

Linkage to 18qter differentiates two clinically overlapping syndromes: congenital cataracts-facial dysmorphism-neuropathy (CCFDN) syndrome and Marinesco-Sjögren syndrome

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The Marinesco-Sjögren syndrome (MSS) (MIM 248800) is an autosomal recessive condition characterised by cataracts, ataxia, and growth and mental retardation. Chronic myopathy is a common feature. Peripheral neuropathy and acute rhabdomyolysis have been described occasionally in MSS. To date, no gene for it has been localised.

Congenital cataracts-facial dysmorphism-neuropathy syndrome (CCFDN) (MIM 604168) is a recently delineated autosomal recessive condition,¹ so far only described in a specific gypsy group originating from Bulgaria. This disorder was localised by linkage analysis to 18qter, telomeric to the marker D18S1141.² CCFDN alleles showed a highly conserved haplotype in the region D18S1141-D18S70-D18S1268 consistent with genetic homogeneity and a single founder mutation. Since then, the disease locus has been reduced to the interval located between markers D18S1095 and D18S1390.^{3,4}

MSS and CCFDN share common clinical features and are considered to be differential diagnoses.

Recently, Merlini *et al*⁵ proposed that the CCFDN syndrome and one subtype of MSS (Marinesco-Sjögren/myoglobinuria), also only described in gypsy patients, are genetically identical. We report here the clinical and linkage analysis of one gypsy family and one Turkish family in which patients presented with congenital or juvenile cataracts and ataxia. Both families were initially diagnosed as MSS. However, our study shows that they are clinically and genetically distinct. We found that the gypsy family had CCFDN features and was linked to 18qter whereas the Turkish family had typical MSS features and was not linked to 18qter. Here, we confirm the clinical overlap between the CCFDN and MS syndromes and show that they are distinct genetic entities.

CASE REPORTS

Family 1

A sister (patient 1) and a brother (patient 2) of Turkish origin were referred to the neuropaediatric clinic because of failure to thrive, psychomotor delay, major ataxia, and hypotonia. They were the fourth and fifth children of healthy, consanguineous parents (fig 1A). Two paternal aunts, who died during adolescence, were reported by the parents to have had a similar phenotype to the index cases.

Both patients were born after a normal pregnancy and delivery. They underwent clinical evaluation at 1.5 and 3 years respectively and were followed up for 15 years.

Short stature and reduced head circumference were present from early childhood (-2 SD for weight, -3 SD for height, and -2 SD for head circumference). No facial dysmorphic feature was found.

A severe static and kinetic cerebellar syndrome has always been present. Deep tendon reflexes were present and there

Key points

- Congenital cataracts-facial dysmorphism-neuropathy (CCFDN) syndrome and Marinesco-Sjögren syndromes are two entities with major clinical overlap including congenital cataracts, growth retardation, psychomotor delay, ataxia, skeletal deformities, and hypogonadism.
- Genetic identity of the two syndromes has been suggested but clinical and molecular studies of two families allowed us to show that these syndromes are clinically and genetically distinct.
- Major features of MSS that distinguish it from CCFDN are the occurrence of more severe mental retardation, marked cerebellar atrophy, chronic myopathy with specific ultrastructural features on muscle biopsy, and the absence of peripheral neuropathy, facial dysmorphism, microcornea, and linkage to 18qter.

was neither sensory deficit nor pyramidal signs. Patient 1 acquired the sitting position at 2.5 years of age and independent walking at 6.5 years of age, but her stance and gait has remained unsteady. At 2.5 years of age, patient 2 was able to sit unsupported and he walked at 9 years of age.

Expressive language occurred at the ages of 4.5 and 7 years, respectively. Both sibs attended special education classes and reading acquisition occurred at 15 and 16.5 years, respectively.

For both patients, magnetic resonance imaging (MRI) of the brain showed marked cerebellar atrophy predominantly affecting the vermis. There was no ventricular dilatation and the corpus callosum was normal (fig 2). Bilateral pes planus valgus and kyphosis related to major hypotonia and muscle weakness were observed. Both patients had distal joint laxity and no muscular retraction. Despite physical therapy, patient 2 developed lumbar scoliosis at 16 years of age. At 16 and 17.5 years of age, respectively, hypotonia was less marked than in infancy and proximal and distal muscle weakness was mild (Medical Research Council scale grade 4/5).

