiology

Choroideremia also often appears outside Finland. About 500 cases have been reported, of which one fourth is from northern Finland.

Finnish experts

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Cohen syndrome

MIM 216550

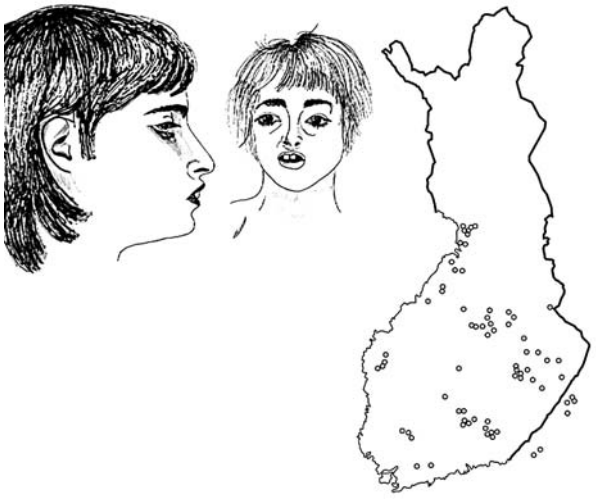

Fig. 5

Cohen syndrome is characterised by mental retardation, typical structural features, slowly progressive visual handicap, granulocytopenia, and cheerful disposition.

Clinical features

Psychomotor retardation is noticed during the first year of life. Muscular hypotonia and hypermobile joints are among the first symptoms. Microcephaly, motor clumsiness and normal or brisk tendon reflexes despite hypotonia are characteristic. The patients learn to walk at two to five years of age and to speak at different ages and in varying amounts. Many patients understand speech better than they can speak themselves. Mental retardation is not progressive. The psychical character is positive, cooperative and sunny. The lifespan may not be shortened.

Typical facial features appear at pre-school age, whereas facial diagnosis in infants is difficult. The patients have beautiful, high-arched or flame-shaped eyelids, long and thick eyelashes and eyebrows, thick hair and low hairline. The root of the nose is prominent. A short philtrum that is unable to cover the upper central incisors properly is a very typical sign.

The hands and feet, fingers and toes are narrow but short. The height proceeds along the lower limits of the normal curves. Contrary to some textbooks, truncal obesity is not a very typical finding. Genu valgum, pes planovalgus and thoracic kyphosis develop with age.

The main ophthalmologic findings are myopia of the refractive type and chorioretinal degeneration, which proceeds slowly and does not lead to total blindness. Cataracts appear early. Symptoms of retinitis pigmentosa become manifest usually at school age.

Diagnostic investigations

No laboratory finding is diagnostic. However, granulocytopenia is typical but intermittent. It does not harm the patients. Accurate ophthalmological investigations, including ERG, are essential, even if not very easy to do on the retarded patients. MRI of the brain often reveals an enlarged corpus callosum, a very rare finding in mentally retarded patients. Low voltage EEG is found frequently.

Pathogenesis

The pathogenesis of this pleiotropic syndrome is unknown. Whether the enlarged corpus callosum has something to do with the cheerful and social disposition is an interesting but unsolved question.

Molecular genetics

The gene (*COH1*, formerly *CHS1*) is mapped to chromosome 8q22-q23, but not characterised as yet. Concluded from the haplotypes, one main mutation and at least two others will be found in Finland.

Management

Because of their social character, these patients often manage at home and in supervised workplaces. Myopia must be corrected by glasses. Bright lighting is important because of night blindness. The patients benefit from speech therapy.

Prenatal diagnosis

For the time being, prenatal diagnosis may be possible only by aid of linkage analysis in some of the risk families.

Historical aspects

The syndrome was described by Michael Cohen Jr. and his collaborators in 1973. In Finland, similar patients were

studied and followed since the 1960s, but the first Finnish report by Norio et al. appeared only in 1984.

Epidemiology

In Finland, over 30 patients are known, the ancestry being mostly from the area of late settlement. The incidence is not greater than 1:100,000, but due to the probably normal survival the prevalence appears greater than that. From other parts of the world more than 100 patients have been described with this diagnosis, but heterogeneity among them certainly exists. Apart from Finland, Cohen syndrome seems to be particularly common in Israel. The haplotypes of Finnish and Israeli patients resemble each other slightly.

Finnish experts

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Congenital chloride diarrhea

CCD (CLD)
(Congenital alkalosis with diarrhea)
MIM 214700

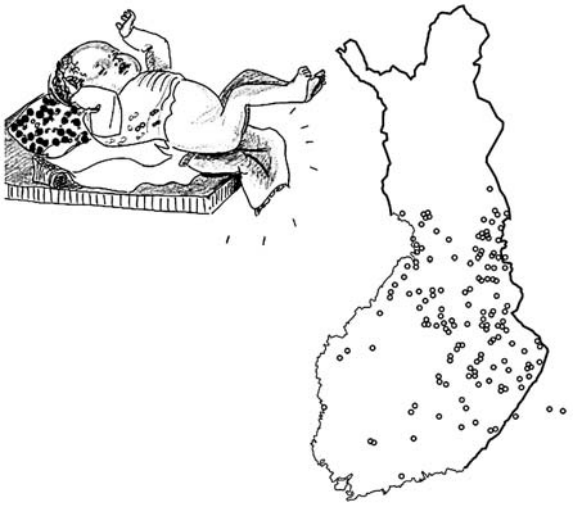

Fig. 6

Congenital chloride diarrhea is a prenatally manifesting, life-threatening watery diarrhea due to impaired absorption of chloride. After the correct diagnosis, treatment is easy.

Clinical features

The first and constant symptom is polyhydramnios during pregnancy. It is due to intrauterine watery diarrhea, which also washes away the meconium from the bowel. The AFP content of the amniotic fluid may be elevated.

The baby is delivered prematurely, shows excessive weight loss during the first days of life, symptoms of dehydration, and hyperbilirubinemia. The abdomen is protuberant, mimicking ileus. The baby wets the diapers incessantly. When looking for the cause for the excessive voiding it is noticed that the fluid is not urine but it comes from the anus.

If correct diagnosis is not achieved, the infants usually die of severe electrolyte disturbances during the first weeks of life.

Those few who survive fail to thrive and may develop renal and brain damage. After the correct diagnosis, in turn, the treatment is simple and the life of the "patient" is normal, although the stools are permanently slightly looser than normal.

Diagnostic investigations

The chloride content of the fluid coming from the intestine is over 90 mmol/l. In the blood investigations, early changes are hyponatremia, hypochloridemia, and acidosis. Later, the patients develop severe hypokalemic alkalosis associated with hypochloridemia. No chloride is secreted in the urine.

Pathogenesis

The absorption of chloride from the colon and ileum is disturbed because the exchange of intestinal chloride ion into bicarbonate ion of the blood is impaired. The excess of chloride in the intestine causes osmotic diarrhea, the excess of bicarbonate in the blood causes alkalosis. Severe disturbances of fluid balance develop through complicated regulation mechanisms. Over-production of renin and aldosterone causes alterations in renal microanatomy and function.

Molecular genetics

The gene (*CLD*, *DRA, SLC26A3*) regulating the anion transport in the intestine is in chromosome 7q31. All the investigated Finnish families have a GGT deletion in nucleotides 951–953, causing a deficiency of one valine molecule (V317del) in the SLC26A3 protein. Elsewhere, over 20 mutations are known in the same locus.

There is some confusion concerning the clinical and genetic abbreviations of this disease. The early clinical

abbreviation was CCD, which I prefer still. The disease and the gene were then named CLD (Cl = chloride), until the gene was noticed to be identical with *DRA* (down-regulated in adenoma) found earlier. Recently, the gene causing CCD was recognised to be a member of *SLC26* anion exchanger gene family and renamed *SLC26A3* (SLC = solute liquid carrier). Thus, it might now be appropriate to leave the abbreviation CLD for another Finnish disorder, congenital lactase deficiency.

Management

After diagnosing CCD, the neonatal fluid balance disturbances are treated conventionally. After that, treatment is a life-long peroral use of sodium chloride and potassium chloride and surplus of water. These supplementary doses must be adjusted so that the blood electrolyte values and pH remain within normal limits and chloride is secreted in the urine. The life-long substitution therapy is important also because interrupting it will lead to renal lesion, even to end stage renal failure. During acute infectious diseases, one must be prepared to avoid fluid balance disturbances. The transport defect proper of the intestine cannot be corrected.

Prenatal diagnosis

In Finland, prenatal diagnosis can be achieved by a gene test, but the need of it is questionable because the treatment of CCD is so easy. If a fetal ultrasound scan is done because of polyhydramnios, distended intestinal loops should lead the thoughts to the diagnosis of CCD immediately after birth.

Historical aspects

First descriptions of CCD were published by Gamble et al. (1945) and by Darrow, also in 1945. The first Finnish publication was by Perheentupa et al. in 1965.

Epidemiology

From Finland, over 50 patients are known. The majority of ancestors come from the late settlement area of the 1500s. From other parts of the world, more than a hundred solitary families are known. In addition, accumulations of CCD like the Finnish one have been reported from Poland (40 patients, main mutation 2025_2026insATC = I675–676 ins) and from Kuwait and Saudi Arabia (total of 50 patients, main mutation 559G>T = G187X).

Finnish experts

Clinical

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Molecular genetics

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Congenital lactase deficiency

CLD
MIM 223000

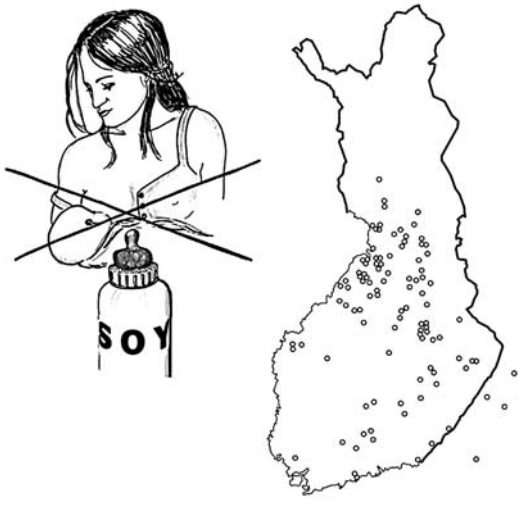

Fig. 7

Because the enzyme lactase does not function properly, the newborn baby suffers from severe diarrhea and failure to thrive, both of which are corrected by a lactose-free diet.

Clinical features

The newborn baby manifests with severe watery diarrhea, usually after the first meal. Despite that, the patient is vigorous, hungry, and does not vomit. The weight gain is nonexistent; the weight on admission is below the birth weight. During the lactose-free diet the symptoms disappear rapidly; the prognosis is excellent ().

Diagnostic investigations

The stools are acid and contain reducing sugars demonstrable by Clinitest. The diarrhea ceases by lactose-free

(milkless) diet. When the condition of the baby has improved, a peroral lactose loading test can be done. During the test, the blood glucose concentration rises less than 1 mmol/l and diarrhea reappears. A definite diagnosis is achieved by intestinal biopsy: the activity of lactase is minimal or lacking, whereas the structure of intestinal mucosa is normal. Untreated patients may show hypercalcemia of unknown cause and renal calcifications by ultrasound. During the treatment, hypercalcemia disappears but nephrocalcinosis may persist.

Pathogenesis

The function of lactase phlorizin hydrolase is lacking in the epithelial cells of the small intestine (cf. Molecular genetics).

The common lactose intolerance, where the function of lactase enzyme is diminished with age, must not be confused with CLD.

Molecular genetics

The gene locus of CLD is in chromosome 2q21. It is not identical with the lactase enzyme gene (which is already known), but is situated in its vicinity (2 Mb) in the same chromosome. Apparently the gene regulates the lactase gene, and thus the mutated gene makes the ordinary lactase gene inactive. The structure of the mutated gene is not known as yet. According to the haplotype investigations, a major gene is represented in more than 90% of the Finnish families.

Management

The acute disturbances of the fluid balance must be corrected in the conventional manner. The lactose-free diet makes the patients symptomless. At advanced age some patients may tolerate low lactose milk products in which the lactose is hydrolyzed.

Prenatal diagnosis

Prenatal diagnosis may succeed by linkage analysis in some risk families. Its need is questionable because of the benign character and easy management of the disease.

Historical aspects

The first description is by Holzel et al. in 1959, the first Finnish publication by Launiala et al. in 1966. I may have treated the first known Finnish patient in 1962.

Besides congenital lactase deficiency, the abbreviation CLD has been used for congenital chloride diarrhea. About the settling of this confusion, see the section preceding this one on congenital chloride diarrhea.

Epidemiology

Over 40 patients are known in Finland, which is more than from other countries altogether. The patient series of 16 cases published in 1983 by Savilahti et al. was overwhelmigly the largest published so far.

Finnish experts

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Molecular genetics

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Congenital nephrosis of the Finnish type

CNF, (NPHS1)
MIM 256300

Fig. 8

Congenital nephrosis of the Finnish type is a nephrosis which manifests in newborns and without renal transplantation is lethal.

Clinical features

As sign of the intrauterine origin of the disease, the placenta is always large, more than 25% of the birth weight. The baby is often born prematurely. Proteinuria is seen in the first specimen investigated. Edema manifests in the first days or weeks of life. The patient fails to thrive, abdomen is protuberant, hernias are common, infectious dis-

eases occur frequently. The patients die during the first or second year of life without learning to walk. The cause of death is not renal insufficiency but infection; often the immediate cause remains unknown.

The course and prognosis, however, have changed totally from the description above because of renal transplantation.

Diagnostic investigations

A large placenta and proteinuria in the first urinary specimen are important diagnostic findings. Serum protein changes are those typical of nephrosis. Serum creatinine is normal. Renal histopathology reveals tubular dilatations after the first three months of life. In electron microscopy, a fusion of foot processes of the glomerular epithelial cells, podocytes, is seen.

Pathogenesis

Protein leakage through the glomerular filter begins in utero, as soon as the urinary secretion begins. The damaged cell adhesion protein nephrin located at the slit diaphragm between glomerular podocytes has a central role in this leakage. The basement membrane is intact. The damage of the slit diaphragm also explains the electron microscopic finding of fusion of the foot processes of the podocytes. The lethal failure to thrive of the infants was caused by starvation due to a severe protein leakage into the urine.

Molecular genetics

The gene *NPHS1* is in chromosome 19q13.1. Mutation Fin major, a deletion of two nucleotides (121-122delCT), is found in 78% of the Finnish disease chromosomes. Mutation Fin minor, a point mutation (3325C>T = R1009X) is represented in 16% of the Finnish disease chromosomes. Dozens of other mutations have been found in other populations and some others also in Finland. The clinical features caused by different mutations and their combinations may cause different clinical courses. Although even most of them are severe, some milder CN cases as published from different populations may appear and even respond to conventional treatment. Thus, a nephrotic infant with a compound heterozygous genotype Fin major/2227C>T expressed nephrin and responded to enalapril and indomethacin therapy.

