American Journal of Medical Genetics 133A:197–201 (2005)

Clinical Report

Marinesco–Sjögren Syndrome in a Male With Mild Dysmorphism

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Marinesco–Sjögren syndrome (MSS) is a rare, autosomal recessive disorder comprising cataracts, cerebellar ataxia caused by cerebellar hypoplasia, mild to moderate mental retardation, neuromuscular weakness, short stature, hypergonadotrophic hypogonadism, and skeletal anomalies. The syndrome was recently mapped to chromosome 5q31, but there is evidence for genetic heterogeneity, and no gene has been identified. We report a 5-year-old male with cataracts, ataxia, a progressive cerebellar atrophy, developmental delay, seizures, hypotonia, and a sensorimotor neuropathy consistent with many cases of MSS. He also had mild craniofacial dysmorphism consisting of hypertrichosis and synophrys, deep-set eyes with epicanthic folds, a flat philtrum, a high palate, short thumbs, and a wide sandal gap between the first and second toes. Skeletal findings included an increased kyphosis. We reviewed the literature on MSS to determine if craniofacial dysmorphism and the presence of neuropathy and/or myopathy would prove to be diagnostically useful in this phenotypically heterogeneous condition. The majority of cases of MSS do not have craniofacial dysmorphism, but other cases have been reported with features such as ptosis or a myopathic facies that are likely to reflect the underlying myopathic or neuromuscular processes in MSS.

KEY WORDS: Marinesco–Sjögren syndrome; cataracts; cerebellar ataxia; congenital cataracts–facial dysmorphism–neuropathy syndrome; chylomicron retention disease; dysmorphology

INTRODUCTION

Marinesco–Sjögren syndrome (MSS) is a rare, multisystem disorder with marked phenotypic variability. The cardinal findings are cataracts, cerebellar ataxia caused by cerebellar hypoplasia, mild to moderate mental retardation, short stature, hypergonadotrophic hypogonadism, and skeletal anomalies [Williams et al., 1996; Lagier-Tourenne et al., 2003]. However, patients with MSS have also had variable neuromuscular symptoms and signs including hypotonia and muscular weakness, peripheral neuropathy, seizures, and rhabdomyolysis. The inheritance is autosomal recessive. MSS was recently mapped to chromosome 5q31 in two large consanguineous families, but there is evidence for genetic heterogeneity and no gene has yet been cloned [Jones et al., 2003; Lagier-Tourenne et al., 2003]. An accurate description of the clinical features is therefore still important in the diagnosis of this pleiotropic condition.

We report a 5-year-old male who had MSS. His presentation included cataracts, ataxia with progressive cerebellar atrophy, developmental delay, seizures, hypotonia, and a sensorimotor neuropathy. He also had mild but distinctive craniofacial dysmorphism. We, therefore, reviewed the published literature on MSS to delineate the extent of similar dysmorphism in other MSS patients and provide a summary of reported facial and digital anomalies in MSS.

CLINICAL REPORT

The proband (Figs. 1 and 2) was the first child born to healthy, non-consanguineous parents. A paternal aunt had epilepsy, but the family history was otherwise unremarkable. The pregnancy was normal apart from hyperemesis gravidarum, and he was born at 38 weeks gestation with a weight of 3,500 g (75th centile), length of 51 cm (95th centile), and head circumference of 34.5 cm (50th centile). His initial progress was normal, but he had tonic-clonic seizures from 9 months of age. At 1 year, he had a roseola infection, and his development was said to have deteriorated following this illness. At 19 months of age, bilateral cataracts and optic atrophy were seen on ophthalmology examination. His cataracts were not removed as they did not interfere with vision. Investigations with a magnetic resonance imaging (MRI) scan of the brain showed hypoplasia of inferior cerebellar vermis and hemispheres and optic atrophy at 23 months. A follow-up scan at 46 months showed worsening cerebellar vermian and cortical atrophy, smaller optic nerves and chiasm, and evidence for diffuse cerebral cortical atrophy. Nerve conduction studies performed at 13 months were consistent with a neuropathy with a greater reduction in the sensory component (right peroneal nerve