Muscle biopsy performed at 5 and 6.5 years of age, respectively, showed similar myopathic changes including variation in muscle fibre size, acid phosphatase positive rimmed vacuoles, as well as rare necrotic and regenerating fibres. Electron microscopy disclosed several dense membranous structures surrounding myonuclei (fig 3). There were no abnormal mitochondria.

Cataracts developed rapidly and were operated on, in the two sibs, at 4.5 and 6.5 years of age, respectively. Ophthalmological examination disclosed nystagmus in both children, but vision

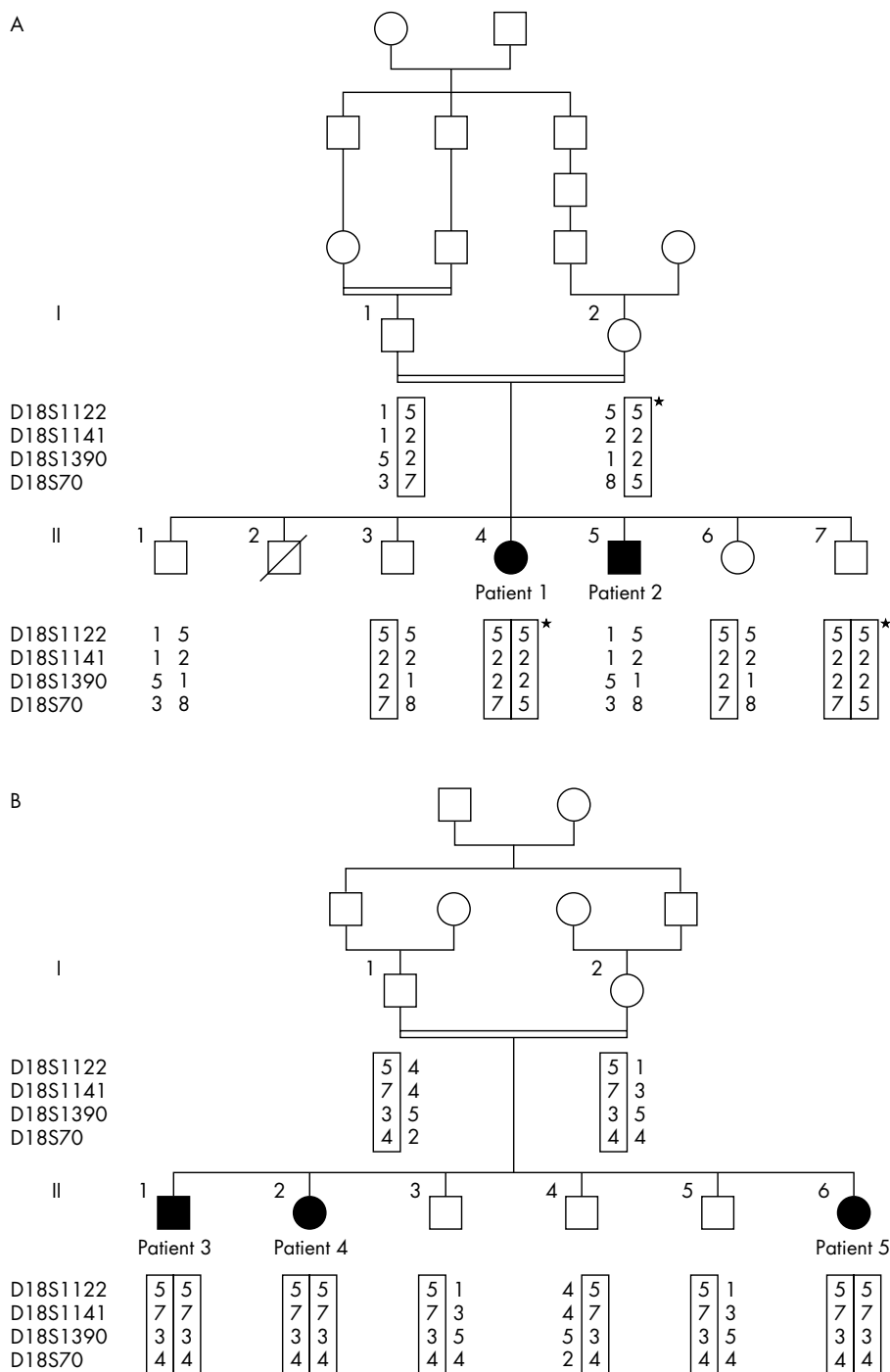


Figure 1 Pedigree of the families and genotyping results. (A) Family 1. (B) Family 2. Markers are indicated on the left and are organised from top to bottom in the centromeric to telomeric order. The *CCFDN* locus is located between markers D18S1141 and D18S1390. One of the two parental haplotypes is boxed. For family 2, the haplotype linked to the disease is boxed.

was satisfactory (patient 1 6/6 for both eyes, patient 2 6/8 for both eyes). No ocular malformation or oculomotor apraxia were found.

