Mulibrey nanism (MUL) is an autosomal recessive disease caused by mutations in the TRIM37 gene encoding the peroxisomal TRIM37 protein of unknown function. In this work, we analysed the clinical characteristics of 85 Finnish patients with MUL, most of whom were homozygous for the Finn major mutation of TRIM37. The patients’ hospital records from birth to the time of the diagnosis at age 0.02–52 years (median 2.1 years) were retrospectively analysed. All except four of the patients (95%) had a prenatal onset growth failure without postnatal catch up growth. The mean length standard deviation score (SDS) was −3.1 and −4.0 at birth and at diagnosis, respectively. In infancy, feeding difficulties, and respiratory tract infections were the most common problems. Congestive heart failure and pericardial constriction were diagnosed during infancy in 12% and 6% of the patients, respectively. At the time of the diagnosis, characteristic craniofacial features of scaphocephaly, facial triangularity, high and broad forehead, and low nasal bridge were evident in over 90% of the patients. In addition, practically all patients were gracile and had thin extremities. Other findings included a peculiar high-pitched voice (96%), yellowish dots in ocular fundi (79%), cutaneous naevi flammei (65%), hepatomegaly (45%), and fibrous dysplasia of long bones (25%). Mild muscular hypotonicity (68%) was the only neurological abnormality. The clinical features of the Finnish patients with MUL formed a distinct entity. The most consistent findings were growth failure and characteristic craniofacial features. However, organ manifestations varied considerably in early childhood. Based on these findings, we propose new diagnostic criteria for MUL.

Mulibrey nanism (muscle-liver-brain-eye nanism, MUL; OMIM #232520) is an autosomal recessive disorder with severe growth failure and multiple organ manifestations first described in the early 1970s. Today, we know of some 110 patients, 85 of them from Finland. Sporadic cases have been reported from various ethnic groups all over the world. All five mutations result in a shift of the reading frame, resulting in a truncated TRIM37 protein. TRIM37 is a 130 kDa protein expressed in many tissues and located in the peroxisomes, suggesting that MUL is a peroxisomal disease. TRIM37 belongs to a new subfamily of zinc finger proteins (previously designated RBCC for ring-B box-coiled coil). The function of the TRIM37 protein and the pathogenetic mechanisms underlying MUL are unknown.

Diagnostic evaluation and clinical care of the patients with MUL in Finland has been centred in our institution. Here we report the clinical findings from birth to the time of the diagnosis in all known Finnish patients, and present revised diagnostic criteria.

Patients and methods

Patients

The series included all the known 85 Finnish patients with MUL diagnosed by the original criteria. DNA was available from 80 patients; 78 of them homozygous for the Finn major mutation, and two compound heterozygotes for the two Finnish mutations. The other five patients had died before mutation analysis became available. In four of those five cases, DNA was obtained from family members; one parent couple, two single parents, and one sibling, all carriers of the Finn major mutation. The phenotype of the remaining patient left no doubt about the diagnosis.

Collection of data

The hospital ethics committee approved the study. We retrospectively analysed the patients’ hospital records from birth to the time of diagnosis. We recorded data on their clinical events and on their appearance and dysmorphic features. The patients were photographed, and x-rays of the skull, thorax, and long bones as well as appropriate laboratory assays were obtained on the first visits. The obstetric and growth histories were collected from hospitals and child welfare centres. The patients’ parents, relatives, and physicians were interviewed for missing details. Birth size and subsequent lengths/heights were expressed as standard deviation scores (SDS) according to the Finnish standards, and postnatal weights as percentage deviations from the mean weight for height and sex.

Abbreviations: SDS, standard deviation score; SGA, small for gestational age; SRS, Silver-Russel syndrome
The clinical data on the 85 Finnish patients with MUL were systematically analysed from birth to time of the diagnosis. The age at the diagnosis varied from 0.02 to 52 years (median 2.1 years). A third of them were younger than 1 year and two thirds were younger than 5 years.