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Received 11 June 2004; Accepted 25 October 2004

DOI 10.1002/ajmg.a.30504

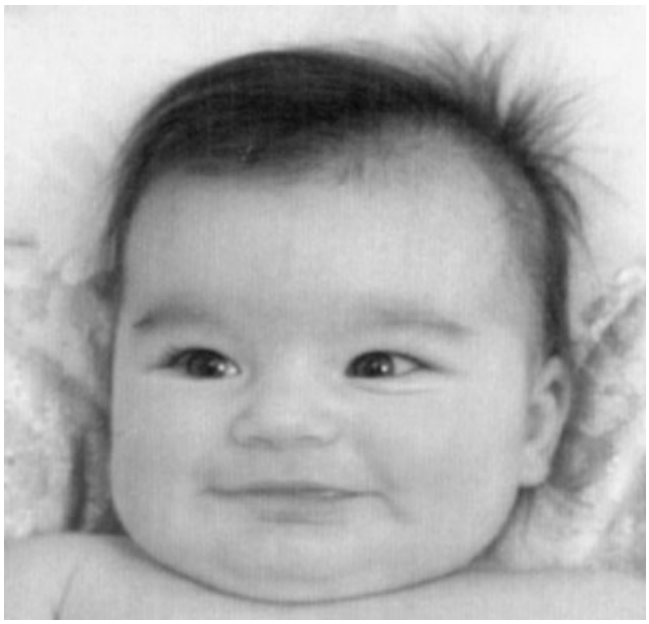

Fig. 1. Facial view of the proband at 3 months of age.

motor conduction 38 m/s, normal range 42.2–62.8; and sural sensory response 33 m/s, normal range 47.6–62). Amplitudes and distal latencies were normal. The electromyogram (EMG) was normal. A sural nerve biopsy revealed thinly myelinated axons and a 30% loss of small and large axons, findings that were suggestive of primary or secondary demyelination. No "onion bulb" formations were noted. The muscle biopsy was essentially normal, and in particular was negative for ragged red fibers or lysosomal inclusions when examined by electron microscopy. An electroencephalogram (EEG) showed bilateral independent epileptiform sharp waves that were consistent with the patient's seizure disorder.

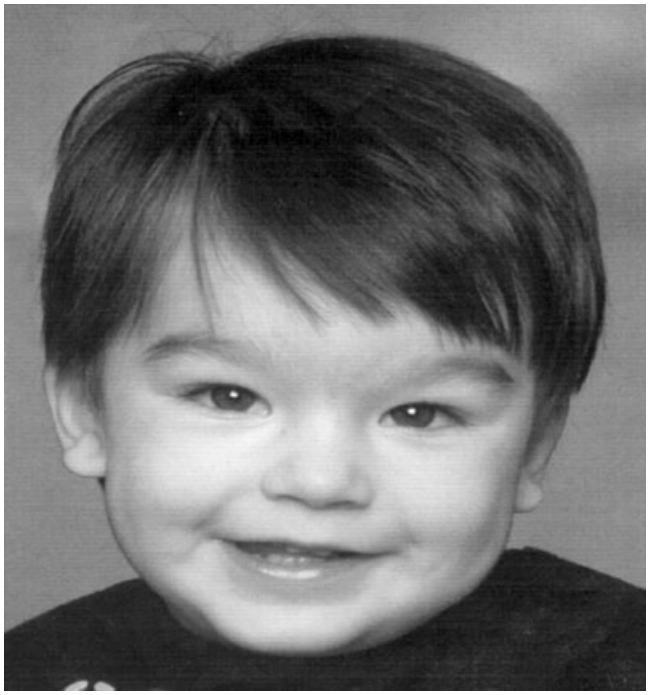

Fig. 2. Facial view of the proband at 18 months of age.