Both sibs had hypogonadism. At 17.5 years of age, patient 1 had primary amenorrhoea with secondary sexual development. Patient 2 presented with non-ectopic small testes and retarded pubic hair growth at 16 years of age. Endocrine investigations showed hypergonadotrophic hypogonadism for them both.

Metabolic, haematological, and lipid investigations were normal. At 16 and 17.5 years of age, respectively, serum creatine kinase levels were slightly increased at 305 UI/l (normal

<200 UI/l) for patient 2 and within the normal range for patient 1.

Family 2

A gypsy family was referred for genetic counselling as three sibs out of six were affected with severe visual and neurological impairment (fig 1B). This family originated from eastern Europe (no other information on the country of origin is available) and has been based in France for at least three generations. The healthy parents were first cousins. Three sibs had a comparable past medical history.

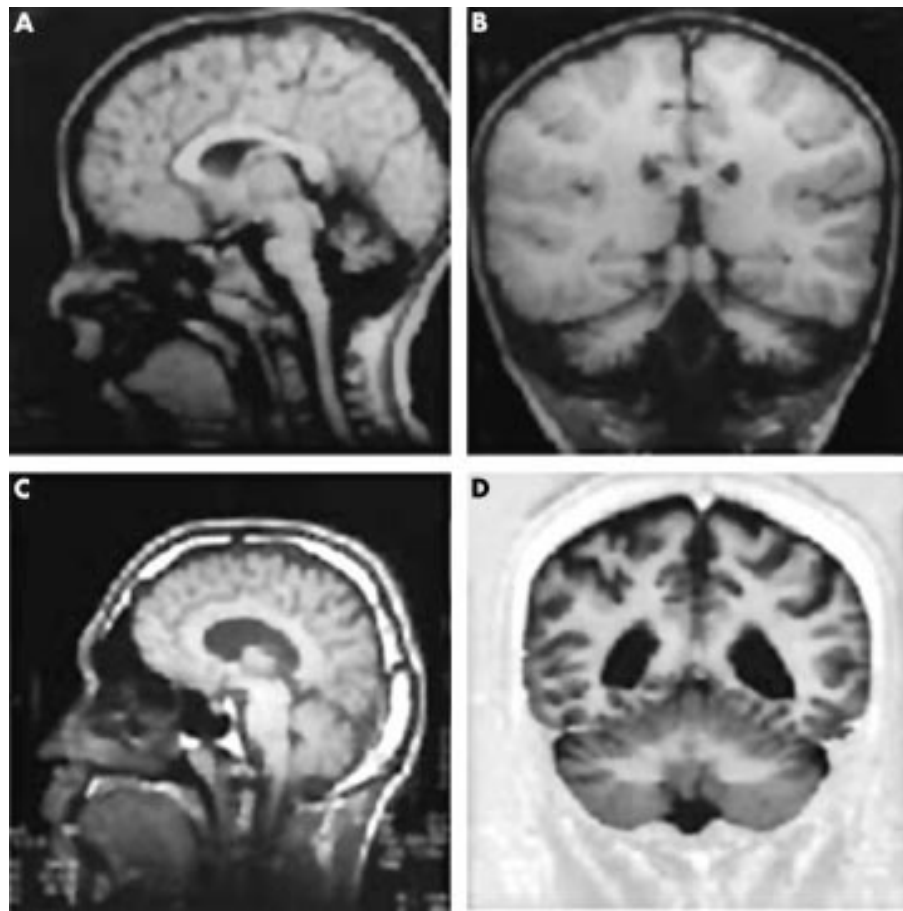


Figure 2 Brain lesions on MRI. (A, B) Patient 1 with MSS: marked cerebellar atrophy. (C, D) Patient 3 with CCFDN: diffuse cerebral atrophy with enlargement of the lateral ventricles, discrete cerebellar atrophy, and thin corpus callosum.