Management

The traditional treatment of nephrosis with corticosteroids and immunosuppressive drugs is without effect in CNF. Renal transplantation has changed the prognosis completely and allowed a normal life, though with continuous immunosuppressive treatment. Before transplantation the infants must gain weight up to 9 kg. This is possible by forced, partly parenteral nutrition, albumine substitution, peritoneal dialysis and often by removal of their own kidneys. Some patients homozygous for the Fin major gene develop nephrosis in the grafted kidney, apparently due to autoimmune reaction against nephrin.

Prenatal diagnosis

In risk families prenatal diagnosis has been possible for years by aid of a hugely (>10 SD) elevated AFP concentration in the amniotic fluid. The massive overproduction of this fetal protein into amniotic fluid is due to heavy fetal proteinuria. In Finland, AFP investigation from maternal serum has been used as a regional screening study.

Recently, it has been found that the CNF gene is able to cause a massive AFP concentration in the amniotic fluid also in heterozygotes. This fetal proteinuria vanishes during pregnancy and the baby is born healthy. Thus, elevated AFP concentration in the amniotic fluid must be controlled. A lower value in the second sample probably points to a healthy fetus.

Today, gene tests solve the problems of prenatal diagnosis in Finland. In other countries this matter is not so straightforward. Moreover, many cases of more or less congenital nephrosis may not present with elevated AFP, nor even with large placenta — but then the prognosis may also be better than in CNF.

Historical aspects

The role of the first report of CN has been given to the description by Gautier and Miville in 1942. The first Finnish article is by Hallman et al. in 1956. CNF is considered to be the prototype of Finnish disorders (see Part I, DOI s00439-002-0875-3), which has given rise to at least 14 thesis investigations, among others.

Epidemiology

More than 300 Finnish patients are known, from elsewhere less than that. The incidence in Finland is 1:10,000 at least. The bulk of ancestors come from the area of late settlement, but several ancestors even come from other parts of Finland. An accumulation of patients is known in Minnesota, USA, a region of active Finnish immigration.

Finnish experts

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Cornea plana congenita

CPC, CNA2
MIM 217300

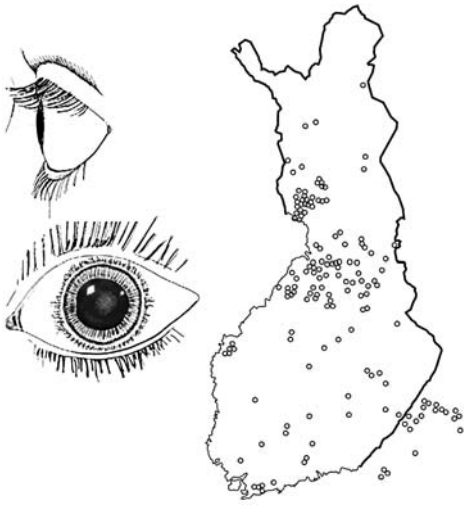

Fig. 9

Cornea plana congenita is an ocular disease causing moderate visual handicap.

Clinical features

The cornea is congenitally "flat", which means that its radius is longer and thus its curvature is slighter than normal. The cornea is also thin and its small refractive power appears as hyperopia. The central opacities of the cornea disturb the visual acuity and a peripheral arcus senilis develops early. The risk for closed angle glaucoma is increased. Systemic findings do not exist.

Diagnostic investigations

An accurate ophthalmologic investigation, including slit lamp inspection, discloses the diagnosis.

Pathogenesis

The detailed pathogenesis is not known. The structure of the gene mutation indicates that the cooperation of certain collagens with small protein-rich proteoglycans is disturbed.

Molecular genetics

The gene, *KERA*, is in chromosome 12q22. The Finnish mutation common to all the studied patients is a point mutation AAC>AGC at codon 247, causing an alteration, N247S, in a leucine-rich proteoglycan called keratocan. At least two other point mutations have been documented.

Management

Hyperopia must be corrected by glasses. At school, the patients usually manage in a normal class.

Prenatal diagnosis

Prenatal diagnosis is possible by a genetic test at least in Finland, but selective abortion may not be ethically justified.

Historical aspects

Rübel of Germany described the disease in 1912. In Finland, extensive investigations have been carried out by Henrik Forsius and his collaborators since the 1950s. His short congress report from 1957 is the first Finnish publication.

Epidemiology

In Finland, about 90 patients are known; from elsewhere considerably less have been published. The disease is concentrated in northern Finland.

Also a dominantly inherited form of CPC is known. Its gene is situated in the vicinity of the *KERA* gene but is not identical with it.

Finnish experts

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Diastrophic dysplasia

DD, DTD
MIM 222600

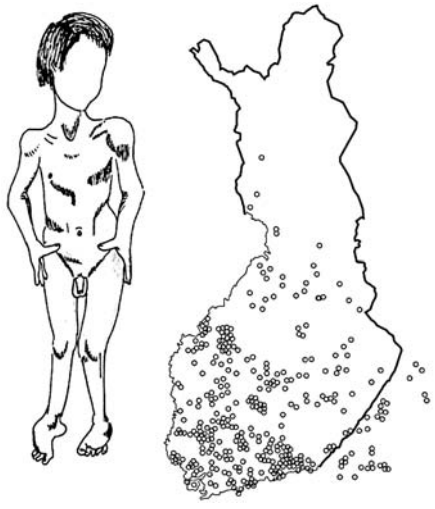

Fig. 10

Diastrophic dysplasia is a congenital short-limbed bone dysplasia, causing deformations and dysfunctions of the joints.

Clinical features

The limbs are found to be short at birth. Other signs visible in newborns are stiffness of the big joints, partial flexion limitations of the finger joints, club-foot-like malformation, cleft palate, and swollen ear lobes that later develop cartilagineous deformities. The often mentioned "hitchhiker's thumb" may not easily be visible in newborns.

With age, deformed knee and hip joints lead to motility restrictions, malpositions, and early arthrosis. Scolioses and kyphoses may be severe. Adult height is 100–160 cm. The severity of the deformations shows great variability, even intrafamilially.

Diagnostic investigations

Diagnosis by inspection is easy to those who know the disease. In X-ray, tubular bones are short and thick, knee and hip joints are broad and flattened, and metatarsal bones spread out forming a metatarsus adductus deformation.

Pathogenesis

The pathogenetic background has been revealed along with the characterisation of the gene. The transport of sulphate into cartilagineous cells is hampered, proteoglycans suffer from lack of sulphate and the growth of cartilage and bone is disturbed.

Molecular genetics

The gene is in chromosome 5q32-q33. It was originally named diastrophic dysplasia sulphate transporter, *DTDST*. In Finland, the main mutation $DTDST_{Fin}$ (c.–26+2T>C) was found in over 90% of the disease chromosomes. Also, two other mutations (262C>T = R279W and 1045–1047delGTT = V340del) are known in Finland, whereas in 4% the mutation is unknown. Elsewhere, about 20% of disease chromosomes have the $DTDST_{Fin}$ mutation, but dozens of other mutations are also known. Recently, it has been recognised that the *DTDST* gene belongs to an anion exchanger gene family called *SLC26*. Thus, the gene has been renamed *SLC26A2*.

Different mutations in the *SLC26A2* gene cause two more difficult skeletal diseases, atelosteogenesis type II and achondrogenesis type I B, and one less severe disorder, viz. multiple epiphyseal dysplasia.

Management

The quality of life of the diastrophic patients depends not so much on short-limbedness as on restricted mobility, deformations and early arthrosis of the joints. Almost all patients need orthopedic operations, including hip prostheses. Physiotherapy is important in order to maintain mobility and to prevent malpositions. Deformations of the upper cervical spine may be life-threatening if the neck is moved into abnormal positions, e.g., in general anaesthesia. The structure of cervical spine must be investigated preoperatively by X-ray.

Prenatal diagnosis

Shortness of the limbs may be seen by ultrasound by the 16th–18th week of pregnancy. At least in Finland, prenatal diagnosis can be achieved earlier and reliably by a gene test from the chorionic villi.

Historical aspects

The first published description of a DD patient is that by Arraga of Argentina in 1897 (see Lapunzina et al. 1998). Lamy and Maroteaux in 1960 separated DD as an entity of its own. In Finland, Perheentupa identified and introduced DD in 1972.

Epidemiology

In Finland, nearly 200 patients are known. DD is not very rare even elsewhere: at least 250 patients have been pub-

lished outside Finland. This is in concordance with the exceptional, southwestern distribution of DD ancestors in Finland. Apparently the gene was brought to Finland thousands of years ago by western immigrants (Part I, DOI s00439-002-0875-3).

Finnish experts

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FSH-RO

Follicle stimulating hormone-resistant ovaries
Hereditary hypergonadotrophic ovarian failure
Aittomäki disease
MIM 233300

Fig. 11

FSH-RO is a deficiency of the female sex hormones presenting with primary amenorrhea and sterility.

Clinical features

Female patients are symptomless until the appearance of primary amenorrhea and sterility. Secondary sexual characteristics are normal or subnormal. The ovaries are small and fibrotic.

(Homozygous men are mostly subfertile: the amount and quality of sperm cells may be subnormal and the testicles are small.)

Diagnostic investigations

The concentration of follicle stimulating hormone (FSH) is high, >40 IU/l, whereas the values of female sex hormones are low. Karyotype is normal XX.

Pathogenesis

The ovaries contain oocytes, but they do not mature despite the overproduction of FSH, because the FSH receptor in the ovarian follicles is defective. Because the follicles do not develop normally, their production of female hormones is not functioning.

Molecular genetics

The gene (*FSHR*) was mapped to chromosome 2p16-p21. It proved to be the already known gene of the FSH receptor, *ODG1*. The Finnish patients have the point mutation 566C>T, which changes alanine to valine in position 189 of the receptor protein. In one Finnish chromosome, a gene with the mutation 1255G>A produces a change A419T in the receptor protein. Apparently several mutations, even in several loci, may cause primary hypergonadotropic amenorrhea with the XX karyotype.

Management

As yet, no treatment is able to normalise the patient's own egg cells nor the production of sex hormones. Menstruation can be started and secondary sex characteristics improved by sex hormone supplementation. This is important also in order to prevent osteoporosis and coronary heart disease. Patients can even become pregnant by aid of ovum donation.

When there are problems with becoming pregnant in the families of the female FSH-RO patient's brothers, this diagnosis of these brothers can be verified or excluded. The fertilising ability of FSH-resistant men can be aided by means used in fertility therapy.

The patients may have considered the sterility problem so delicate that they have not discussed it, even with their siblings who possibly suffer from the same problem. The patients should be encouraged to deal with the problem openly and without shame.

Prenatal diagnosis

Because of the nature of the problem there may be no place for prenatal diagnosis, although a diagnostic gene test is available at least for some patients.

Historical aspects

Kristiina Aittomäki of Finland worked out the whole problem from patient series and genealogical investigations to the gene locus and structure of the mutation in the 1990s.

Epidemiology

Among the over 70 Finnish patients with primary hypergonadotropic amenorrhea and XX karyotype, one third has the Finnish *ODG1* mutation, one third does not have it, and one third has not been investigated as yet. For the time being, this mutation has not been found in other countries. In Finland, the ancestors are mainly from northern Finland.

Finnish expert

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GRACILE syndrome

(Growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, early death)
Fellman syndrome
Lethal lactic acidosis with hemosiderosis
MIM 603358

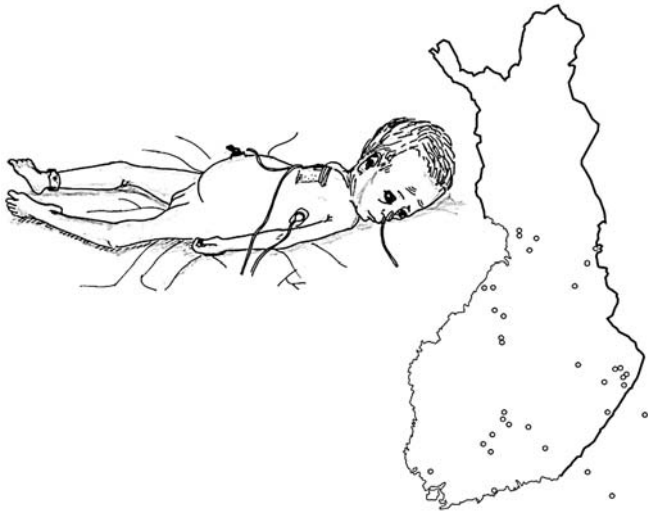

Fig. 12

This neonatally lethal disease causes lactic acidosis resistant to all treatment and accumulation of iron in the liver.

Clinical features

The patients are born extremely small for date. In the first day of life a severe lactic acidosis develops that usually cannot be corrected, even with huge amounts of bicarbonate. The facial expression seems "worried". No neurological or other specific symptoms are revealed. No weight gain appears. The cachectic and acidotic patients succumb at the age of some days or weeks.

Diagnostic investigations

In addition to a fully exceptional acid-base balance the patients show aminoaciduria. The investigations of iron metabolism give abnormal results: serum ferritine concentration is elevated ten-fold, transferrine is mostly saturated but its concentration is low, and free iron appears in the serum.

At autopsy, severe pathological changes with cholestasis are seen in the liver. Hemosiderin is stored in the hepatocytes and in Kupffer cells of sinusoids. Iron deposits can be seen also in the macrophages of the spleen and pulmonary alveoli. Interstitial fibrosis and exocrine atrophy of pancreas and calcifications of the renal medulla are usual findings.

Pathogenesis

How the lactic acidosis and disturbed iron metabolism are associated is not known yet.

Molecular genetics

The gene is in chromosome 2q33-q37. All Finnish patients are homozygous for a missense mutation 232A>G (S78G) in the *BCS1L* gene. The mitochondrial inner-membrane protein BCS1L is known as a chaperone necessary for the assembly of mitochondrial respiratory chain complex III. In the GRACILE syndrome, the mutation apparently disturbs some other function of BCS1L whereas complex III activity is within the normal range.

Management

At present, no treatment has been able to keep the patients alive. Attempts were made to diminish the iron load of the organism by apoferritine and repeated exchange transfusions. The values of iron metabolism shifted towards normal, but the patients died nevertheless.

Prenatal diagnosis

Prenatal diagnosis has been done in one Finnish risk family by linkage and haplotype analysis. Now the diagnosis is possible by gene test in Finland, whereas sequence analysis of the *BCS1L* gene offers a diagnostic option for non-Finnish families.

Historical aspects

The first patients astonished the doctors at the Children's Hospital, University of Helsinki in the 1960s. However, they escaped sufficient attention until Vineta Fellman and her collaborators began to penetrate this problem in the

1980s. The storage of iron was then noticed, and the disease was described as a novel entity in 1998.

Epidemiology

In Finland over 20 patients are known; in Sweden one family with Finnish ancestry. The roots of the Finnish families are mainly in the area of late settlement. In three British patients four other mutations and in four Turkish families also four mutations of the *BCS1L* gene have been found. The phenotypes of these patients differ considerably from the Finnish ones.