When last reviewed at 5 years and 1 month, his medical problems included bilateral polar cataracts, cerebellar atrophy with truncal ataxia, developmental delay, generalized hypotonia, lower extremity weakness, and tonic-clonic seizures controlled by medication. His examination showed mild dysmorphism with hypertrichosis and synophrys, deep-set eyes with epicanthic folds, a flat philtrum and a thin upper lip, and a high arched palate. His thumbs were short, and there was a wide sandal gap between the first and second toes. His muscles had a doughy texture, and he had excess subcutaneous fat. The spine showed a mildly exaggerated kyphosis, and he had dorsiflexion of the toes bilaterally. Neurological examination showed end gaze nystagmus and titubation. He had limb hypertonia with reduced but symmetrical deep tendon reflexes and his plantar responses were extensor.

An MRI scan of the brain at 5 years showed stable atrophy of the cerebellum, optic nerves and chiasm, cerebral cortex with stable, non-specific patchy periventricular white matter T2 prolongation. The spinal cord was normal. He has had extensive metabolic investigations including normal urine amino acids, organic acids and mucopolysaccharides, normal serum lactate, pyruvate, and plasma lysosomal enzymes. A serum creatine kinase (CK) level was within the normal range. Peroxisomal studies showed normal levels of very long chain fatty acids in fibroblasts and normal phytanic acid oxidation, plasmalogen synthesis, pipecolic acid, and catalase distribution. A spinocerebellar atrophy (SCA) panel excluded the trinucleotide expansions associated with SCA6, SCA7, SCA8, Machado–Joseph disease, dentato-rubral-pallido-luysian atrophy (DRPLA), and Friedreich ataxia. Testing for carbohydrate-deficient glycoprotein syndrome was negative and an alpha feto-protein level was normal. Screening for mitochondrial point mutations was negative for the MELAS, MERFF, and NARP mutations. Chromosome analysis showed an apparently normal male karyotype (46XY), and screening with subtelomeric probes was negative. Ceroid lipofuscinosis was excluded by nerve biopsy. Other investigations comprised a normal skeletal survey and echocardiogram.

MATERIALS AND METHODS

We reviewed 75 published cases of MSS. We recorded the ophthalmological, neurological, and orthopedic manifestations together with developmental history, craniofacial dysmorphism, digital anomalies, and MRI scan findings. The cases reviewed were the following: Alter et al. [1962] (4 cases); Skre and Berg [1977] (11 cases); Hakamada et al. [1981] (1 case); Alexianu et al. [1983] (1 case); Walker et al. [1985] (4 cases); Herva et al. [1987] (4 cases); Superneau et al. [1987] (6 cases); Sewry et al. [1988] (3 cases); Komiyama et al. [1989] (4 cases); Bromberg et al. [1990] (2 cases); Katafuchi et al. [1990] (1 case); Tachi et al. [1991] (1 case); Torbergsen et al. [1991] (7 cases); Kodama et al. [1992] (2 cases); Zimmer et al. [1992] (6 cases); Ishikawa et al. [1993] (1 case); Brogdon et al. [1996] (9 cases); McLaughlin et al. [1996] (3 cases); Williams et al. [1996] (1 case); Farah et al. [1997] (2 cases); Mller-Felber et al. [1998] (4 cases); Aguglia et al. [2000] (2 cases); Reinker et al. [2002] (2 cases). The case reports of Brogdon et al. [1996] and Superneau et al. [1987] appear to describe the same family, and the total number of patients counted from both reports was 9 rather than 15.

RESULTS

We undertook a literature review in order to determine if craniofacial dysmorphism and minor anomalies were useful aids to diagnosis and to document the incidence of physical

findings in MSS. We reviewed 75 published cases of MSS, among them 37 males, 35 females, and 3 cases in which the sex of the patient was not stated. Parental consanguinity was noted in 30/75 (40%) parents, including the consanguineous pedigree of Skre and Berg [1977]. The cardinal clinical findings of MSS from this review have been summarized in Table I and compared to one previous large study [Williams et al., 1996]. Data on developmental delay was omitted from the Table as information from case reports was frequently lacking.

Cataracts were stated to be present in 68/75 (91%) of patients. The age of onset of the cataracts ranged from birth to 8 years of age in one case [Herva et al., 1987]. Strabismus was also very common and was found in 33/75 (44%) of patients. Additional ophthalmological findings included optic atrophy, glaucoma, microphthalmia, and retinal degeneration.