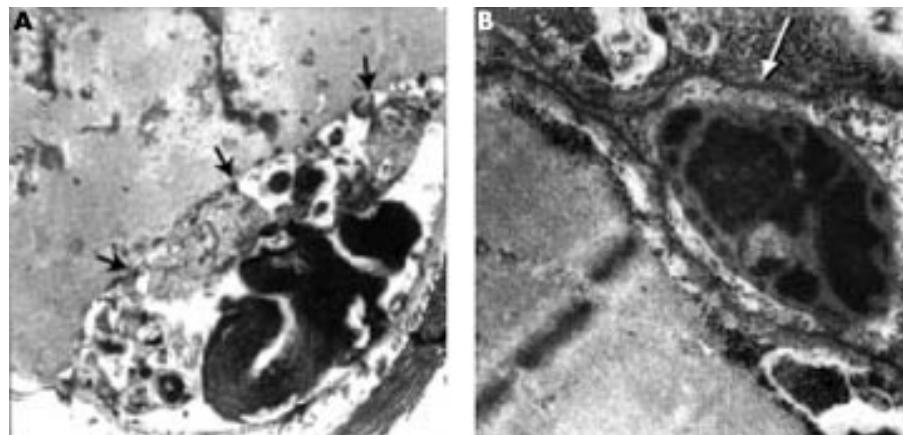


Figure 3 Electron microscopy on muscular biopsy of patient 2. (A) Subsarcolemmal rimmed vacuole (arrows) containing numerous small sarcoplasmic debris and pseudomyelinic whorls. Foci of myofibrillar disorganization close to the vacuole. (B) Dense membranous structure (arrows) surrounding an apoptotic nucleus with fragmented chromatin.

They were born after a normal pregnancy and delivery. The first manifestation of the condition was congenital cataracts operated on during the first months of life. The clinical course was marked by mild psychomotor delay with acquisition of walking between 2 and 3 years of age. Distal muscle weakness and skeletal deformities appeared during childhood.

We examined the patients at the age of 22 years (male patient 3), 16 years (female patient 4), and 12 years (female patient 5), respectively. The height of patients 3 and 5 was 1.50 m (-4 SD) and 1.30 m (-3 SD), respectively. The height of

patient 4 could not be measured because of major kyphoscoliosis. Weight was at -2 SD for all three patients. The head circumference was within normal limits. Mild dysmorphic features with prominent midface and wide lips were only found in male patient 3. The three sibs presented with kyphoscoliosis, foot deformities (pes cavus or equinovarus), and genu recurvatum. Patient 4 needed surgery for major disabling kyphoscoliosis. Neurological examination showed in the three sibs lower limb areflexia and amyotrophy while these features were subtle for the upper limbs. The deficit was predominantly



Figure 4 Close up photographs of the midface showing microcornea in all the affected sibs of family 2. The horizontal diameter of the cornea was respectively (A) 8 mm (the right eye, RE) in patient 3 (left eye (LE) is buphthalmic owing to an accidental trauma). (B) 8 mm (RE) and 10 mm (LE) in patient 4. (C) 9 mm (RE) and 10 mm (LE) in patient 5.

Table 1 Comparison of MSS and CCFDN features

Clinical features	MSS	CCFDN	Family 1		Family 2		
			Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Short stature	+	+	+	+	+	+	+
Microcephaly	+/-	-	+	+	-	-	-
Facial dysmorphism	-	+	-	-	+	-	-
Microcornea	-	+	-	-	+	+	+
Cataracts	+	+	+	+	+	+	+
Nystagmus	+	+	+	+	+	+	+
Skeletal deformities	+	+	+	+	+	+	+
Psychomotor delay	Mild to severe	Mild	+	+	+	+	+
Hypotonia	+	-	+	+	-	-	-
Cerebellar ataxia	+	Mild	+	+	Mild	+	+
Peripheral neuropathy	+/-	+	-	-	+	+	+
Acute rhabdomyolysis	-	+/-	-	-	-	-	-
Raised serum creatine kinase	+/-	-	-	+	-	-	-
Myopathic changes on biopsy	+	-	+	+	NA	NA	NA
Hypogonadism	+ Hypergonadotrophic	+ Hypogonadotrophic?	+	+	-	-	-
Cerebellar atrophy	+	+/-	+	+	Discrete	NA	Discrete
Cerebral atrophy	+/-	+	-	-	+	NA	+

NA: not available.

motor but was associated with vasomotor disturbances and mild sensory deficit with hypoesthesia and decreased pallesthesia of the four extremities. These findings were consistent with a sensorimotor polyneuropathy. Moreover this polyneuropathy was associated with mild cerebellar ataxia more pronounced in patients 4 and 5 than in patient 3.