Finnish experts

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Herva disease

Lethal congenital contracture syndrome
LCCS
Multiple contracture syndrome, Finnish type
(Cf. Lethal arthrogryposis with anterior horn cell disease = *Vuopala disease*)
MIM 253310

Fig. 13

Due to a fetal deficiency of the anterior spinal cord, severe intrauterine contractures have developed in the stillborn patient.

Clinical features

The fetus grows slowly and moves poorly or not at all. Profuse hydrops develops in the first half of pregnancy. Severe contractures and malpositions of the big joints appear, usually flexion contractures in the elbows and extension in the knees. On the flexor side of the elbow, a skin fold, pterygium, is often formed. The muscles are almost nonexistent. The long bones and ribs are extremely thin and may be fractured in utero or at delivery. The facial features are abnormal with hypertelorism, low set ears, micrognathia, and flat nose. The lungs are hypoplastic. The umbilical cord is often short. The pregnancy ends in the stillbirth of a small-for-date fetus.

Diagnostic investigations

The sick fetus cannot be helped, but achieving the right diagnosis is essential for the future pregnancies of the family. Photos and autopsy are truly important. At autopsy, spinal cord and muscle samples must also be investigated.

Pathogenesis

The syndrome described above is called fetal akinesia deformation sequence or Pena-Shokeir phenotype. It is an outcome of the immobility of the fetus due to different causes. In LCCS, motor neuron cells in the spinal cord are lacking almost entirely and those that exist are calcified remnants. The whole anterior spinal cord is atrophic. The pathogenesis of the spinal damage and the mechanism of intrauterine death are not known.

Molecular genetics

The gene *LCCS* is situated in chromosome 9q34, at a locus different to that of the gene for spinal muscular atrophy (Werdnig-Hoffman disease). The structure of the gene is not known yet, but haplotype analysis speaks in favour of one Finnish major mutation.

Management

The disease cannot be treated nor prevented. Prenatal diagnosis is an important aid to the families.

Prenatal diagnosis

Ultrasound may reveal the disease as early as in the 14th week of pregnancy.

Historical aspects

The disease was first documented by Riitta Herva and coworkers of Oulu, northern Finland in 1985.

Epidemiology

In Finland, over 60 patients are known in Kainuu and northern Savo. In other countries some patients resembling LCCS have been published, but differential diagnosis outside Finland is difficult. In Finland a similar, slightly less severe disease exists, with possible survival of some days or weeks; this is called Vuopala disease or LAAHD.

Finnish expert

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HOGA

Hyperornithinemia with gyrate atrophy of the choroid and retina
GA
MIM 258870

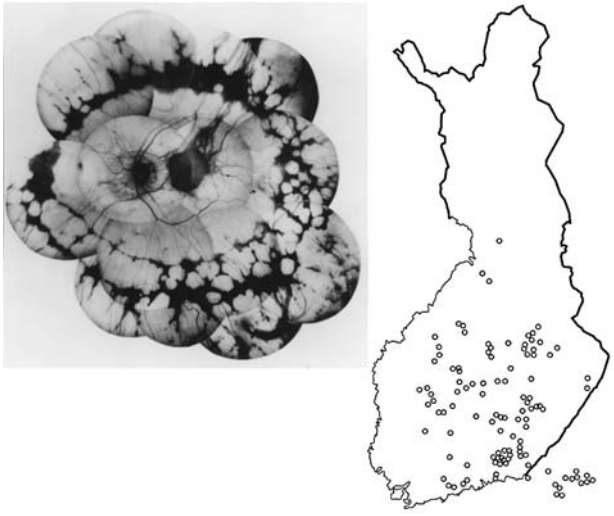

Fig. 14

HOGA is an ophthalmological disease with a disturbance of the amino acid metabolism, leading gradually to blindness.

Clinical features

Myopia and symptoms resembling retinitis pigmentosa often begin before ten years of age and progress into blindness by 40 years of age. Cataract may develop before 20 years of age. Mild muscular weakness can occur.

Diagnostic investigations

In ophthalmoscopy, retinochoroidal atrophy appears as whitish, sharp-edged patches, beginning in the periphery and spreading and confluing over the whole eye fundus. ERG abolishes early. The ornithine concentration in plasma is increased (10–20× normal values) and ornithine is also secreted abundantly in the urine. Enzyme and gene diagnosis are also possible, but because of the pathognomonic eye finding and hyperornithinemia they are seldom needed in practice.

Pathogenesis

The activity of the enzyme ornithine aminotransferase is almost totally lacking. Because of failure of the degradation of ornithine its concentration in tissues, blood and urine is increased. How the enzyme defect affects the eye is not known. In the muscle biopsy, atrophy of type 2 muscle cells and tubular aggregates in electron microscopy are seen.

Molecular genetics

The gene *OAT* is situated in chromosome 10q26. Its structure and about 80 different mutations are known. Among the Finnish patients, 90% have the same mutation 1205T>C = L402P not found in other countries. The remaining 10% carry mutation R180T or some unknown mutation. The mode of function of the mutated gene is not known.

Management

Different treatments affecting the ornithine metabolism have been tried. Results as to vision have been scanty, but biochemical abnormalities tend to diminish. In transgenic mice some prevention of eye fundus alterations has been achieved. Muscular symptoms can be removed with creatine.

Preliminary data suggest that arginine-deficient diet normalises plasma ornithine concentration and may prevent the progression of the fundus changes, at least when started early in life. Thus, low-arginine diet is recommended for the patients, although its maintenance is not easy.

Early cataract operation, often in the third decade of life, improves the vision considerably.

Prenatal diagnosis

Prenatal diagnosis is possible with enzyme determination and, at least in Finland, by a gene test. However, the family size is usually final, as the diagnosis of first affected child is reached. The ethical principles of prenatal diagnosis in diseases causing blindness in adulthood have not been established as yet.

Historical aspects

The ophthalmological findings of the disease have been known since the 1800s (Jacobsohn 1888; Cutler 1895). The

association of hyperornithinemia was found by Simell and Takki of Finland in 1973.

Epidemiology

In Finland, over 80 patients are known, most of them descending from the late settlement area. The disease is not very uncommon elsewhere, either.

Finnish experts

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Hydrolethalus syndrome

MIM 236680

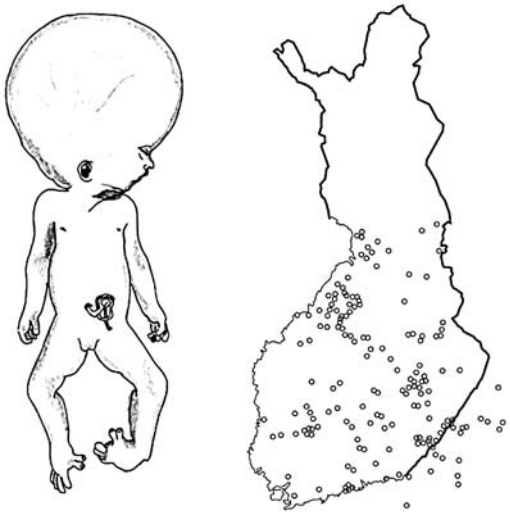

Fig. 15

Hydrolethalus syndrome is a combination of several severe congenital malformations leading to perinatal death.

Clinical features

The pregnancy is complicated by polyhydramnios. The baby is stillborn or dies in the first day of life. The most prominent abnormality is a huge hydrocephaly. Other findings are listed in the Diagnostic investigations.

The syndrome is usually revealed in the intrauterine ultrasound scan due to the atypical hydrocephaly. In such case most families choose an abortion, and that is why only a few full-term newborns are currently born.

Diagnostic investigations

Autopsy with accurate photos is of utmost importance for the genetic counselling. The lateral brain ventricles are wide open, and the remnants of the brain lacking midline structures are surrounded by cerebral fluid. The foramen occipitale magnum is not roundish but keyhole shaped. The eyes are deep-set and small. The nose is small or bifid, the chin is small or nonexistent, cleft lip and/or palate may occur. The tongue, larynx, trachea and bronchi may be deformed. The lobulation of the lungs is abnormal. Heart anomaly is often of canalis atrioventricularis communis type. The abdominal organs are usually normal and there is no cystic liver nor kidneys in contrast to the Meckel syndrome. The genitals may show slight abnormalities such as a double uterus, but there is no confusion about the sex. Polydactyly (postaxial in fingers, preaxial in toes) and club-foot-like deformity are common.

As is usual in syndromes, all the described abnormalities may not appear in every patient.

Karyotype analysis is important, because especially trisomy 13 may resemble the hydrolethalus syndrome.

Pathogenesis

Nothing is known about the pathogenesis of this pleiotropic syndrome. However, it has many features in common with midline field defects.

Molecular genetics

The gene is situated in chromosome 11q23-q25. Its structure is not known as yet. Judging by the haplotype in common, all the Finnish patients have the same mutation.

Management

Achieving the right diagnosis is the best aid for the future children of the family.

Prenatal diagnosis

Prenatal diagnosis may succeed in risk families, even in the 12th week of pregnancy, by ultrasound scan. Abnormal structure of the brain is noted at the 18th week at the latest, although the overgrowth of the skull may not become visible before the 20th week.

Historical aspects

The syndrome was separated from the Meckel syndrome as late as in 1981 by Salonen et al. in Finland. The name

of the syndrome was put together from its three most prominent features: (poly)hydramnios, hydrocephaly, and lethality.

Epidemiology

In Finland over 80 patients are known, most with the ancestry from the late settlement area. From other parts of the world about ten cases have been reported with this diagnosis, but most of them show atypical features. This may mean that the disease is really rare elsewhere, especially as it has been described frequently and well in the literature.

Finnish expert

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INCL

Infantile neuronal ceroid lipofuscinosis
Santavuori-Haltia disease
CLN1
MIM 256730

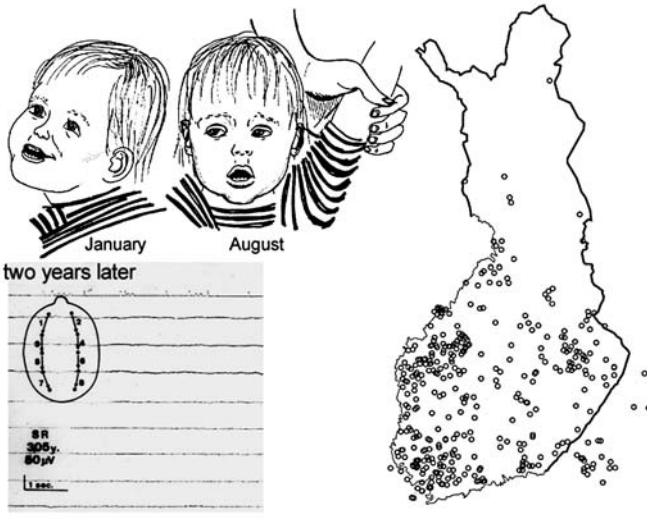

Fig. 16

See also *Neuronal ceroid lipofuscinoses*

INCL manifests itself soon after the first year of life and rapidly leads to an extraordinarily profound mental and motor retardation.

Clinical features

The early development is normal. Around its first birthday the infant gradually begins to lose the gained psychomotor skills. The rapid deterioration is accompanied by hyperexcitability, crying, sleeping disturbances, myoclonic jerks, and knitting hand movements. In the eye fundi, signs of progressing atrophy are seen. Microcephaly is an early finding. Blindness and spasticity belong to the end state. The average survival is ten years.

Diagnostic investigations

EEG shows an exceptional reaction to opening and closing of the eyes, loss of sleep spindles and isoelectricity by three years of age. Also ERG, VEP and SEP become extinguished. MRI of the brain shows hypointense signals in the thalami and hyperintense signals in the periventricular white matter, already present by 7–8 months of age, viz. before the appearance of the clinical symptoms. SPECT shows hypoperfusion especially in the cerebrum and cerebellum.

Electron microscopic investigation from rectal mucosal biopsy shows granular osmiophilic deposits (GROD) in the cytosomes. The autopsy shows extraordinary atrophy of the brain: neurons, axons and myelin sheats have disappeared, whereas astrocytic glial tissue is left with fluorescent lipopigment deposits in the brain and other organs.

Pathogenesis

The activity of the lysosomal enzyme palmitoyl-protein thioesterase (PPT) is missing. Details of the destruction of the brain cells are not known. The abnormal deposit material consists mainly of lysosomal sphingolipid activator proteins called saposins A and D.

Molecular genetics

The gene (*CLN1* or *PPT1*) is in chromosome 1p32. Of the Finnish patients 98% has mutation 364A>T changing arginine to tryptophan in the PPT enzyme, position 122. Over 30 other mutations are known elsewhere.

Management

Curative treatment does not exist, but hopes are raised by the advancement of the molecular genetic investigations. Trials with bone marrow transplantation with normally functioning PPT in the monocytes may have delayed the progression of the disease.

The patients need active physiotherapy, alleviation of pain and other symptomatic therapy.

Prenatal diagnosis

In no disease is prenatal diagnosis needed more urgently than in INCL. This has been possible for a long time through GROD alterations in the chorionic villus cells in the first trimester of the pregnancy. In Finland, gene test is the primary choice, whereas PPT enzyme assay is suitable for all patients irrespective of the mutation.

Historical aspects

The disease was described the first time by Hagberg et al. of Sweden in 1968. The first report from Finland was pub-

lished in 1973 by Santavuori, Haltia, Rapola and Raitta. If in the past the diagnosis of Tay-Sachs disease (which is extremely rare in Finland) had been set in Finland, the correct diagnosis would probably have been INCL.

Epidemiology

In Finland over 160 patients are known, elsewhere more than 200. The ancestors have three accumulation regions, two in the area of late settlement and one, exceptionally, in southwestern Finland.

Finnish experts

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IOSCA syndrome

Infantile onset spinocerebellar ataxia
Former name OHAHA syndrome = ophthalmoplegia-hypoacusis-ataxia-hypotonia-athetosis
MIM 271245

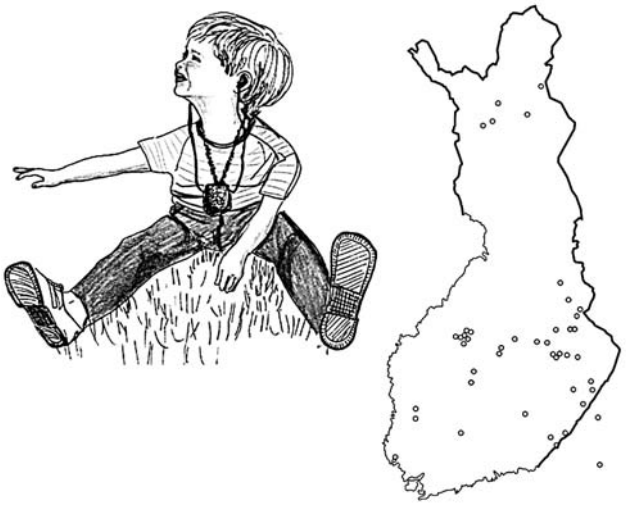

Fig. 17

IOSCA syndrome is a multisymptomatic neurological disease with infantile onset and severe, progressive handicap.