Pregnancy and delivery
Most of the pregnancies were uneventful. Complications included pre-eclampsia (three cases), anti-Rhesus immunisation (a pair of siblings), gestational diabetes (one), and varicella zoster infection (one). Nineteen of the pregnancies (23%) had been monitored because of poor fetal growth. Fifteen mothers (18%) had had miscarriages in previous pregnancies. Length of gestation varied from 32 to 42 weeks (median 39 weeks); 90% of the children were born at full term. Labour was uncomplicated in all but three cases, in which an urgent caesarean section was performed because of threatened asphyxia. Apgar score at 5 minutes was on average 8 (range 2–10).


Newborn period
Of the newborns, 81 (95%) were small for gestational age (SGA), with birth length SDS below −2.0 for gestational age (fig 1). Birth length SDS was on average −3.1 (range −6.4 to 0.7), and mean birth weight SDS was −2.8 (range −4.0 to 0.5). Occipitofrontal head circumference SDS ranged from −0.9 to 0.8 (mean −0.5) indicating macrocephaly relative to length in the majority of children.


Later infancy
The growth failure progressed over the first 2 years of life in 63 patients (74%) with an SDS decrease of more than 1.0 (range −1.0 to −3.5). Catch up growth with a gain in length SDS of more than 1.0 (range 1.1 to 2.9) occurred in five (6%) of the infants. One boy and two girls reached a length SDS above −2.0 at the age of 2.0 years; one girl grew steadily from birth staying at an SDS of −1.4. At the age of 2.0 years, length SDS was on average −4.4 (range 0.1 to −7.8) (fig 1). Weight gain was also poor. Mean relative weight for height at the age of 2.0 years was −21% (range −35 to 3%).

Half of the patients failed to thrive. Feeding difficulties were the most common clinical problem such that one third needed nasogastric feeding and five children needed a percutaneous gastrostomy (table 1). A high frequency of upper respiratory infections and middle ear infections was evident; pneumonias were diagnosed in nearly half of the infants by the age of 2.0 years (table 1). Episodes of respiratory failure induced by an infection occurred in 25% of the infants. Nine infants had to be resuscitated (table 1).
Four and nine patients had congestive heart failure by the age of 1.0 and 2.0 years, respectively; four of them died.

Psychomotor development was normal or slightly delayed in a great majority of the infants. Mild hypotonicity was evident in nearly half of the infants, and a delay in both motor development and speech was noted in nearly one third. Age at the first steps and the first words ranged from 0.8 to 2.6 years (mean 1.2 years) and 0.9 to 3.1 years (mean 1.3 years), respectively. A mildly hydrocephalic skull with frontal bossing and abnormally wide fontanelles evoked suspicion of hydrocephalus in 15% of the infants (table 1).

Findings at the time of diagnosis
Clinical findings
At the time of the diagnosis all but four (96%) of the patients were below length SDS of –2.5. Nearly all the patients were gracile with relative macrocephaly, and thin extremities with proximal relative shortness and narrow shoulder (fig 2). The characteristic triangular face with high, broad forehead and low nasal bridge was present in over 90%, and scaphocephaly with occipitofrontal bossing was seen in over 80% of the patients (table 2, fig 3). Fifteen patients (18%) had signs of heart disease (table 3). Ten of them met the criteria of congestive heart failure, and four had pericardial constriction necessitating pericardiectomy. One woman had been pericardiectomised at the age of 32 years (12 years before the diagnosis) due to constrictive pericarditis. Eighteen patients (15%) had structural heart anomalies (table 3).

Thirty eight patients (45%) had hepatomegaly and six of them had liver tumours. Wilms’ tumour was detected in two patients before MUL was diagnosed. Both patients had nonsymptomatic haematuria with a palpable abdominal mass as the only signs. Renal and genital anomalies were observed in 18% and 9% of the patients, respectively (table 3).