Nerve conduction studies performed in the three patients showed reduced motor and sensory nerve conduction velocities, at 30 m/s and 40 m/s, respectively, indicating a demyelinating neuropathy. Motor action potentials were of more reduced amplitude than sensitive action potentials. Electromyographic examination showed a neurogenic atrophy pattern affecting the distal segments. These findings were consistent with a predominantly motor demyelinating peripheral neuropathy.

Brain MRI, performed on patients 3 and 5, showed diffuse cerebral atrophy with enlargement of the lateral ventricles and discrete cerebellar atrophy. The corpus callosum of patient 3 was thin (fig 2).

Ophthalmological examination showed microcornea in all affected subjects. The axial length of the eyes was within normal limits on ultrasound examination, excluding associated micropthalmos (fig 4). Visual impairment with nystagmus was noted in the three sibs: patient 3 only had remaining light perception and the vision of the two sisters was no more than 6/60 in both eyes. Fundus examination showed optic atrophy in patient 3. No feature of hypogonadism was observed in the three patients.

Endocrine, biochemical, haematological, and lipid investigations were normal.

MATERIAL AND METHODS

Genomic DNA was extracted from peripheral blood by standard methods. Samples were available from the parents and all the affected and healthy children. Informed consent was obtained from both families.

We genotyped the Genethon markers D18S1122, D18S1141, D18S70,⁵ and marker D18S1390,^{3,4} amplified by the forward

primer 5'-AACGGTTTGGTATTTCCTCA-3' and the reverse primer 3'-CAGTTCAACAAGGGATTGG-5'.

We amplified all markers by PCR using one of the primers labelled with γ -32P-dATP (3000 mCi/mmol/l). PCR was performed using for each reaction 150 ng of template DNA, 0.4 μ mol/l of each primer, 1 U of *Taq* polymerase (Sigma), and 2 μ l of buffer (10 mmol/l tris HCl, pH 8.3, 50 mmol/l KCl, 200 μ mol/l of each deoxynucleotide triphosphate, 1.5 mmol/l MgCl₂) in a final reaction volume of 10 μ l. PCR amplification consisted of 35 cycles (94°C for 10 seconds, 50°C-60°C for 15 seconds, 72°C for 20 seconds). PCR products were separated on 6% denaturing polyacrylamide gels followed by autoradiography. Alleles were scored manually with allele 1 being the smallest.

RESULTS

The two families were tested for linkage at the CCFDN-MSS/myoglobinuria locus, which is located between markers D18S1095 and D18S1390 on chromosome 18qter.²⁻⁴ Patients 1 and 2 from family 1 share no parental haplotype over the region distal to D18S1141, therefore excluding linkage to the CCFDN locus. In addition, the healthy children II.1 and II.7 share identical haplotypes with patients 1 and 2, respectively, further supporting exclusion of linkage to 18qter (fig 1A). In family 2 (fig 1B), all three affected sibs were homozygous for the four consecutive 18qter markers (D18S1122 to D18S70), while the three healthy children were heterozygous for the same haplotype. Lod score calculation, including the consanguinity loops,^{6,7} gave a maximum value of 2.57 at $\theta=0$ for linkage to the D18S1122-D18S70 haplotype (the frequency of the haplotype was estimated at a safe upper value of 0.05). Linkage of family 2 to the CCFDN locus is therefore considered proven,⁸ a conclusion also supported by the ethnic origin and clinical features of the patients.

DISCUSSION

The presence of congenital cataracts associated with mental retardation, ataxia, and peripheral neuropathy in an inbred family narrows the diagnostic search to a few syndromes:

Marinesco-Sjögren syndrome, Marinesco-Sjögren-like syndrome (MIM 248810),⁹ CCFDN,¹ polyneuropathy-cataract-deafness-retardation syndrome (MIM 212710),¹⁰ or cataract-deafness-cerebellar ataxia-psychosis and dementia (MIM 117300).¹¹

The patients of family 1 were classified as presenting a classical MS syndrome in regard to the cerebellar atrophy on MRI and characteristic pathological findings on light and electron microscopy of the muscle.

The patients of family 2 were initially diagnosed as presenting a MSS phenotype because of the association of cataracts, mental retardation with ataxia, and skeletal findings, but they differed clinically from the previous family by the presence of microcornea, marked peripheral neuropathy, and a moderate cerebellar atrophy on MRI.