Clinical features

The neonatal period and development of the first year of life are normal. Soon after that, clumsiness, disturbances of gait, hypotonia, ataxia and athetosis appear. Tendon reflexes become abolished. Deterioration of hearing and ophthalmoplegia begin by school age. Variations of vigilance appear. By puberty, symptoms from peripheral nerves develop: tactile, proprioceptive and kinesthetic sensations become impaired and Babinski's sign becomes positive as a manifestation of damage of long corticospinal tracts. Optic atrophy develops. Injury of autonomous nervous system presents as sweating and functional disturbances of the bowel and urinary bladder. The pubertal development of girls is deficient, showing amenorrhea and underdevelopment of secondary sex characteristics.

New symptoms often appear in association with common infectious diseases. Young adults are wheelchair bound. They also may get severe epileptic crises with abdominal pains and vomiting. These attacks can be life-threatening. The oldest Finnish patients are in their forties.

Diagnostic investigations

No investigations are pathognomonic. Neurological tests may reveal a slowing of conduction velocity of the sensory nerves and abnormal SEP. With age cerebellar and brain stem atrophy develop.

Pathogenesis

The pathogenesis is unknown. Although the clinical features resemble those of mitochondrial diseases, no investigations are in favour of such etiology so far.

Molecular genetics

The gene *SCA8* is situated in chromosome 10q24. It is not characterised as yet, but haplotype analysis reveals that all Finnish patients have one and the same mutation.

Management

There is no cure. The right diagnosis helps to direct symptomatic treatment and rehabilitation properly. These patients with hearing deficit and athetosis may be misdiagnosed as mentally retarded.

Prenatal diagnosis

Prenatal diagnosis may be possible in Finland by linkage analysis.

Historical aspects

The disease was first described in Finland by Kallio and Jauhiainen in 1985 as OHAHA syndrome (see former name above). As the patients grew older, the cerebellar and sensory symptoms became apparent. The disease was renamed as IOSCA in order to point out that it is a clearly defined entity in the entangled group of spinocerebellar ataxias.

Epidemiology

In Finland over 20 patients are known, most of them from eastern Finland. The disease is not described from other countries.

Finnish expert

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Jansky-Bielschowsky disease, Finnish variant

Variant late infantile neuronal ceroid lipofuscinosis
JB, vLINCL$_{Fin,}$ CLN5
MIM 256731

Fig. 18

See also *Neuronal ceroid lipofuscinoses*

This disease of the central nervous system begins at preschool age and leads to blindness and profound psychomotor retardation.

Clinical features

The development in the first few years of life is normal. At the age of 4–7 years, clumsiness, visuomotor problems and mild mental retardation appear. The first misdiagnosis at that age may be MBD syndrome. At school age, the mentioned symptoms become worse, and epileptic seizures, myoclonic jerks, ataxic gait, and difficulties in speech appear. Problems in the activities of daily living develop. Eye fundi show signs of atrophy of the retina and optic nerves. All patients become blind by ten years of age. They lose the ability to speak and move, become spastic and deeply retarded. The life expectancy is 20 (14–40) years.

The classical LINCL differs from the Finnish variant by more rapid progression: beginning at 2–4 years, continuation at 5–6 years, death at 10–20 years.

Diagnostic investigations

From imaging investigations of the brain, CT is useless, as in all NCL disorders. In MRI, hypointense signals are seen in the thalamic region, hyperintense signals in the white matter, and very early appearing atrophy in the cerebellum. SPECT shows cerebellar hypoperfusion. In EEG, basal activity is disturbed and low-frequency flash causes occipital spikes. Typical neurophysiological findings of giant flash-VEP and SEP appear at 7–9 years of age. ERG becomes isoelectric by seven years. Thus, in contrast to the early appearing cerebellar atrophy, most of the electrophysiological investigations do not reveal the disease until several years after its beginning.

In the chorionic villi, the rectal mucosal biopsy, and in the brain specimen at autopsy, s.c. curvilinear bodies and fingerprint profiles are seen in the cytosomes. Vacuoles in the leukocytes, such as in Spielmeyer-Sjögren disease, are not seen. In classical LINCL curvilinear bodies, but no fingerprint patterns, are found. The gene test is an early, easy, and reliable diagnostic tool in Finland.

Pathogenesis

The basic mechanism may be associated with the defective lysosomal trafficking.

Molecular genetics

The gene, *CLN5*, is in chromosome 13q22. It has been characterised. In Finland, all the families except one have mutation 2467delAT = Y392X. The remaining family has mutation 1517G>A = W75X.

Management

Curative treatment does not exist. Symptomatic treatment and rehabilitation are important, not least in order to offer the patient a good quality of life for as long as possible.

Prenatal diagnosis

Prenatal diagnosis can be done by electron microscopy from chorionic villi in the 14th–15th week of pregnancy. Gene diagnosis is safer and can be done earlier in Finland.

Historical aspects

The first publication was from Finland, by Santavuori et al. in 1982.

Epidemiology

From Finland over 30 patients are known. All ancestors come from a small area in western Finland, where the incidence is 1:1,500 and carrier frequency according to gene tests 1:25. The Finnish variant is known in one Dutch and one Swedish family. Other variants of LINCL have been described outside Finland in about 100 patients.

Finnish experts

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Lysinuric protein intolerance

LPI
MIM 222700

Fig. 19

In this metabolic disorder tolerance for proteins is poor, but the disease can be treated and tolerated reasonably well.

Clinical features

The infants tolerate mother's milk well. The shift to formulae containing bigger amounts of proteins brings on vague intolerance symptoms: poor appetite, failure to thrive, vomiting, diarrhea. If protein feeding continues, the symptoms become worse. Gain of weight and height is poor, muscles are thin, fractures appear easily due to osteoporosis; proneness to infections and hepato- and splenomegalia are found. Meals rich in protein may cause ammonium intoxication, manifesting itself as comatous central nervous symptoms, and even as mild mental retardation. On the other hand, the patients develop an aversion to protein, which protects them against worsening of the symptoms, if they are not forced to eat protein-rich meals.

Recently it has been noticed that some adult patients develop odd pulmonary complications: acute or chronic respiratory insufficiency, pulmonary fibrosis, proteinosis or hemorrhages. Also renal damage simulating glomerulonephritis may appear and sometimes lead to renal insufficiency.

Diagnostic investigations

The urinary excretion of dibasic amino acids lysine, arginine and ornithine is increased and their concentration in the plasma is diminished. As accessory findings, anemia, leukopenia, thrombocytopenia and increased serum concentrations of lactate dehydrogenase and ferritine may appear. A reliable diagnosis can be achieved in Finland by a gene test.

Pathogenesis

The basic disturbance is in the transportation of dibasic amino acids through the basolateral membrane of intestinal epithelial cells. In renal tubuli the reabsorption of these amino acids is also deficient. Thus, the organism suffers from the deficiency of lysine, arginine, and ornithine. The lack of ornithine disturbs the function of the urea cycle, which should metabolize ammonium, toxic for the organism, to harmless urea. The lack of lysine probably causes growth retardation.

Molecular genetics

The gene, *LPI* or *SLC7A7*, is in chromosome 14q11.2. It encodes a protein called y+LAT-1 needed for the transporting of dibasic amino acids. All the Finnish patients studied have had the splice site mutation LPI_{Fin} = 1181–2A>T. This has not been found in other populations, where more than ten other mutations in the same locus have been detected.

Management

Peroral administration of neutral amino acid citrulline supports the function of the urea cycle. Then, ammonium becomes degraded, ornithine concentration in plasma rises and symptoms are alleviated. Even so, a diet moderately low in

protein is needed. Treated in this way, the patients remain symptomless, at least if pulmonary or renal complications do not appear later. Psychic development is normal, although hyperammonemia may cause difficulties in mathematics and other kind of abstract thinking for some patients.

Prenatal diagnosis

Prenatal diagnosis, easily done in Finland by a gene test, is hardly needed because of easy treatment and good prognosis. Whether the threat of pulmonary and renal complications alters this consideration, remains to be seen.

Historical aspects

The first description was given by Perheentupa and Visakorpi of Finland in 1965. In the beginning, the name of the disorder was familial protein intolerance with deficient transport of basic amino acids.

Epidemiology

In Finland about 50 patients are known, elsewhere over 100. The chain of Finnish ancestors reaches from southern Savo through eastern Finland to Lapland.

Finnish expert

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Meckel syndrome

Former names: Gruber syndrome; Dysencephalia splanchnocystica
MIM 249000

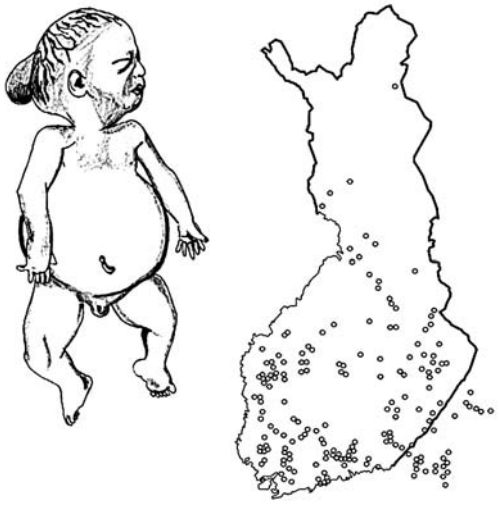

Fig. 20

This perinatally lethal malformation syndrome comprises a triad of neural tube defect, cystic and dysplastic liver and kidneys, and polydactyly.

Clinical features

Typical components of the neural tube defect are microcephalus and encephalocele, whereas hydrocephaly is rare (cf. *Hydrolethalus syndrome*). Polydactyly is postaxial. Kidneys and liver are dysplastic, cystic and so large that they may make a vaginal delivery impossible. Among other possible malformations are cleft lip and palate, congenital heart defects, ambiguous genitalia, and club feet. The placenta may be large. The patients are stillborn or survive for some hours.

Today, at least in Finland, very few patients are born after a full-term pregnancy because the malformation is verified in the second trimester ultrasound scan screening and most families choose an abortion.

From other countries, patients claimed to have Meckel syndrome have been reported with more or less different manifestations and longer survival. The problems of heterogeneity cannot be solved before gene diagnosis is available.

Diagnostic investigations

An accurate description of the malformations, photos, and autopsy are important for the correct diagnosis. Contrary to polycystic diseases of the kidney, normal nephrons are lacking almost totally (multicystic dysplasia). In the liver, microscopical fibrosis, in the fetus ductal plate malformation is always seen. Chromosome anomalies should be exluded.

Pathogenesis

The pathway from the mutated gene to the phenotype is not known.

Molecular genetics

Most of the Finnish patients are homozygous for the gene *MKS1* in the chromosome 17q22-q23. It is not characterised as yet. According to haplotypes, about 75% of the Finnish patients have one and the same mutation and possibly five other mutations exist. In other populations, the Meckel locus is not always the same. Another known locus *MKS2* is at 11q13 in patients (fetuses) from Northern Africa and the Middle East. A third locus (*MKS3*) is reported recently at 8q24 in Indian and Pakistani populations.

Management

The patients cannot be helped. The delivery must happen without endangering the mother. It is imperative to distinguish Meckel syndrome from other, incidental malformation complexes because of the recessive recurrence risk and possibility for prenatal diagnosis.

Prenatal diagnosis

In case of an open neural tube defect, AFP concentration in the amniotic fluid may be increased. In an accurate ultrasound scan, the cranial malformations and even enlargement of the kidneys may be distinguishable already in the 12th week of pregnancy. Later, the amount of amniotic fluid decreases and may totally disappear by the 18th week. This makes diagnosis by ultrasound difficult.

Historical aspects

Meckel described "his" syndrome as early as in 1822. In Finland, the first publication was by Aula et al. in 1977.

Epidemiology

In Finland, more than 100 patients are known, and incidence is about 1:15,000. Exceptionally, the map of ancestors is congruent with the density of population, thus being densest in western Finland). The disease is not very rare elsewhere either: Beduins in Kuwait, Hindues in Gujarat, Tatars, and Belgians show greater incidence figures than the Finns. There has been a discussion whether or not Meckel syndrome should at all be included in the Finnish Disease Heritage. On the other hand, in many Meckel cases outside Finland, the Finnish gene locus is excluded. Thus, the Finns may have not only a mutation of their own but even their own gene locus.

Finnish expert

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Meretoja disease

Corneal lattice dystrophy — amyloidosis
Gelsolin-related amyloidosis
Familial amyloidosis, Finnish type (FAF)
Familial amyloidotic polyneuropathy, type IV
Amyloidosis V (so numbered by OMIM)
MIM 105120

Fig. 21

This *autosomal dominant* disease with a confusing multitude of different names is an amyloidosis characterised by corneal lattice dystrophy in adult age.

Clinical features

The patients are symptomless until the third, often the fourth decade of life. Then a corneal lattice dystrophy appears with symptoms of irritation and, often, dysesthesia. Visual acuity decreases only slowly. Glaucoma is common. From the fifth decade of life onwards other signs of amyloid storage appear: cranial nerve palsies, symptoms from peripheral nerves, and renal damage. "Hanging" facial skin is the most typical finding. Skin elsewhere can be brittle and atrophic. Tendency to bruising or postoperative bleeding and sleep apnea are recent findings. The lifespan is nearly normal.

Diagnostic investigations

The ophthalmological findings can be verified by biomicroscopic investigation of the cornea. ENMG may show signs of cranial and peripheral neuropathy. A histopathological demonstration of amyloidosis is seldom needed. In Finland, a gene test is the best method, which also makes predictive diagnosis possible.

Pathogenesis

The structure of the actin-modulating protein gelsoline (gel>sol) is abnormal. Its altered degradation produces amyloid, which accumulates in certain tissues. The abnormality of the gelsolin may also cause disturbances independent of amyloid such as deficient plasticity of the thrombocytes.

Molecular genetics

The gelsoline gene (*GSN*) is in chromosome 9q34. The Finnish point mutation 654G>A, common to all Finnish patients, causes a change of aspartic acid to asparagine in the gelsoline protein, position 187 (D187N). Another mutation (654G>T = D187Y) in the same locus and position has been found in a Danish and a Czech family.

Management

Corneal symptoms are treated by moisturing drops and ointments. Symptomatic treatment of corneal inflammations must be aggressive enough. Corneal transplantation is needed only exceptionally. Hanging facial skin is treated by plastic surgery. Carpal tunnel syndrome is not infrequent and may need operative treatment. The development of amyloid cannot be delayed.

Prenatal diagnosis

Prenatal diagnosis is possible by a gene test, but its need and ethical guidelines are not established.

Historical aspects

The disease was described by the Finnish ophthalmologist Jouko Meretoja in 1969.