A peculiar voice characterised by high pitch and slight coarseness was noted in nearly all of the prepubertal patients. Characteristic ocular findings were yellow dots in the midperiphery of ocular fundi, seen in 80% of the patients. Additional ocular findings were retinal hypopigmentation and pigment dispersion with clusters of pigment in the retina. Two thirds of the patients had cutaneous naevi flammei, most commonly in the lower limbs (80%).

Radiological findings
Slender long bones with thick cortex and narrow medullary channel (fig 4) and a low, shallow (J shaped) sella turcica (fig 5) were the characteristic radiological findings present in nearly all patients (table 4). More than half of the patients had true orbital hypertelorism. The orbital fossae were slightly upward slanting with laterally rotated axis (fig 5). Fibrous dysplasia was present in 15% of the patients, mostly in the lower limbs (fig 4). Six patients had fibrous dysplasia in more than two locations (range 2 to 4). A slight asymmetry
of extremities was noted in 17 patients (20%), which in two thirds was due to shortening by fibrous dysplasia. The thoracic cage was small and bell shaped with unusually thin ribs in nearly all patients (table 4, fig 6). Twelve patients had an enlarged heart on chest radiography.

**Laboratory findings**

Serum levels of the aminotransferases were slightly elevated in nearly half of the patients, AST up to 110 U/l (mean 61 U/l) and ALT up to 193 U/l (mean 41 U/l). Blood haemoglobin, white cells and platelets, glucose, gas analysis, and serum concentrations of electrolytes and creatinine were within the normal limits in the majority of patients. No other laboratory parameters were commonly abnormal.

**DISCUSSION**

In this work, we analysed retrospectively the clinical characteristics of patients with MUL in all 85 known Finnish patients at the time of diagnosis. At least 79 were homozygous for the Finn major mutation of the TRIM37 gene. The results confirm that MUL is a distinct but variable entity. The most consistent findings were intrauterine onset growth failure and characteristic craniofacial features. Organ manifestations varied considerably in early childhood. In seven of the families, there was an affected sibling. In five of these, the clinical findings were quite similar in the siblings, but in two families the phenotype showed great variation.

The clinical features have been previously reported.121 01 61 7 These reports, however, were based on small numbers of genetically unconfirmed patients. In our present series we verified the TRIM37 mutations and concentrated on the phenotype in infancy and at the time of diagnosis.

The clinical diagnosis of MUL is a challenge during the first months of life. Infants with intrauterine growth failure are a heterogenous group, and the facial features of patients with MUL are not unique in this group. In addition, relative macrocephaly with wide fontanelles might give a false impression of prematurity or hydrocephalus. However, the pre- and post-natal growth characteristics narrow the group in which MUL should be looked for. Generally, infants with MUL are both abnormally short and light for length.18 Further, most (>70%) healthy infants born SGA show a good catch up growth during the first few months of life.18 19 Consequently, it is in the small subgroup of children born SGA and lacking postnatal catch up growth that the possibility of MUL should be considered.