The commonest neurological findings in this cohort attributed to cerebellar hypoplasia were truncal or limb ataxia in 54/75 (72%) and dysarthria in 34/75 (45%). Nystagmus was present in 27/75 (36%) and tremor was noted in 12/75 (16%), but dysmetria, dysdiadochokinesis, and titubation were less common. Muscle atrophy was reported in 38/75 (51%) patients, truncal or limb hypotonia in 40/75 (53%), and muscle weakness in 27/75 (36%). Cerebellar atrophy was the commonest MRI finding and was noted in 26/75 (37%). Cerebral and brainstem atrophy was found in 5/75 (7%). Two patients had cerebellar atrophy with brain atrophy and MRI findings suggestive of white matter disease (3%). Rare findings were optic atrophy, pachygyria, a posterior fossa cyst, and absence of the septum pellucidum or corpus callosum [Georgy et al., 1998]. Developmental milestones were delayed and developmental achievement from mild delay to severe mental retardation was reported.

The presence of myopathy or neuropathy may help in differentiating between types of MSS. In our review, in over half of the cases for which a biopsy was performed, a myopathy was noted. Features were variable and included variable fiber size, central nuclei, split fibers, and other evidence of degenerating and regenerating fibers. Ultrastructural analysis has shown mitochondrial abnormalities and an unusual membranous structure surrounding or contiguous with the nuclear membrane. Neuropathy has been reported in approximately 1/3 of the cases and is quite similar to that observed in our patient, with thinly myelinated fibers and loss of both small and large caliber fibers. The myopathy group may be genetically distinct from those patients with neuropathy, as MSS has been linked to 5q31 in families with cerebellar atrophy and myopathy whereas in two families with atypical MSS and a peripheral neuropathy, no linkage to 5q31 could be established [Lagier-Tourenne et al., 2003].

Orthopedic manifestations were important additional anomalies and pes planus or pes planovalgus was noted in 21/75 (28%), genu valgum in 15/75 (20%), scoliosis in 14/75 (19%), and kyphoscoliosis in 12/75 (16%). Joint contractures were documented in 13/75 (17%), and pectus deformities including pectus excavatum were found in 7/75 (9%).

In these cases, the frequency of craniofacial dysmorphism in MSS patients was low, but many authors did not describe a detailed physical examination. Many of the reported features can be explained by an underlying myopathic or neuromuscular process in MSS. Ptosis was listed as a feature of MSS without specific patient examples [Tachi et al., 1991]. Three patients from two families had mild ptosis and changes suggestive of a mitochondrial myopathy on muscle biopsy [Torbergsen et al., 1991]. One male from a sibling pair had ptosis, and both siblings had variation in muscle fiber size with small vacuoles on muscle biopsy [Sewry et al., 1988]. Similarly, two siblings were reported to have a slightly myopathic facies, and the male child had a prominent forehead at 14 years of age [Herva et al., 1987]. Three children from the same family had long and narrow facies with hypertelorism and horizontal or upslanting palpebral fissures [Walker et al., 1985]. Two siblings had thin facies and sparse hair with low-set but normally formed ears [Newton, 1991]. Borderline microphthalmia with ocular hypotelorism (inner canthal distance < -2 SD) and small palpebral fissures were described in one male [McLaughlin et al., 1996]. One boy had epicanthic folds with bilateral single transverse palmar creases. An unrelated male with MSS had coarse facial features and a depressed nasal bridge, right epicanthic fold, a flat philtrum, and micrognathia with a single transverse palmar crease [Walker et al., 1985].