Epidemiology

In Finland over 400 patients are known. The affected grandparents of today's patients come from two areas, which have historical population connections. Most probably this extremely rare disorder has originated in Finland from one point mutation several centuries ago. Very few patients have been described outside Finland. The Finnish mutation has been found in one kindred from Holland and Great Britain, five in USA and four in Japan.

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Mulibrey nanism

MUL
MIM 253250

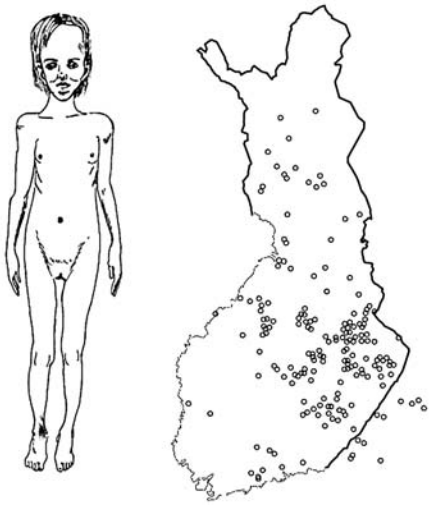

Fig. 22

Mulibrey nanism is a growth disturbance disease associated with a singular combination of abnormalities from different organs.

Clinical features

Growth failure starts prenatally. The proportion between trunk and extremities is normal. Adult height is 130–150 cm.

In infancy, feeding difficulties are common. Triangular face, high and broad forehead, thin extremities, gracile and weak muscles and high-pitched voice are characteristic. Naevi flammei appear in the ankles or soles. Liver is enlarged due to cardial congestion. Myocardial insufficiency may endanger life in infancy. More characteristic still is fibrotic thickening of the pericardium, which hampers the contractions of the heart. Fibrous dysplasia of tibiae and hypogonadism are common findings. Mental retardation does not belong to the disease, but psychosocial deprivation is common as in many chronic abnormalities.

Diagnostic investigations

No diagnostic laboratory investigation exists. The skull is dolichocephalic, sella turcica narrow and J-shaped. The cerebral ventricles are often wide. In eye fundi, yellowish spots are typical. Pertinent cardiological investigations are important. Endocrinological studies may be needed.

Pathogenesis

How one gene brings about these pleiotropic manifestations, is totally open.

Molecular genetics

The gene (*TRIM37,* formerly *MUL*) is in chromosome 17q22-q23, in a region overlapping with the Meckel syndrome gene. It encodes the TRIM37 protein, which belongs to the group of RING-B-box-coiled-coil (!) family of zinc finger proteins and is located in the peroxisomes. The detailed function of TRIM37 protein is not known. Of the Finnish *TRIM37* genes, 98% show one and the same mutation, Fin_{major} = c.493–2A>G. Mutation Fin_{minor}, found in two Finnish disease chromosomes, is c.2212delG. Two further mutations are known, from the USA and the Czech Republic. All these are frameshift mutations causing different truncations of TRIM37 protein.

Management

Cardiological monitoring and follow-up throughout life are imperative. Pericardiectomy becomes often necessary. The family of the affected infant needs support because of feeding difficulties and problems of growth and development. A close contact with an expert doctor is important also later.

Prenatal diagnosis

A gene test is possible at least in the Finnish risk families.

Historical aspects

The disease is one of the many detected by Jaakko Perheentupa (1970) in Finland. The name mulibrey is an acronym compiled of muscle, liver, brain and eye. Today this selection would not be the same, but the name is well established and deserves not to be changed at least until the pathogenesis joining together the different manifestations is solved.

Epidemiology

In Finland, over 80 patients are known, elsewhere less than 20. The map corresponds typically with the late settlement area.

Finnish experts

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Muscle-eye-brain disease

MEB
MIM 253280

Fig. 23

The triad of MEB comprises congenital muscular dystrophy, mental retardation, and severe ocular findings.

Clinical features

The babies are born at term. Muscular weakness manifests in the early infantile period, causes among others sucking difficulties and is severe by six months of age. Motor development is greatly disturbed: only few patients learn to walk even aided. In childhood, spasticity and joint contractures may develop in the lower extremities. Tendon reflexes are brisk or weak according to age.

The head is often large. Four patients have needed surgical treatment because of hydrocephaly. The forehead is high and temporally narrowed. The midface is flat and expressionless, the palate is narrow. Epileptic seizures are common. Psychic development is usually severely retarded and may deteriorate further with age.

The ocular findings are varied, often severe. Congenital myopia, glaucoma due to structural abnormalities of

the anterior chamber, dystrophy of the retina, optic atrophy and cataract show varying combinations. The visual handicap is severe, as is predictable from the nystagmus or wandering eye movements. Lifespan is often shortened although the disease in itself may not be lethal.

Diagnostic investigations

Serum creatine kinase concentration rises moderately during the first year of life, but may become normal in adult age. EMG shows a myopathic pattern by two years of age. The findings in muscular biopsy vary from nearly normal to severe dystrophic alterations. Different EEG changes appear after one year of age. MRI of the brain reveals migration disturbance of pachygyria with a nodular cortical surface called cobblestone cortex. Further findings are large ventricles, flat pons, and cerebellar cysts. The midline structures may be defective. The ERG is low or extinguished, flash-VEP shows delayed giant responses.

The features of MEB vary considerably as concerns composition, severity and time scale. Many syndromes resemble MEB greatly, such as Fukuyama congenital muscular dystrophy (FCMD), cerebro-ocular dysplasia-muscular dystrophy (COD-MD), and Walker-Warburg syndrome (W-W, HARD+-E). Their nosology is disputed. At least the gene loci of MEB and Fukuyama disease are not identical.

Pathogenesis

The pathogenetic defect is a loss of the enzymatic activity of the protein POMGnT1 (O-mannose beta-1,2-N-acetylglucosaminyltransferase) needed in O-mannosyl glycosylation and leading to a deficiency of alpha-dystroglycan. This defect may offer a sensible pathogenetic connection between muscular dystrophy and migration disorder of the brain.

Molecular genetics

The gene *POMGnT1* (cf. above) is in chromosome 1p32-p34. It has been characterised by a Japanese group. They identified six different mutations in one French and five Turkish patients. The mutation of Finnish patients is not reported as yet.

Management

Myopia and raised intraocular pressure should be treated properly. Physiotherapy is beneficial.

Prenatal diagnosis

Prenatal diagnosis may be or become possible in risk families, if the mutation is known.

Historical aspects

Santavuori, Leisti and Kruus of Finland described MEB in 1977.

Epidemiology

About 30 patients are known in Finland. Over 20 more or less similar cases may be described from elsewhere.

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Table 2 The neuronal ceroid lipofuscinoses (CLNs) in Finland*

Abbreviation	Names	Age at onset	Gene	Pathoanatomy
INCL	Infantile neuronal ceroid lipofuscinosis, Santavuori-Haltia disease	Infancy	CLN1 PPT	Granular osmiophilic deposits=GROD
$vLINCL_{Fin}$	Variant late infantile NCL, Finnish type Jansky-Bielschowsky variant	Preschool age	CLN5	Curvilinear bodies, fingerprint profiles
JNCL	Juvenile NCL Spielmeyer-Sjögren disease Spielmeyer-Vogt disease Batten disease	School age	CLN3	Fingerprint profiles
EPMR	Northern epilepsy	School age	CLN8 EPMR	Curvilinear bodies (GROD)

*The genes of NCL diseases rare or absent in Finland are: *NCL2* classical LINCL; *NCL4* adult NCL = Kufs disease; *NCL6, NCL7* rare LINCL variants

Neuronal ceroid lipofuscinoses

NCLs

Neuronal ceroid lipofuscinoses are a group of diseases in which ceroid- and lipofuscin-like material is accumulated in neural and other tissues. Common features are recessive transmission, progressive mental retardation after a normal initial development, retinal degeneration and early death. Distinguishing factors are age at onset, additional neurological symptoms, neurophysiologic and neuropathological findings and survival time.

Earlier these diseases were thought to be somehow genetically related to each other. However, for each of them separate gene loci have been detected. Despite that, their pathogenesis might have some factor(s) in common, especially as exceptional, interesting overlappings have been noticed between genes, clinical pictures and neuropathological findings. Peculiarly enough, outside Finland more than ten patients have been described with a clinical picture resembling Spielmeyer-Sjögren disease (JNCL) but caused by mutations of the INCL gene. In these patients, the electron microscopic storage material also resembles that of INCL, and the patients have no vacuolated lymphocytes. Additionally, several other overlappings of similar character have been observed.

Four NCL diseases belong to the Finnish Disease Heritage (Table 2).

Confusion in the polyform nomenclature is caused by the fact that some authors use Batten disease as a collective name for all NCL diseases, while others as synonym for JNCL.

In this article, different NCL diseases are described separately according to the alphabetical site determined by the name most commonly used in Finland: INCL, Jansky-Bielschowsky variant, Northern epilepsy, and Spielmeyer-Sjögren disease.

Finnish experts

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Histopathology

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Nonketotic hyperglycinemia

NKH
MIM 238300

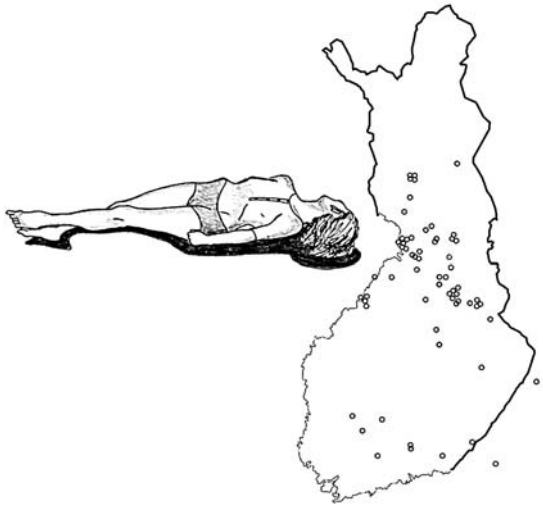

Fig. 24

NKH is a metabolic disease manifesting in the first few days of life and leading to either neonatal death or profound mental retardation.

Clinical features

Among many forms of nonketotic hyperglycinemia, the Finnish one is of the most severe neonatal type. In the first days of life, the patients develop a picture of serious brain damage: floppiness, lethargy, muscle jerks, diminishing reaction to pain, and respiratory distress. The patients often die of respiratory insufficiency. If not, a most profound psychomotor deterioration develops rapidly. Survival in a decerebrated state may last for more than ten years.

Diagnostic investigations

The glycine concentrations of plasma, urine and especially of cerebrospinal fluid are increased in the absence of ketosis and metabolic acidosis. The proportion between the glycine concentrations of the cerebrospinal fluid and plasma is greater than normal. EEG shows burst suppression pattern in the first days of life, later hypsarrhythmia. In MRI of the brain, a diminished amount of cerebral parenchyma, thin corpus callosum, and delayed myelinization may be seen. Quantitative proton magnetic resonance spectroscopy may disclose high glycine concentration in the neonatal brain. Gene diagnosis is successful in most Finnish cases.

Pathogenesis

In the glycine cleavage, four enzyme proteins, P, H, T and L are needed. In most of the Finnish patients, P-protein, viz. pyridoxal phosphate-regulated glycine decarboxylase, is inactive. Undegraded glycine cumulates and damages the brain.

Molecular genetics

The gene *GCSP*, (glycine cleavage system P) is in chromosome 9p13 or 9p22-p24 (?). Several mutations are known. Of the genes of Finnish patients, 70% present with the point mutation 1691G>T, which alters serine to isoleucine in position 564 of the P-protein. This mutation is not known in other populations. In Finland, two additional point mutations and one deletion are known.

Management

Curative treatment is not available, although trials with many substances affecting glycine metabolism, such as strychnine and dextrometorphane, have been made. It is most important to suspect and diagnose NKH in the first days of life. If an evident diagnosis of NKH can be made, the newborn should probably not be put in a respirator, because surmounting the respiratory distress would mean a futile struggle of many years against a hopeless disease.

Prenatal diagnosis

The determination of glycine/serine proportion in the amniotic fluid is unreliable. The activity of glycine degradation can be measured in the chorionic villi. A gene test is available for most of the Finnish risk families.

Historical aspects

The disease was described in the same year by Gerritsen et al. 1965 of the USA and Visakorpi with his collaborators 1965 from Finland.

Epidemiology

In Finland nearly 50 patients are known, elsewhere about 100. The majority of the Finnish patients are from northern Finland.

Finnish experts

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Northern epilepsy

Progressive epilepsy with mental deterioration
CLN8
MIM 600143

Fig. 25

See also *Neuronal ceroid lipofuscinoses*

This disease is a combination of epilepsy and later manifesting mental deterioration.

Clinical features

Epileptic seizures manifest at five to ten years of age, become more frequent at puberty and diminish in adult age. Mental development begins to deteriorate two to five years after manifestation of the seizures and proceeds to mental retardation. Yet most patients get through their elementary school. Behavioural problems, clumsiness, and disturbances of balance may add to the picture. The duration of life is not known as yet.

Diagnostic investigations

EEG shows slowing of background activity and disappearance of sleep patterns. In MRI, signs of cerebellar, brain stem, and later also cerebral atrophy can be seen.

Pathogenesis

Surprisingly, in autopsy, curvilinear bodies and granular osmiophilic deposits typical of neuronal ceroid lipofuscinoses have been found. That is why Northern epilepsy has been added to NCL diseases, although no ophthalmologic findings belong to this disease. This classification, however, does not explain the pathogenetic mechanism.

Molecular genetics

The gene (*EPMR, CLN8*) is in chromosome 8p23. All the Finnish patients have a point mutation 70C>G = R24G. It

may cause disturbance in an endoplasmic reticulum resident membrane protein, whose structure and mode of action is not known.

Management

The most effective antiepileptic is clonazepam. The careful treatment of epilepsy tends to retard the progression of the disease. It is important to understand the nature of the disease in order to deal with the behavioural problems in the right way, to seek individual solutions at school and to find a purposeful job.

Prenatal diagnosis

Prenatal diagnosis might be needed in the last pregnancies of the family. It is uncertain whether this will succeed from chorionic villus biopsy by pathoanatomic means. A gene test, however, is easy and reliable.

Historical aspects

The disease was first reported by Hirvasniemi and Leisti in 1991, but had probably already been described in the 1920s and 1930s by Ilmari Kianto in his novels about the life of rural people in Kainuu.

Epidemiology

Until now, the disease has been found only in one rural district in Kainuu, northeastern Finland. Almost all the patients have been shown by church records to be remotely related to each other via one ancestor.

Finnish experts

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PEHO syndrome

Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy
MIM 260565

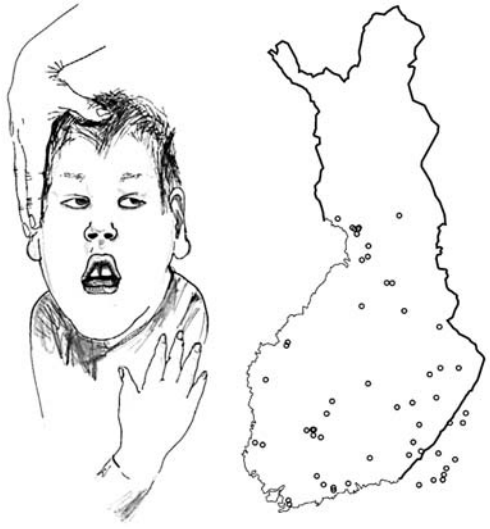

Fig. 26

Peho syndrome is an early manifesting brain disease leading to profound mental retardation and blindness.