**Table 3** Organ manifestations at the time of diagnosis in 85 patients with Mulibrey nanism

<table>
<thead>
<tr>
<th>Feature</th>
<th>Findings in age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1 year (n = 29)</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Signs of heart disease</td>
<td>6</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4</td>
</tr>
<tr>
<td>Prominent veins on upper body</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>6</td>
</tr>
<tr>
<td>ASD</td>
<td>3</td>
</tr>
<tr>
<td>VSD</td>
<td>1</td>
</tr>
<tr>
<td>Open ductus arteriosus</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure (CHF)</td>
<td>4</td>
</tr>
<tr>
<td>Pericardial constriction</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>16</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>4</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
</tr>
<tr>
<td>Liver tumours</td>
<td>2</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
</tr>
<tr>
<td>Renal anomaly</td>
<td>4</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>2</td>
</tr>
<tr>
<td>Abnormally located kidney</td>
<td>1</td>
</tr>
<tr>
<td>Hypoplastic kidneys</td>
<td>1</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>1</td>
</tr>
<tr>
<td>Male genital anomaly*</td>
<td>6</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>1/13</td>
</tr>
<tr>
<td>Female genital anomaly†</td>
<td>2</td>
</tr>
<tr>
<td>Hyperplastic labiae</td>
<td>0/16</td>
</tr>
<tr>
<td>Prominent clitoris</td>
<td>0/16</td>
</tr>
<tr>
<td>Wilms’ tumour</td>
<td>0</td>
</tr>
<tr>
<td>Benign renal neoplasia</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
</tr>
<tr>
<td>Yellowish dots in the ocular fundi</td>
<td>20</td>
</tr>
<tr>
<td>Muscular hypotonicity</td>
<td>23</td>
</tr>
<tr>
<td>Large cerebral ventricles</td>
<td>16</td>
</tr>
<tr>
<td>and basal cisterns</td>
<td></td>
</tr>
<tr>
<td>Slow speech development</td>
<td>7</td>
</tr>
<tr>
<td>Slow motor development</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Cutaneous naevi flammei</td>
<td>16</td>
</tr>
</tbody>
</table>

*Males (n = 39); †females (n = 46)
Silver-Russell syndrome (SRS) is the other dysmorphic growth disorder characterised by severe intrauterine growth failure with absence of postnatal catch up growth. The fact that patients with MUL and SRS both are gracile with similar facial dysmorphism makes SRS the most important differential diagnosis. In early infancy, feeding difficulties occur in both MUL and SRS. These two conditions, however, develop their own distinct characteristics. Clinodactyly, small face with marked triangularity, micrognatia, downturned mouth corners, and skeletal asymmetry with hemihypertrophy are characteristics of SRS. Hepatomegaly, heart failure due to pericardial constriction or cardiomyopathy, yellow dots in ocular fundi, cortical thickening, and fibrous dysplasia of long bone do not occur in SRS. SRS, however, is considerably variable both clinically and genetically. A mild phenotype, for example, is observed in SRS patients with maternal uniparenteral disomy of chromosome 7. Furthermore, atypically mild cases with MUL have been diagnosed in three Finnish infants since the analysis of TRIM37 became available.

The TRIM37 protein is localised to peroxisomes, but its function is unknown. It is expressed in several tissues. Thus, it is no surprise that MUL shares features with other peroxisomal disorders. These include growth failure, facial dysmorphism with midface hypoplasia, retinal pigmentary changes, skeletal dysplasia, skin changes, cardiac involvement, muscular hypotonicity, and hepatomegaly. In particular, Refsum’s disease, with its cardiac manifestations such as cardiomyopathy leading to congestive heart failure, resembles many of the features of MUL. Lack of major neurological manifestations and mental retardation are the most notable differences between Mulibrey nanism and the known peroxisomal disorders. The only neurological dysfunctions occurring in MUL are mild muscular hypotonicity and slight delay in motor and speech development.

Constrictive pericarditis with restrictive cardiomyopathy, when present, dominates the clinical state as well as the prognosis. However, only 12% of our patients had congestive heart failure at the time of diagnosis (median 2.1 years) and even half of the adult patients were free of major heart problem. In contrast, almost all patients...
Clinical features of MUL

Clinical features of MUL 97
tumour development remains to be solved. 27 29

are particularly well suited for eating by sucking, with the

respiratory function and nutrition, and may also contribute

important because dysphagia poses a threat to the child's

delay,17 and muscular hypotonicity all probably contribute to

delay,17 and muscular hypotonicity all probably contribute to

Infants with MUL, however, have a hypoplastic and ante-

In conclusion, we have delineated the phenotype and
defined the clinical diagnostic criteria in the genotypically

Hepatomegaly was obvious in half of the patients at the
time of the diagnosis. Histopathological studies showed
chronic passive congestion, indicating that the liver enlarge-

Feeding difficulties are a major clinical problem during
infancy. In general, swallowing is poorly coordinated in
infants born prematurely or SGA and the degree of
dysfunction is inversely related to the degree of immaturity
and growth failure.27 28 The oral anatomy of mature infants
are particularly well suited for eating by sucking, with the
tongue being relatively large, filling the oral cavity. 27 29