Digital findings were also relatively infrequent. Fifth finger brachydactyly was noted in three children [Alter et al., 1962]. Four had short metacarpals and eight had short metatarsals [Brogdon et al., 1996; Farah et al., 1997] whereas three children had short toes [Komiyama et al., 1989] and one child

TABLE I. Common Clinical Features of Marinesco–Sjögren Syndrome

Clinical feature	This review, 81 cases (%)	Williams et al. [1996] (125 cases)
Ophthalmological features		
Cataracts	68/75 (91)	98%
Strabismus	33/75 (44)	NS
Cerebellar signs		
Truncal/limb ataxia	54/75 (72)	Cerebellar dysfunction in >98%
Dysarthria	34/75 (45)	
Nystagmus	27/75 (36)	
Intention tremor	12/75 (16)	
Other neurological signs		
Truncal/limb hypotonia	40/75 (53)	Hypotonia, muscle weakness, and muscle atrophy in 89%
Muscle atrophy	38/75 (51)	
Muscle weakness	27/75 (36)	
Orthopedic manifestations		
Pes planus/planovalgus	21/75 (28)	Skeletal anomalies in 58/125 (46%)
Genu valgum	15/75 (20)	
Scoliosis	14/75 (19)	
Kyphoscoliosis	12/75 (16)	
Joint contractures	13/75 (17)	
Pectus deformities	7/75 (9)	

was reported to have hammer toes [Bromberg et al., 1990]. One child had a wide sandal gap [Farah et al., 1997]. Doughy muscles were mentioned in two cases [Herva et al., 1987]. Joint laxity was described in three patients from two separate families [Sewry et al., 1988], and one child had hyperextensible hands [Reinker et al., 2002]. Finally, the hypogonadism found in MSS was rarely reflected on examination and cryptorchidism or small and/or atrophic testes were reported in five males [Sewry et al., 1988; McLaughlin et al., 1996; Farah et al., 1997], and four males had a small penis [McLaughlin et al., 1996; Farah et al., 1997].

DISCUSSION

MSS was first described in three siblings in 1904, and the phenotype was enlarged by the reports of Marinesco et al. [1931] and Sjögren [1950]. The inheritance pattern in this panethnic disease is autosomal recessive, but the pathogenesis is not yet known. MSS has been considered to be a lysosomal storage disease because histological studies have shown enlarged lysosomes containing whorled lamellar or amorphous inclusion bodies in some patients [Walker et al., 1985; Zimmer et al., 1992]. However, several patients with MSS have had elevated CK levels and myopathic features on muscle biopsy [Komiyama et al., 1989; McLaughlin et al., 1996; McLaughlin et al., 1996]. Neurogenic muscular atrophy [Zimmer et al., 1992], demyelinating polyneuropathy [Zimmer et al., 1992; Müller-Felber et al., 1998], and sensorimotor peripheral neuropathy with segmental demyelination [Alexianu et al., 1983] have also been observed. Muscle biopsies have revealed increased variation of fiber size with fiber-type disproportion and scattered atrophic fibers, vacuolar degeneration of the muscle fibers, necrosis, and increased adipose tissue [Zimmer et al., 1992; Ishikawa et al., 1993; McLaughlin et al., 1995; Müller-Felber et al., 1998]. MSS has also been suspected to be a mitochondrial disease because muscle biopsies have occasionally revealed ragged red fibers with clumped mitochondria, concentric cristae, and paracrystalline inclusions [Borud et al., 1989; Torbergsen et al., 1991; McLaughlin et al., 1995]. One patient had cytochrome-C-oxidase deficiency [Kodama et al., 1992].