Clinical features

Floppiness and feeding difficulties appear during the first few days of life. Edema of hands and feet, narrow forehead, short nose, out-turned ear lobuli and tapered fingers are typical. Already in early infancy the eyes are wandering or upturned as a sign of severe visual failure. The patients do not learn to sit, walk or speak. Severe microcephaly develops. Infantile spasms begin during the first year of life and change later to epileptic seizures of the Gastaut-Lennox type. Despite the floppiness, tendon reflexes are brisk. With time spasticity and contractures develop. Data on survival time are still lacking.

Diagnostic investigations

There are no specific laboratory investigations. Many patients with severe mental retardation show some solitary features typical of PEHO. The most important diagnostic finding is cerebellar and brain stem atrophy. In MRI, myelinization is delayed. EEG is hypsarrhythmic, SEP and VEP often abnormal. Optic atrophy is seen in the ocular fundi, but ERG is normal.

Pathogenesis

The disease process is not known.

Molecular genetics

The gene is not mapped as yet.

Management

Physiotherapy in order to prevent contractures, stimuli through hearing and touch, and antiepileptic medication are needed throughout life.

Prenatal diagnosis

Prenatal diagnosis does not exist.

Historical aspects

Riitta Salonen with her colleagues detected the disease among her Finnish counselling patients and described it in 1991.

Epidemiology

About 30 evident patients are known in Finland. In addition, there are several retarded patients resembling PEHO, yet without verifiable cerebellar atrophy. These are called PEHO-like patients. In other populations about ten cases are published, four of them from Japan.

Finnish expert

Dr. Mirja Somer (e-mail: mirja.somer@vaestoliitto.fi)

PLO-SL

Polycystic lipomembranous osteodysplasia — sclerosing leukoencephalopathy
Frontal lobe dementia with bone cysts
(Nasu)-Hakola disease
MIM 221770

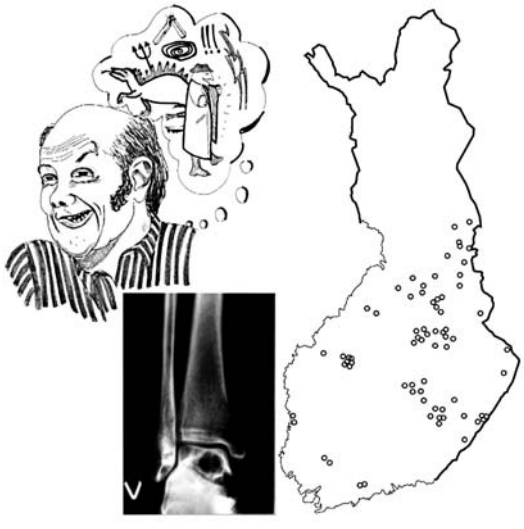

Fig. 27

PLO-SL is a disease of the central nervous system and cystic osseous lesions, beginning in middle age and leading to presenile dementia and early death.

Clinical features

The patients are symptomless until 20 years of age. After that, pain, swelling and possible fractures may appear in the ankles or wrists, due to juxta-articular bone cysts. At over 30 years of age, neuropsychiatric symptoms begin: disturbances of memory, deteriorating of personality and other characteristics of frontal lobe syndrome. The patients become euphoric, without feeling of illness. Later, agnostic-apractic-aphasic symptoms, myoclonic twitchings, and epileptic seizures appear. The progression continues into deep dementia and death by 50 years of age.

Diagnostic investigations

Bone X-ray reveals juxta-articular cysts. They contain necrotic fat tissue with fatty acid crystals and PAS-positive lipomembranes. In CT and MRI of the brain, atrophy of the white matter especially in the frontal area, enlarged ventricles and signs of demyelinization are seen. EEG shows synchronous, episodic and diffuse 6–8 Hz activity and the alpha rhythm is replaced by diffuse theta and delta activities. On autopsy, brain alterations include demyelinization and gliosis of the white matter, calcifications in the basal nuclei, sudanophilic granules in the perivascular macrophages, microangiopathy, and axonal changes.

Pathogenesis

Despite the characterisation of the gene, the basic mechanism is not known. Proposed "macroscopic" pathogenetic theories include microangiopathy and disturbance of fat metabolism.

Molecular genetics

The gene is in chromosome 19q13.1, in the vicinity of the gene for congenital nephrosis. All the 26 Finnish patients investigated have the mutation $PLOSL_{Fin}$: a 5.3-kb deletion covering exons 1–4 in *TYROBP*, which is the same as the *DAP12* gene known beforehand. The only Japanese patient investigated so far had a different mutation in this gene. The transmembrane protein TYROBP participates in the tyrosine metabolism and is a membrane receptor component in myeloid and natural killer cells. Their function, however, is shown to be normal in the PLO-SL patients.

Surprisingly, other, non-Finnish patients with definitely similar phenotype do not have any mutations in *TYROBP*, but in *TREM2* located in chromosome 6p21-p22 and belonging to the immunoglobulin superfamily. These

two genes probably encode different subunits of one receptor signalling complex, the function of which behind the phenotype is not known.

Management

The disease cannot be cured nor delayed. The family needs support and thorough knowledge about the disease in order to avoid bad emotional and other crises. Fractures and epilepsy are treated in the usual manner.

Prenatal diagnosis

The sibship has reached its final size as the first affected member manifests the disease.

Historical aspects

The skeletal findings were described the first time by Terayama of Japan in 1961. They had been observed also in Finland (Järvi et al. 1964). Järvi and Hakola with their collaborators combined the orthopedic and psychiatric features to one entity in 1968. After that, Hakola has studied this disease extensively and in Finland it is mostly called Hakola disease. The Japanese scientists have named it Nasu disease after their own principal investigator. In international literature the combination name Nasu-Hakola disease is common.

Epidemiology

In Finland more than 30 patients have been diagnosed. A greater accumulation of about 100 patients is known in Japan. This combination has urged Hakola to study a possible linguistic interrelationship between Finnish and Japanese (Part II, DOI s00439-002-0876-2, Classical Finnish studies). In Finland, the map of ancestors is most typical for the late settlement area; in nearly all the known families both parents were born in the same commune.

Except in Finland and Japan, *TYROBP* mutations have been found in a few patients from Sweden, Norway, and Brazil. Patients with *TREM2* mutations are known in Sweden, Norway, Italy, USA and Bolivia.

Finnish expert

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Progressive myoclonus epilepsy, Unverricht-Lundborg type

PME, PME-UL, EPM1
MIM 254800

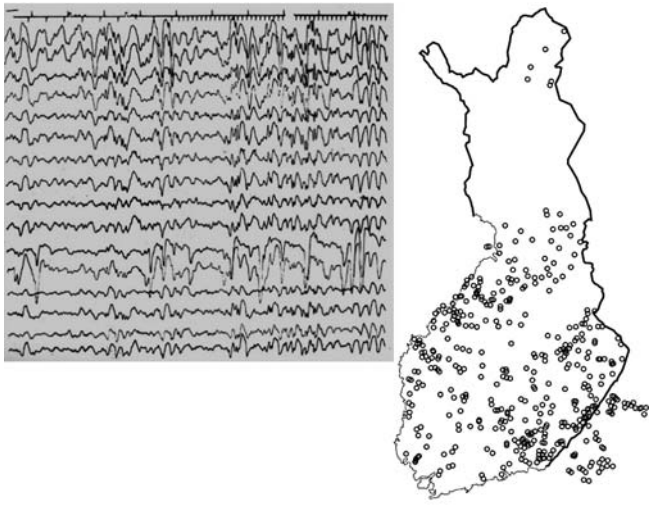

Fig. 28

PME is an epileptic disorder with myotonic jerks and motility difficulties.

Clinical features

The first years of life are normal. At the age of 6–15 years epileptic seizures begin and also involuntary myoclonic jerks provoked by different stimuli, such as moving the limbs or flashlight. The jerks had tendency to extend to series or to epileptic seizures, especially in the mornings. Dysarthric speech, lability of mood and slight decline of psychic capacity were common. The exaggerated jerks prevented moving about and the use of hands. The patients became bedridden and died in early adult age.

Modern treatment has totally changed the prognosis and the disease hardly affects the life span.

Diagnostic investigations

Typical EEG changes are spike and polyspike slow wave discharges (3–5/sec), with marked photosensivity. VEP and SEP may show giant reactions. In the imaging studies of the brain nothing pathological appears. Increased amounts of indican are secreted in the urine.

Pathogenesis

The basic disturbance may be connected with the metabolism of nerve impulse transfer.

Molecular genetics

The gene (*EPM1, CSTB*) is in chromosome 21q22.3. It encodes the formation of cystatin B, an inhibitor of cystathione proteinase. Some different mutations are known. The most common Finnish mutation is of a rare type of minisatellite dodecamer expansion in the promoter of the *CSTB* gene resulting in reduced cystatin B expression.

Management

PME is a prime example of diseases in which new treatment has totally changed the course and prognosis of a severe disorder. The prevention of jerks and seizures must be done with sodium valproate alone or in combination with clonazepam. Most of the other epilepsy medicines are ineffective or even cause serious side effects. As add-on treatment, especially against myoclonus, piracetam and zonisamide have shown promising results. With appropriate treatment the jerks appear only seldom and do not invalidate the patients. They must tenaciously hang on to normal life and they must be given effective physical and psychic rehabilitation.

Prenatal diagnosis

At the time when PME is diagnosed in the oldest affected sib, the family often already is of planned size. If not, gene diagnosis is available at least in Finland.

Historical aspects

The disease has been known since the 1890s because of Unverricht's thorough description from Estonia and Lundborg's report from Sweden. In Finland, Harenko and Toivakka published their observations on PME in 1961.

The nomenclature of this and related diseases is manifold and confusing. The Finnish form of PME is exactly similar with the descriptions by Unverricht and Lundborg, or PME-UL. Lafora disease (gene *EPM2A*) is totally different with its intracellular inclusions, later manifestation, excessively degenerative psychic component and shorter survival. Juvenile myoclonus epilepsy is milder than PME-UL, does not progress, but morning attacks are typical, too. Actually, the abbreviation PME is used today as a group term for diseases with epileptic fits and myoclonus. In Finland, however, this abbreviation is established to refer to the Unverricht-Lundborg disease, and there may be no reason to alter this practice. With today's knowledge, Baltic myoclonus is a misnomer (cf. Epidemiology).

Epidemiology

In Finland, about 200 patients are known. PME or at least a disease resembling it has been described from different populations, but especially from Mediterranean countries, where it has been called Mediterranean myoclonus, viz. Ramsay-Hunt disease. However, the disease, the gene and its main mutation seem to be identical in Finland and in the Mediterranean countries. That is why Baltic myoclonus is no longer an appropriate name for the Finnish-Estonian-Swedish disease. In Finland, the gene has spread into most areas of the country, but the southeastern part (Karjala) shows the greatest concentration of ancestors. It is quite possible, that the Finns have got the PME gene from the Mediterranean areas brought by foreign traders thousands of years ago (Part I, DOI s00439-002-0875-3, Age of gene mutations).

Finnish experts

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Molecular genetic

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Rapadilino syndrome

MIM 266280

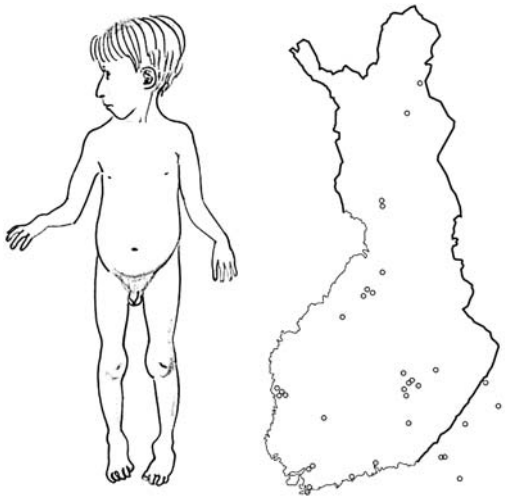

Fig. 29

Rapadilino syndrome comprises several skeletal abnormalities, typical face, growth disturbance and inexplicable diarrhea in infancy.

Clinical features

Skeletal malformations consist of aplasia or hypoplasia of the radii, thumbs and patellae and dislocations or malpositions of the joints of the lower extremities. Because of

the longish face, slender and long nose, cleft or narrow palate and micrognathia, the patients resemble each other more than their unaffected sibs. The voice is high-pitched. The stools are loose by unknown mechanism, but become normal without any treatment at the age of 2–3 years. The proportionate growth disturbance is of prenatal onset. The growth curves are below the normal curves, parallel with them. The intelligence is normal.

Diagnostic investigations

The skeletal X-ray investigations are important. If the diagnosis is evident, special investigations of the diarrhea are of no use. Differentiation from other syndromes with radial aplasia, such as TAR, Holt-Oram syndrome, and Fanconi anemia, is important.

Pathogenesis

The way of function of the gene is not known.

Molecular genetics

The localisation of the gene is not known because the patient series has been too small for study.

Management

The malpositions of the lower extremities may demand orthopedic correction even in newborns. The cleft palate is corrected in the usual way. The diarrhea is treated symptomatically. Corrective operations of the upper extremities are considered in due time. The patients learn to use their hands very cleverly. The face is beautiful in a way, although unusual. The psychic burden caused by the singularity must be alleviated by encouragement.

Prenatal diagnosis

The abnormalities of the upper limbs may be visible in accurate ultrasound scan.

Historical aspects

The "mother" of the syndrome is Helena Kääriäinen who found these patients among her Finnish counselling patients in the 1980s. The name rapadilino is not Italian language but an acronym: ra =radial aplasia, pa = absent patellae and cleft palate, di = diarrhea and dislocated joints, li = little size and limb malformations, no = long, slender nose and normal intelligence.

Epidemiology

More than ten patients are known in Finland. Three case reports have been published from elsewhere.