Patients with MUL are prone for respiratory tract infec-
tions and have an exceptionally high risk for pneumonia. No
immunological defects have been demonstrated in
MUL and the basis of this susceptibility is not known.
Possibly, the pneumonia may result from aspiration.
Interestingly, infections quite easily lead to respiratory
failure, suggesting that the ability to cope with the stress of
an infection is subnormal. In our study, two patients
died in infancy from an infection. At autopsy, both were
found to have adrenal cortical hypoplasia. Subnormal stress
tolerance could be due to adrenal hypoplasia with adenocor-
tical failure.

While growth failure, the craniofacial features, and
hepatomegaly are important clinical consequences of MUL,
they are also common features of other dysmorphic condi-
tions. Hence, the characteristic ocular and radiological
findings, cutaneous naevi flammei, fibrous dysplasia of the
long bones, or signs of the Mulibrey heart disease are
confirmatory of the MUL diagnosis. Based on our present
findings and clinical experience, we propose revised diag-

Table 5 Diagnostic signs and their prevalence in 85
patients with Mulibrey nanism (46 females and 39 males)
For the diagnosis, three major signs with one minor sign are
required, or two major signs with three minor signs

<table>
<thead>
<tr>
<th>Signs</th>
<th>Frequency(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major signs</td>
<td></td>
</tr>
<tr>
<td>Growth failure (A or B or C)</td>
<td></td>
</tr>
<tr>
<td>A) small for gestational age (SGA)</td>
<td>95</td>
</tr>
<tr>
<td>B) height in children 2.5 SDS below population</td>
<td>94</td>
</tr>
<tr>
<td>C) height in adults 3.0 SDS below population</td>
<td>90</td>
</tr>
<tr>
<td>Characteristics radiological findings (A or B)</td>
<td></td>
</tr>
<tr>
<td>A) slender long bones with thick cortex</td>
<td>93</td>
</tr>
<tr>
<td>B) low and shallow (U-shaped) sella turcica</td>
<td>89</td>
</tr>
<tr>
<td>Characteristics craniofacial features</td>
<td></td>
</tr>
<tr>
<td>Scaphocephaly, triangular face, high and</td>
<td>90</td>
</tr>
<tr>
<td>broad forehead, low nasal bridge and telecanthus</td>
<td></td>
</tr>
<tr>
<td>Characteristics ocular findings</td>
<td></td>
</tr>
<tr>
<td>Yellowish dots in retinal mid peripheral region</td>
<td>79</td>
</tr>
<tr>
<td>Mulibrey nanism in a sibling</td>
<td>17</td>
</tr>
<tr>
<td>Minor signs</td>
<td></td>
</tr>
<tr>
<td>Peculiar high pitched voice</td>
<td>96</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>70</td>
</tr>
<tr>
<td>Cutaneous naevi flammei</td>
<td>65</td>
</tr>
<tr>
<td>Fibrous dysplasia of long bone</td>
<td>25</td>
</tr>
</tbody>
</table>

Figure 6 The small bell shaped thoracic cage with thin ribs (arrow). Note the characteristically rounded heart shadow frequently seen in children with MUL.

We want to thank the families of our patients. We also express our
grateful recognition and gratitude to the patients’ local physicians, particularly Drs S Friman, J Komulainen, H-L Lenko and M Pere, for decades of co-work. This study was supported by grants from the Finnish Foundation for Paediatric Research, the Finnish Academy, and Finska Läkaresällskapet.

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Owing to a fault in the production process an error was introduced to figure 2 of this paper. The last gene at the bottom of the figure should correspond to CASQ1, and not to ATP1A2, which is mapped just above it. We apologise for this error.
Mulibrey nanism: clinical features and diagnostic criteria

N Karlberg, H Jalanko, J Perheentupa and M Lipsanen-Nyman

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