The clinical discordance between the two families was confirmed by molecular studies. Indeed the localisation of the disease gene in family 2 to the telomeric part of chromosome 18q indicates the diagnosis of CCFDN and will allow indirect prenatal diagnosis requested by the relatives. However, linkage to 18qter was ruled out for family 1 with typical MSS. Molecular studies in these two families allowed us to differentiate the MS and CCFDN syndromes as being distinct genetic entities. Whereas Merlini *et al*⁸ proposed that the CCFDN syndrome and one subtype of MSS with acute rhabdomyolysis are genetically identical, we show here that a family with classical MSS is not linked to the 18qter region.

Comparison of the reported features of MS and CCFDN syndromes (table 1) shows a clinical overlap including congenital cataracts, nystagmus, somatic and mental retardation, ataxia, skeletal deformities, and hypogonadism. Major differences between the two syndromes are the occurrence of mild facial dysmorphism, microcornea, and demyelinating neuropathy in the CCFDN syndrome and the presence of myopathic changes and marked cerebellar atrophy leading to severe ataxia in the MSS.

Facial dysmorphism described in the CCFDN seems to become more obvious during late childhood and appears to be more prominent in males than in females.¹ Indeed, in family 2, the male patient was the only affected person presenting dysmorphic features.

Concerning ocular abnormalities, cataracts in MSS are usually congenital but may also occur during childhood. No other developmental abnormality of the eye has been reported in MSS, as opposed to microcornea which appears to be a major clinical and probably a diagnostic criterion of CCFDN.

Moreover MSS and CCFDN syndromes differ regarding myopathic changes. Progressive muscle weakness and muscle atrophy were reported to be among the cardinal signs of MSS.¹² Most muscle biopsy reports have described myopathic changes including variation in muscle fibre size, rimmed vacuoles, necrotic and regenerative fibres, numerous internal nuclei, nuclear degeneration, endomysial fibrosis, and fatty replacement.¹²⁻¹⁷ Sewry *et al*¹³ suggested that a unique dense membranous structure associated with nuclei in muscle fibres could be a specific ultrastructural feature of MSS. Sasaki *et al*¹⁶ and Suzuki *et al*¹⁷ confirmed its presence in MSS patients, whereas it was shown to be inconstant in other studies.¹⁵ Muscle biopsy of the patients in family 1 showed structures characteristic of MSS (fig 3B). No muscle biopsy was available from the patients in family 2, but Tournev *et al*¹⁹ described only neurogenic changes on muscle biopsy of a CCFDN patient.

Recently, patients with MSS and acute rhabdomyolysis without underlying chronic myopathy were shown to be linked to the CCFDN locus.⁴ However, all patients from the three gypsy families reported had peripheral neuropathy, all males had facial dysmorphism, and one patient had microphthalmia. They differ from classical CCFDN patient by cerebellar dysfunction in all of them and cerebellar atrophy in two cases, these signs not usually being features of CCFDN. Even if these patients could be considered as atypical MS patients, we propose that rhabdomyolysis could, in fact, be a rare feature of CCFDN.

Ataxia is a leading feature of MSS usually because of marked cerebellar atrophy. Mild cerebellar ataxia has been described in CCFDN patients,¹ but MRI showed cerebral and spinal atrophy with enlargement of the lateral ventricles without cerebellar atrophy except in one case. We illustrate in fig 3 the differences between the MRI features of MSS and CCFDN.

Demyelinating peripheral neuropathy is a leading CCFDN feature but was also reported in several cases of MSS.¹⁸⁻²⁴ Again, the patients described by Muller-Felber *et al*²⁰ are the same as those who were subsequently reported by Merlini *et al*⁸ as being linked to the CCFDN locus. Further genotype-phenotype correlation should clarify whether all Marinesco-Sjögren patients with peripheral neuropathy are linked to the CCFDN locus or not. However, we have proven by molecular studies that a family with classical MSS without peripheral neuropathy and a family with CCFDN syndrome are genetically distinct. Family 1 should help to identify the genetic localisation of the classical MSS gene, since the maximum expected lod score for this family alone is 2.9.

For the time being, we propose to restrict the diagnosis of Marinesco-Sjögren syndrome to patients with cerebellar atrophy, hypotonia, and myopathic changes but without facial dysmorphism, microcornea, or peripheral demyelinating neuropathy. However, clinical overlap between MSS and CCFDN is obvious and molecular investigations should help to achieve a final classification of these conditions.

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