Finnish expert

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Retinoschisis

X-linked juvenile retinoschisis
RS, XLRS
MIM 312700

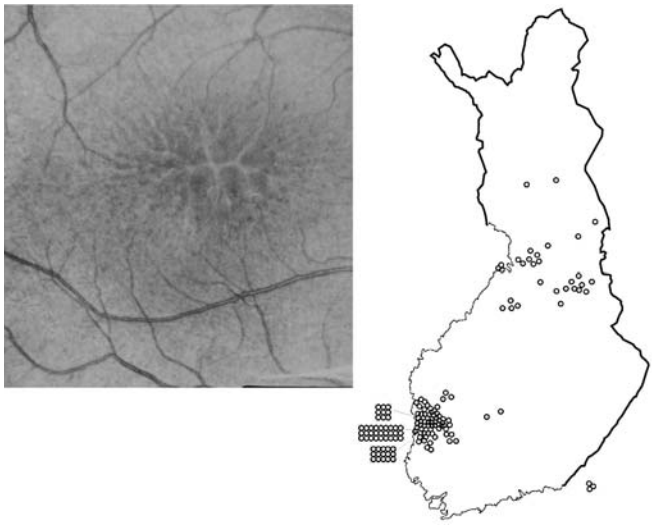

Fig. 30

This type of retinoschisis is an *X-chromosomal* ocular disease causing progressive visual handicap of varying degree in boys.

Clinical features

The disease is found usually in the first eyesight investigation at school. The grade of the visual handicap is different in different patients, but usually remains considerably constant until late middle age. Then, the visual acuity decreases, causing difficulties especially in reading.

In the ocular fundi, macular degeneration with a wheel spoke figure is the first, mild manifestation. In one third of the cases, the superficial layer of the retina is loosened, especially in the temporal periphery, and large holes may be seen, sometimes also folds called vitreous veils. In the rare, grave cases, a large area of the retina may be destroyed and become rolled.

Nothing other than ocular features belong to this disease.

Diagnostic investigations

The ophthalmoscopic diagnosis is easy for the ophthalmologist acquainted with the disease. The green light in the ophthalmoscope helps to perceive the wheel spoke figure. In Finland, gene tests are available for diagnosis.

Opposite to choroideremia, female carriers cannot be verified by ophthalmoscopy but certainly by gene tests. The pedigree compatible with X-linked inheritance affirms the diagnosis for its part.

Pathogenesis

Microcystic degeneration in the deep nerve fiber layer of the retina causes loosening of the retinal layers from each other.

Molecular genetics

The gene, *XLRS1* or *RS1*, is in chromosome Xp22.2. Its structure and over 100 different mutations are known. It encodes a secreted protein, retinoschisin, which is expressed in photoreceptors of the outer retina and bipolar cells of the inner retina and may function as a cell adhesion protein. In Finland three mutations prevail: in Satakunta, southwestern Finland, the mutation 214G>A (E72K) represents 70%, eastwards from there the mutation 221G>T (G74 V) stands for 6%, and in the district of Oulu, northern Finland, the mutation 325G>C (G109R) covers 20% of the Finnish mutations. All these also have their own basic haplotypes. As solitary findings, four other mutations have been found.

Management

The disease cannot be cured or delayed. Precautionary measures such as avoiding sport are not indicated. "Preventive" treatments cause more harm than benefit.

In rare cases, retinoschisis patients may get a true detachment of the retina, which must, of course, be treated by an immediate operation.

Prenatal diagnosis

Prenatal diagnosis is possible by a gene test, if the mutation is known. The need and ethical principles of it are not established.

Historical aspects

Haas of Germany described the disesase in 1898. In Finland, Henrik Forsius with his collaborators have studied retinoschisis comprehensively since the 1960s.

Epidemiology

In Finland over 300 patients are known, among them one female homozygote. The disease is concentrated in the regions of Satakunta and Oulu, where retinoschisis is the commonest cause of bilateral amblyopia of schoolboys. The disease is not very rare in other populations, either.

Finnish experts

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Molecular genetics

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Salla disease

Sialic acid storage disease, Finnish type
MIM 269920

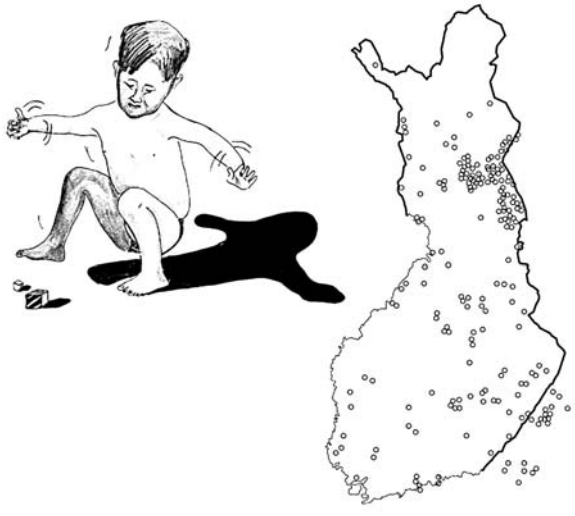

Fig. 31

Salla disease is a slowly progressive storage disease causing mental retardation and motility disturbances.

Clinical features

The first weeks of life are normal. At the age of 4–12 months, floppiness, clumsiness, ataxia, and later, stiffness appear. Transient horizontal nystagmus is often seen. The milestones of psychomotor development are delayed. The speech ability may comprise single words, but many pa-

tients understand speech better than they can speak themselves. A third of the patients do not learn to walk. The development makes slow progress until the third decade of life and begins to go downhill after that. Cheerfulness is a typical characteristic. The degree of severity varies considerably between patients. The age of the oldest known patient is over 70 years.

Diagnostic investigations

In neuroradiological studies, loss of the white matter and deficient myelinization are seen. In difficult cases and in time, cerebral and cerebellar atrophy appear. Corpus callosum is thin. Signs of dysmyelination may be found also in the peripheral nervous system. The concentration of free sialic acid (N-acetyl neuraminic acid) is increased in the urine and in several tissues. Vacuoles appear often in the blood lymphocytes. Lysosomes are expanded by stored sialic acid in skin biopsies.

Pathogenesis

The membrane transport of sialic acid from the lysosomes is impaired, causing a storage of this material in the lysosomes.

Molecular genetics

The gene *SLC17A5* (formerly also *SIASD, SLD, AST*) is in chromosome 6q14-q15. The gene has been characterised. In Finland, mutation 115C>T (R39C) causes 95% of the Finnish cases in a homozygous form and the rest as compound heterozygous with four other mutations.

In the same locus, other mutations are known that in a homozygous state cause a more severe, infantile sialic acid disease (ISSD). It seems that different mutations in different combinations of compound heterozygotes form a clinical continuum of different grades of severity.

Some principles are understood of the protein coded by the gene, sialine, but the structural details are not known.

Management

Curative treatment does not exist. Communication therapy is important.

Prenatal diagnosis

Prenatal diagnosis is possible by determining the concentration of free sialic acid in the chorionic villi. A gene test is available, if the mutation is known, as it is in Finland.

Historical aspects

Salla disease was found as a byproduct in 1979 by Aula et al., when AGU patients were sought for in northern Finland. Salla is a commune in Lapland.

Epidemiology

Over 100 patients are known in Finland, most of them from northern Finland. Elsewhere, over 20 patients have been published. Half of them are from Sweden; the Finnish mutation has been found in most of them.

Finnish experts

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Selective malabsorption of vitamin B_{12}

Megaloblastic anemia 1
Gräsbeck-Imerslund disease
SMB_{12}, MGA1
MIM 261100

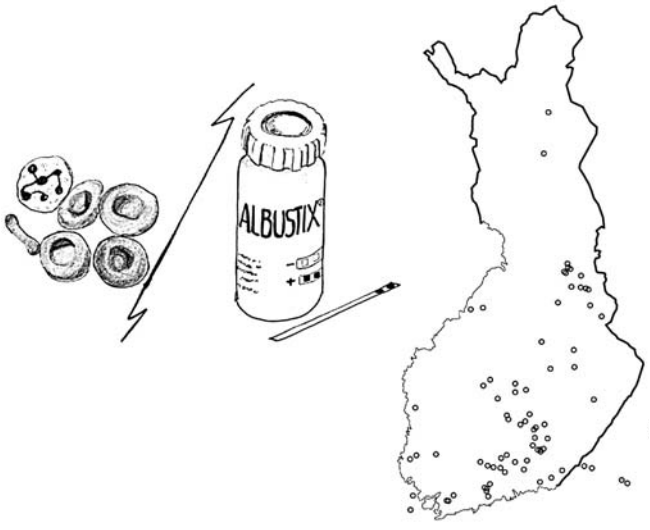

Fig. 32

This disease is a megaloblastic anemia caused by impaired absorption of vitamin B_{12} from the small intestine.

Clinical features

The first symptoms are vague: fatigue, failure to thrive, pallor, poor appetite, vomiting. They appear around 12 months of age. The anemia behind these symptoms would without proper treatment lead to death. Most patients have proteinuria that apparently causes no harm. Untreated patients also develop neurological symptoms.

Diagnostic investigations

Anemia is macrocytic. The concentration of vitamin B_{12} in the blood is very low, but the intrinsic factor of gastric juice needed for the absorption of vitamin B_{12} is normal. The activity of the urinary receptor for the intrinsic factor

— cobalamin complex can be measured by a radioisotope-binding assay. In Finland the gene test gives a reliable diagnosis.

Pathogenesis

Vitamin B_{12}, needed for the maturation of the red blood cells, is not absorbed from the alimentary canal. The activity of the intrinsic factor — cobalamin receptor in the mucosa of the small intestine and probably also in the kidney is low.

Molecular genetics

The gene *MGA1, CUBN*, is in chromosome 10p12.1. Its mutations lead to an impaired recognition and loss of affinity of the intrinsic factor — cobalamin-binding region of the protein cubilin in the cells of intestinal mucosa and renal tubuli. In more than 90% of the Finnish disease genes, mutation FM1 (3916C>T = P1297L) is found. Also two other mutations (FM2 and FM3) are known in Finland. No data are available on the mutations in other populations.

Management

Parenteral administration of vitamin B_{12} cures the anemia totally but does not affect the proteinuria. Diagnosed properly and treated regularly, the "disease" is fully harmless.

Prenatal diagnosis

Prenatal diagnosis is hardly needed because the treatment is curative.

Historical aspects

The disease was described simultaneously by Olga Imerslund of Norway (1959, 1960) and Ralph Gräsbeck with his collaborators in Finland (1960).

Epidemiology

In Finland about 40 patients are known; in Norway about 15, in the Near East about 20 and in other populations more than 100.

The ancestors of the Norwegian patients come mainly from a small area in southeastern Norway (Valdres) where the "Forest Finns", first having immigrated from Savo to Sweden, moved in the 1500–1600s. It would be tempting to assume that the genes of the Norwegians and the Finns had a common origin. This seems, however, not to be the case: three Norwegian patients investigated so far do not have any of the Finnish mutations.

The appearance of the disease in Finland has been erratic. As 16 patients born in the 1950s were diagnosed, only three patients born in the 1970s, one in the 1980s and three in the 1990s have been seen. Some doctors have even doubted the existence of this whole disease, but this doubt has been proved wrong because of the many studies in Finland and elsewhere. True, this disease has not been a favourite disease of any Finnish pediatrician. It is not probable that an anemia, lethal without proper treatment, could in modern times escape diagnosing. It could have been treated outside the university hospitals in a "natural" way by parenteral administration of vitamin B_{12}. The incidence of no other Finnish disease has diminished so drastically because of internal migration into cities. It is even not impossible that some changes in environmental, say dietary factors, would have contributed in some way to the resorption of vitamin B_{12} during the last 20 years.

Finnish expert

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Spielmeyer-Sjögren disease

Juvenile neuronal ceroid lipofuscinosis
Spielmeyer-Vogt disease, (Late onset) Batten disease
SS, JNCL, CLN3
MIM 204200

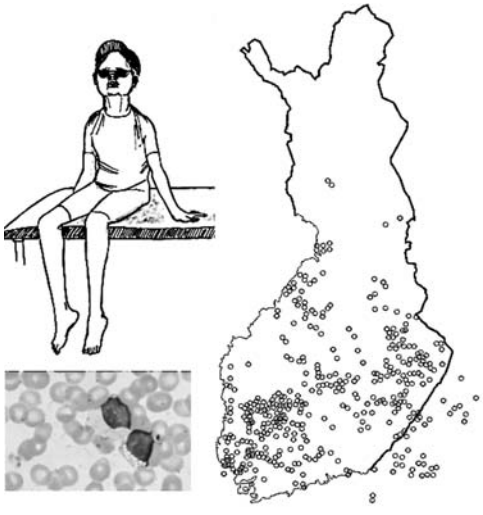

Fig. 33

See also *Neuronal ceroid lipofuscinoses*

Spielmeyer-Sjögren disease begins before or at school age with impairing of the visus and leads to neuropsychological deterioration and death.

Clinical features

The first feature is the gradual impairing of vision at the age of 4–8 years. Severe visual handicap and even blindness follow at 8–15 years of age. Epileptic seizures, extrapyramidal speech and motor problems, as well as the deterioration of psychic abilities appear at 10–15 years. The lifespan is 18–35 years. The final, bedridden period lasts for only some months. Great inter- and intra-familial variability exists in the succession, severity, and age at manifestation of the different components of the disease.

Diagnostic investigations

In the eye fundi, macular degeneration, and later, attenuated vessels, optic atrophy and "salt and pepper" alterations develop. Abolishing ERG and decreasing and delaying flash-VEP appear. EEG alterations are unspecific. MRI of the brain is normal at the early stage, but hypointense signals in the thalami and hyperintense signals in the white matter appear in the second decade of age. SPECT shows local hypoperfusion. The late appearance of these findings is important for differentiating this disease from the Finnish variant of Jansky-Bielschowsky disease.

Blood lymphocytes show vacuoles. Thus, a combination of deteriorating visus, degenerative alterations of eye fundi and vacuolated lymphocytes is almost pathognomonic for Spielmeyer-Sjögren disease.

In brain samples at autopsy, fingerprint patterns are seen in the neurons in electron microscopy. In chorionic villus biopsy of the fetus and rectal biopsy of the patient, a mixed picture of fingerprint patterns and curvilinear bodies are seen. The gene test confirms the diagnosis, if the mutation is known.

Pathogenesis

Also this disease can be called a lysosomal storage disorder. Many theories, a.o. peroxidation disturbance of fatty acids, have been proposed, but none of them has been confirmed as yet. The fault in some lysosomal membrane protein possibly hampers the function of the nerve synapses.

Molecular genetics

The gene *CLN3* is in chromosome 16p12. Over 30 different mutations are known. The most common is a deletion of 1.02 kb (461–677del), which is found in 90% of the Finnish and 80% of other populations' disease genes. In Finland, four additional mutations are known, all of them as compound heterozygotes with the main mutation. The lysosomal protein CLN3 is expressed in neuronal synapses but not in synaptic vesicles. The mutated protein seems to be arrested in the neuronal cell soma and cannot reach the axons and synapses. The details of the function of the CLN3 protein are not known.

Management

Since the 1970s the patients have been treated with antioxidants, viz. vitamins B_2, B_6, E, and selenium. This treatment seems to retard the progression of other features except the deterioration of the visus. Additionally, many kinds of symptomatic treatment are needed for the epilepsy, extrapyramidal symptoms, and psychiatric problems. In the physical and psychic rehabilitation, the visual handicap has a central role, but also many kinds of other rehabilitation, such as physiotherapy, riding etc., are beneficial.