A homozygosity mapping strategy was recently employed in two large families with classical MSS and linkage was obtained to a 9.3 cM interval between markers D5S1995 and D5S436 on chromosome 5q31 [Lagier-Tourenne et al., 2003]. Two separate families with atypical MSS were not linked to this locus [Lagier-Tourenne et al., 2003], and affected individuals from both families had peripheral neuropathy and optic atrophy, whereas the two families linked to 5q31 had myopathies with normal nerve conduction studies. Further evidence for genetic heterogeneity stems from the clinical overlap between MSS and congenital cataracts–facial dysmorphism–neuropathy syndrome (CCFDN), both syndromes share common findings of cataracts, ataxia, developmental delay, growth retardation, hypogonadism, and skeletal anomalies [Tournev et al., 1999a; Merlini et al., 2002]. However, CCFDN has been linked to chromosome 18q with a locus between markers D18S1095 and D18S1390, a region that has been excluded in at least one family with MSS [Lagier-Tourenne et al., 2002]. The recent identification of the CCFDN gene [*CRDP1*; Varon et al., 2003] should allow for more complete comparison between these phenotypic groups. Finally, the differential diagnosis of MSS also includes ataxia with isolated vitamin E deficiency. Two brothers with MSS were shown to have vitamin E deficiency caused by chylomicron retention disease (CMD) on electron microscopy of the intestinal membrane [Aguglia et al., 2000]. Recently, homozygosity mapping identified the causative gene for CMD as S*ARA2*, a member of the Sar 1-ADP-ribosylation factor family of small GTPases, which are vital for the intracellular trafficking of proteins in coat-protein-coated vesicles [Jones et al., 2003]. A homozygous missense mutation resulting in a null allele in the *SARA2* gene was identified in the two brothers with MSS and CMD described above [Jones et al., 2003]. However, CMD is rare in MSS, and we are unaware of further mutations in this gene in MSS patients.

The facial features in CCFDN have been described as mild ptosis, a prominent midface with a large nose, anteriorly directed incisor teeth, fleshy perioral tissues with wide and thickened lips, and hypognathism [Tournev et al., 1999a; Merlini et al., 2002]. This physical appearance develops during childhood, becoming more obvious in early adolescence and is more common in males [Tournev et al., 1999b]. These features are clearly distinguishable from those observed in MSS, which are far more likely to reflect the underlying myopathic (ptosis, long and narrow face) or neuromuscular process. The relative paucity of dysmorphism in these patients may reflect the phenotypic and genetic heterogeneity of MSS, in which patients with a predominantly myopathic process may show facial changes, but others with a different pathogenesis may not. However, it may also reflect incomplete reporting of many patients with this condition. In our patient, hypertrichosis, deep-set eyes with epicanthic folds, a flat philtrum and a thin upper lip, a high arched palate, short thumbs, and a wide sandal gap are non-specific findings that are not diagnostic. However, we believe that such minor dysmorphic features may be important in recognizing an underlying genetic condition. This child also had a mildly exaggerated kyphosis with bilateral dorsiflexion of the toes. Orthopedic manifestations proved to be frequent additional findings in this review (Table I). We would consider that they are likely to be diagnostically useful.

Although this child did not have congenital cataracts, he developed opacities at 19 months of age. The cataracts in MSS have classically been described as congenital, but the rapid development of postnatal cataracts has also been reported [Herva et al., 1987; Ishikawa et al., 1993; McLaughlin et al., 1995; Farah et al., 1997] and thus the postnatal onset of lens opacities in our patient does not exclude MSS. It is also intriguing that deterioration following a febrile episode has been described in other patients with MSS. Three children had acute rhabdomyolyis with marked weakness and elevated CK levels following a viral infection [Müller-Felber et al., 1998; Reinker et al., 2002]. Muscle pain and weakness was also observed during febrile illnesses and associated with intermittently raised CK levels in two siblings of Roma gypsy descent [Walther et al., 1991]. Another Roma child developed an acute, generalized myopathy with an extremely elevated CK after an upper respiratory tract infection, but muscle biopsy did not show inflammatory changes and the myopathy resolved with steroid therapy [Walther et al., 1991].

CONCLUSION

We report a 5-year-old male with MSS and mild dysmorphism comprising hypertrichosis and synophrys, deep-set eyes with small epicanthic folds, a flat philtrum and a thin upper lip, and a high arched palate. He had short first fingers, a wide sandal gap between the first and second toes, and his muscles had a doughy texture. Skeletal findings were an increased kyphosis with dorsiflexion of the toes bilaterally. Although a literature review showed that the majority of cases of MSS do not have craniofacial dysmorphism described in the reports, other cases have been reported with ptosis, myopathic facies, and a long and narrow face, features that are likely to reflect the underlying myopathic or neuromuscular process in MSS. However, in addition to the ophthalmological and neurological manifestations of MSS, orthopedic manifestations were

common, and thus are likely to prove more useful for supporting the diagnosis.

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