Prenatal diagnosis

Prenatal diagnosis succeeds from the chorionic villi with both electron microscopic investigation and gene test. The problem is that the final size of the sibship has often been reached before the diagnosis of the eldest affected child is made.

Historical aspects

The first description is from Norway by Stengel in 1826. In Finland, the pioneer both in diagnosis and treatment has been Pirkko Santavuori for this disorder, as also in other NCL diseases. The Finnish doctors von Bagh and Hortling were the first to describe the vacuolated lymphocytes in this disease in 1948.

Epidemiology

About 200 patients are known in Finland, where the incidence is 1:20,000 and carrier frequency about 1:70. The disease is not very rare elsewhere either. As an overall incidence even a figure of 1:25,000 has been proposed. It may be an overestimate rather than vice versa.

Finnish experts

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Tibial muscular dystrophy

TMD
MIM 600334

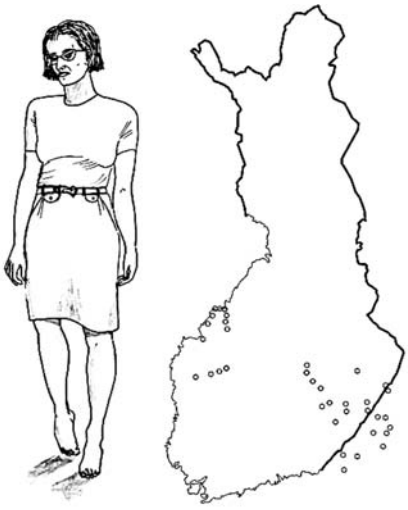

Fig. 34

This *autosomal dominant* myopathy presents with a mild weakness of the anterior tibial muscles in adult age.

Clinical features

TMD is a very mild and limited muscular disease. The "patient" notices that the feet flap in walking (impaired dorsiflexion of the ankle) and walking on heels is impossible. Later, a mild foot drop develops. This dystrophy does not cause marked invalidisation even after years.

Diagnostic investigations

In CT or MRI of the leg, the tibialis anterior muscle shows fatty degeneration. Similar focal alterations may be seen even in other, asymptomatic muscles. In the biopsy from the affected muscle, common dystrophic changes and, possibly, rimmed vacuoles are found. In ENMG, signs of muscular dystrophy, but not those of neural damage, are seen. Serum creatine kinase values are normal or slightly raised. A gene test is available for the Finnish patients.

Pathogenesis

Muscular damage is caused by a fault in the titanic skeletal muscle protein titin (formerly connectin). Titin keeps the contractile elements of the sarcomere in place and provides multiple ligand binding sites for several other muscle proteins. One of these, calpain-3 shows secondary deficiency, which may be an important part in the pathogenesis of TMD.

Molecular genetics

The gene *TTN* is in chromosome 2q31. It is a giant gene with 363 exons. The Finnish mutation in Mex6 is an 11-bp change in the 363rd and last exon, changing four amino acids in the titin protein. All Finnish patients investigated have this unique mutation and the LGMD patients of the TMD kindreds are homozygous for it (cf. Historical aspects).

Management

The symptoms are so mild that usually no treatment is needed. It is important to inform the "patients" that they do not need to fear a severe worsening of the disease. However, in some patients the foot drop may become so difficult that tibial posterior tendon transposition may be indicated.

Prenatal diagnosis

Prenatal diagnosis is not needed. "Screening" by the gene test among the spouse candidates of near relatives might be sensible in order to avoid homozygosity of the TMD gene on its core areas (cf. Historical aspects).

Historical aspects

TMD was revealed when the Finnish neurologist Bjarne Udd investigated a severe muscular dystrophy of the limb girdle type in a coastal isolate Larsmo in Ostrobothnia, western Finland. Then, mild weakness of the legs was noticed in close relatives of the patients. It turned out that the homozygosity of the gene causes the severe disorder (LGMD2J), whereas the same gene in heterozygous individuals causes TMD. Among the confusing group of distal muscular myopathies, TMD is a distinctly delineated entity.

Epidemiology

Except in Ostrobothnia, TMD was soon found also in eastern Finland and nowadays even all over the country. According to the haplotypes and genotypes, all occurrences have a common source. In Finland, more than 300 affected individuals are known. Elsewhere, in Belgium, France, and the USA, one kindred in each has been found so far. In addition, affected descendants of the Finnish immigrants have been found in Sweden, Germany and Canada.

Finnish expert

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Usher syndrome type 3

USH3
(The old Finnish name is dystrophia retinae pigmentosa — dysacusis = Nuutila disease)
MIM 276902

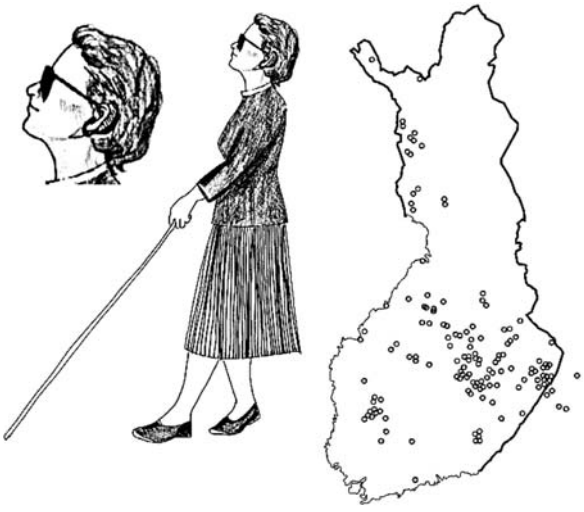

Fig. 35

Usher syndrome is a combination of hearing loss and visual failure of the retinitis pigmentosa type.

Clinical features

Three main types of Usher syndrome exist. In all of them, the visual findings of retinitis pigmentosa type manifest in childhood, show night blindness, photophobia, narrowing of visual fields, decreasing visual acuity and early cataract, and end in a severe visual handicap if not in blindness. The hearing loss is congenital and severe in type 1 and congenital and moderate in type 2. In type 3, the hearing loss develops gradually but becomes at least moderately severe. The age at manifestation and speed of the progress vary considerably. In type 1, a disturbance of balance is also common.

In Finland, type 1 may be as prevalent as elsewhere and patients with type 2 are also seen. However, type 3 belongs to the Finnish Disease Heritage. It is described in the following.

Diagnostic investigations

The hearing investigations show inner ear damage. The audiogram is declining or U-shaped. Audiograms from different ages should be compared in order to be assured of the existence of type 3. The responses of the vestibular organ are normal or slightly decreased.

The ocular investigations are made along lines common in retinitis pigmentosa. Often, hyperopia and astigmatism are also found.

Pathogenesis

Despite active investigations on both retinitis pigmentosa and inner ear, the pathogenesis and common denominator of these components are only fragmentarily known.

Molecular genetics

Several gene loci are responsible for Usher 1 and 2. The gene for the Finnish Usher 3 (*USH3A*) is in chromosome 3q21-q25. The gene encodes the transmembrane protein clarin-1, which may have a role in cochlear hair cell and retinal photoreceptor cell synapses. The main mutation (Fin_{major}) in 56 Finnish patients investigated is c.300T>G = Y100X. Four patients in two kindreds were compound heterozygotes between Fin_{major} and Fin_{minor} = c.131T>A = M44K. In one consanguineous Italian family a third mutation, c.231–233 delATT, has been found.

Management

Any component of the Usher syndromes cannot be cured or retarded. However, both hearing and seeing can be aided with many kinds of devices and rehabilitative measures. Finally, the patients become both auditorily and visually impaired, and thus communication may be extremely difficult. Fortunately, most patients have learned normal speech before the loss of hearing, in contrast to Usher 1.

Prenatal diagnosis

The characterisation of the gene has made prenatal diagnosis possible. However, its demand and the ethical principles have not been established in diseases like this.

Historical aspects

Usher syndrome has been known since the 1800s by different names after the classical investigations by von Graefe, Lindenow and Hallgren. In Finland, the neurologist Arto Nuutila carried out a nationwide investigation of "dystrophia retinae pigmentosa — dysacusis" in the 1960s. The existence of type 3 was considered questionable for a long time, until the Finnish doctors Leenamaija Pakarinen and Eeva-Marja Sankila delineated it and mapped its gene.

Epidemiology

In Finland, nearly 300 Usher patients are known, out of whom about 100 belong to type 3. Their region of predilection is in Eastern Finland, whereas type 1 is prevalent in Lapland. Type 1 is considerably common in several populations and thus Usher syndrome should not be included in the Finnish Disease Heritage without the exceptional abundant occurrence of type 3.

Finnish experts

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Ophthalmology and molecular genetics

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Vuopala disease

Lethal arthrogryposis with anterior horn cell disease
LAAHD
Cf. Lethal congenital contracture syndrome = *Herva disease*
MIM —

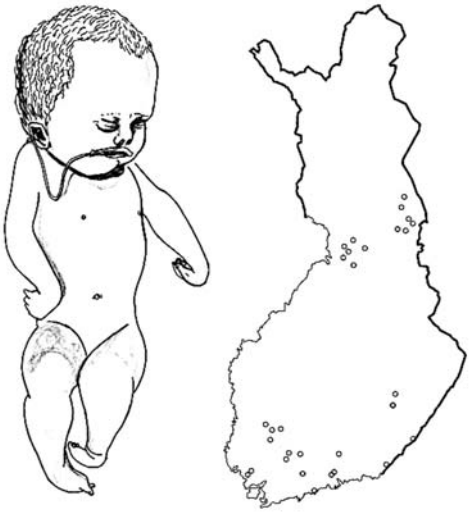

Fig. 36

This fetal immobility syndrome is due to intrauterine spinal anterior horn cell damage and causes perinatal death.

Clinical features

The findings resemble those of Herva disease. However, more than half the patients are born full-term. Compared with Herva disease, these newborns have more muscles, but do not have edema or pterygia. The upper limbs are often rotated in pronation. The patients are stillborn or die soon after birth. The longest survival age has been one month.

Diagnostic investigations

Although all newborns die, the correct diagnosis is imperative for the genetic counselling of the family. Photos and autopsy are of utmost importance. At autopsy, the spinal cord and muscle samples must also be investigated.

Pathogenesis

The clinical findings are due to immobility of the fetus, while the immobility is due to degeneration and diminished number of the spinal anterior horn motor neurons. The muscles show a microscopic picture of neurogenic damage as in spinal muscular atrophies. The disease cannot be called spinal muscular atrophy (SMA) as long as, by definition, congenital contractures are not allowed in SMA.

Molecular genetics

The gene is not mapped, still less characterised. The locus of either Herva disease in chromosome 9q34 or that of SMAs in 5q is not excluded as yet.

Management

The patients are beyond reach of effective help. If the diagnosis is certain, respirator treatment can hardly produce a sensible prolongation of life.

Prenatal diagnosis

Prenatal diagnosis may be possible by ultrasound in risk families.

Historical aspects

The Finnish pediatric pathologists Katri Vuopala and Riitta Herva separated this disease from Herva disease to a distinct entity in the 1990s.

Epidemiology

In Finland about 20 evident and as many probable patients are known from two areas in Häme and Kainuu. Some solitary cases with similar phenotype have been described from elsewhere.

Finnish experts

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New candidates for addition to the Finnish Disease Heritage

At least five diseases are already waiting to be added to "Perheentupa's steps" (see Part I, DOI s00439-002-0875-3, Description and definition of FDH, Fig. 2).

Two of them have been known in Finland for a long time. *Tyrosinemia type I* appears in a concise area resembling that of Jansky-Bielschowsky disease. About 20 patients are known in Finland and 200 in the world, most of them in Saquenay-Lac-Saint-Jean, Canada, settled by French immigrants. The gene *FAH* is in chromosome 15q23-q25 and the Finnish mutation is 786G>A = W262X. Curiously enough, Visakorpi in 1972 described tyrosinemia type I, together with lysinuric protein intolerance and nonketotic hyperglycinemia, in an article of the Finnish medical journal Duodecim, in the issue in which the Finnish Disease Heritage was introduced to the Finnish doctors. Because tyrosinemia has been considered a classical disease, it has not been included in the Finnish Disease Heritage. In fact, it is globally much rarer than assumed and thus its "classical" character seems questionable.

The other classical disease is the recessively inherited *nephronophthisis*. The preliminary investigations were done in Finland in the 1970s, but detailed studies were not carried out until the 1990s, by Sirpa Ala-Mello. According to these studies, over 40 patients have been found in Finland and over 100 elsewhere. The gene is mapped to chromosome 2q13 and the commonest mutation in Finland, as well as elsewhere, is a 250-kb deletion. Detailed gene studies are in progress.

The three other candidate diseases are not classical. *Bernard-Soulier syndrome* is a disorder of the hemostasis. Platelets are diminished, large, short-lived and do not agglutinate by ristocetin. The fault is in one of the four glycoproteins of the cell membranes: GPIb alfa, GPIb beta, GPV, and GPIX, each determined by a different gene locus. Genetically speaking, Bernard-Soulier syndrome is not one disease but a group of diseases like retinitis pigmentosa. According to the studies by Riitta Kekomäki and Satu Koskela, 30 patients in Finland are known, elsewhere about 70. Four mutations of two genes are known in Finland. One of them, mutation N45S in the gene of GPIX might be a Finnish speciality especially as its clinical picture seems to differentiate more or less from the complex. Detailed studies are in progress.

LCHAD-deficiency is a severe metabolic disorder, a disturbance of the mitochondrial oxygenation of long-chain fatty acids causing severe chronic failure to thrive, acute metabolic crises and marked ocular findings in infants. LCHAD stands for long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. The disease was described ten years ago. According to the recent investigations by Tiina Tyni, Helena Pihko and others, over 30 patients in Finland are known, elsewhere about 50. The gene locus and structure are known. All the Finnish patients and most of the others show the same mutation G1528C (E510Q) in the chromosome 2p23. The epidemiological studies, among others, are not finished as yet.

The *recessive incisive hypodontia (RIH)* is a new odontological syndrome. The most typical features are missing of all four lower incisors and lateral upper incisors. Atopic eczema, childhood asthma, symptoms of nails and some facial features may accompany the syndrome. In the investigations by Sinikka Pirinen, Sirpa Arte, and their collaborators, more than 40 patients are known in Finland and new patients seem to present themselves continuously. Two similar patients have been described from Egypt and one family from Lebanon.

Structural anomalies of the teeth are usually dominantly inherited and defects of the lower incisors are rare indeed. In both respects, RIH makes an exception. When the investigations are finished, this disease most probably will be included in the Finnish Disease Heritage.

Acknowledgements My warmest thanks to all the expert doctors for the patient data and for checking the manuscript on their respective section; to Markku Löytönen, Mari Markkanen-Leppänen and Publishing Company Otava for the figures; to Kari Markovaara, Jonna Mervelä, Taina Miikkulainen, Liisa Savolainen, and Leena Toivanen for their everlasting patience in different kinds of support, and to the Finnish Cultural Foundation for the grants.

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