CLINICAL AND MOLECULAR PATHOLOGICAL FEATURES OF SEVERE CHILDHOOD AUTOSOMAL RECESSIVE MUSCULAR DYSTROPHY IN SAUDI ARABIA

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Severe childhood autosomal recessive muscular dystrophy (SCARMD) has recently been identified as a unique form of muscular dystrophy (MD) that resembles X-linked Duchenne type but affects both sexes (Ben Hamida and Fardeau 1980; Salih 1980, 1982; Ben Hamida *et al.* 1983; Salih *et al.* 1983; Walton and Gardner-Medwin 1988). It is characterized by onset usually before 5 years, pseudohypertrophy of calf muscles, inability to walk by 12 years and death before 20 years of age. The disease was mainly described in communities with high consanguinity rates in Sudan (Salih 1980, 1982; Salih *et al.* 1983), Tunisia (Ben Hamida and Fardeau 1980, Ben Hamida *et al.* 1983), Libya (Dubowitz 1980) and Algeria (Azibi *et al.* 1993) in North Africa; and Kuwait (Farag and Teebi 1990) and Qatar (Dubowitz 1980) in the Arabian Peninsula. Confirmation that the disease is different from Duchenne MD was shown in a study from Tunisia, where all the 20 cases of SCARMD examined were found to have a normal quantity and quality of dystrophin (Ben Jelloun-Delagi *et al.* 1990). Recently, a specific deficiency of adhalin, the 50 kDa glycoprotein, was found in the sarcolemma of biopsied skeletal muscles of patients with SCARMD (Matsumura *et al.* 1992).

This paper highlights the clinical, biochemical, histological and histochemical features of SCARMD seen over ten years (1982 to 1993) at a large referral centre in Riyadh, Saudi Arabia. It also examines the status of dystrophin and the dystrophin-glycoprotein complex in cases seen since 1992.

Method

SUBJECTS

The patients were examined by one of the authors (MAMS or AHM) and investigated at King Khalid University Hospital (KKUH), College of Medicine, King Saud University, Riyadh, between 1982 and 1993. Pedigrees were drawn in familial cases, and classification of functional stages of the disease was based on a scheme of 11 grades (0 to 10) reported by Walton (1981) and modified from Vignos *et al.* (1963). Grade 0 of this scheme denotes preclinical stages of the disease when all activities are normal, and grade 10 refers to the stage when the patient is confined to bed and requires help for all activities.

Investigations done in all cases included serum creatine kinase (CK) estimation, electrocardiography (ECG) and electromyography (EMG). An open muscle biopsy was obtained from the vastus lateralis in each patient except in two families. One had four affected children, of whom a boy and a girl were chosen for biopsy. The other family had a boy and a girl affected, but consent for biopsy was

given only for the older sibling.

Diagnostic criteria for SCARMD were based on clinical and laboratory data. These consisted of the occurrence of progressive muscle weakness starting proximally in the first decade of life with similar distribution to that of Duchenne MD. Pseudohypertrophy (usually of the calf muscles) is a prominent feature and inheritance is autosomally recessive, as evidenced by the disease's appearance in either sex. Serum CK is raised and muscle biopsy reveals dystrophic features (Ben Hamida *et al.* 1983, Salih *et al.* 1983, Walton and Gardner-Medwin 1988). Isolated male cases who were dystrophin-positive were also included (Ben Jelloun-Dellagi *et al.* 1990).

Muscle was frozen in isopentone cooled in liquid nitrogen. Cryostat sections of 10μm were prepared for histological and histochemical examination using standardized methods (Dubowitz 1985, Pearse 1985). Stains used included haematoxylin and eosin, modified Gamori trichrome, myofibrillary ATPase at routine (9.4), reversed (4.3) and intermediate (4.6) pH; NADH–tetrazolium reductase (NADH–TR); periodic acid-Schiff (PAS), with and without diastase; Sudan black B, myophosphorylase, acid phosphatase and non-specific esterase. Immunohistochemistry was done for the muscle specimens of the six patients who had been seen since 1992 using three dystrophin antibodies: Dys 1, Dys 2 and Dys 3 (Novocastra, Newcastle, UK).

Portions from muscle biopsies of the last three patients were shipped, frozen in dry ice, to the University of Iowa. Indirect immunofluorescence analysis of dystrophin and dystrophin-associated proteins was performed on 7μm cryosections at room temperature as described by Roberds *et al.* 1993, using an affinity-purified rabbit polyclonal antibody against the C-terminus of dystrophin (Ervasti *et al.* 1990) and affinity-purified sheep polyclonal antibodies against dystrophin-associated proteins (Ohlendieck and Campbell 1991).

Results

Between 1982 and 1993, 14 children (five males and nine females) were seen who fulfilled the diagnostic criteria for SCARMD based on clinical and laboratory data. Of these, eight (four boys and four girls) were siblings belonging to three families (Fig. 1). Another two girls (patients 9 and 10) had history of the disease in their families including six affected siblings (three males and three females). However it was not possible to examine these since they lived outside Riyadh. The remaining four patients, three girls and a boy, were isolated cases. The final diagnosis in that boy (patient 13) was based on immunohistochemistry that revealed a normal dystrophin pattern. Eleven patients were Saudis. A boy and a girl belonged to a Syrian family (family 3, Fig. 1) and one 11-year-old girl (patient 11) was a Yemeni.

The landmarks of the disease are summarized in Table I. Symptoms were observed by the parents between three and nine years (median 3 years, mean 4.3 years), either when the child became clumsy in walking, fell frequently or had difficulty in running. History of delayed walking was evident in only two patients (7 and 9). Loss of the ability to walk occurred between 10 and 12 years of age in three females and one male. Only one girl, aged 12 years, and a boy aged 13 years, were still walking at or after 12 years of age. The oldest patient seen (patient 14) was completely dependent when examined at age 16 years and had congestive cardiomyopathy. There had been one death (reported by a family) of an affected boy at the age of 15 years (a brother of patient 9).

Muscle weakness started proximally and had the same selective symmetrical distribution in the upper and lower limbs as is seen in Duchenne MD. Pseudohypertrophy of the calf muscles was a prominent feature in all cases except in an 11-year-old girl (patient 11) who had an advanced stage of the disease. In the nine patients who were seen when they were mobile, toe-walking was evident in two boys (patients 7 and 13) when first seen at ages 9 and 10 years, respectively.

Deformities started with tendo Achilles shortening at about age 10 years (progressing later to equinovarus) and were followed by contractures of the hip, knee and elbow joints at the wheelchair stage.

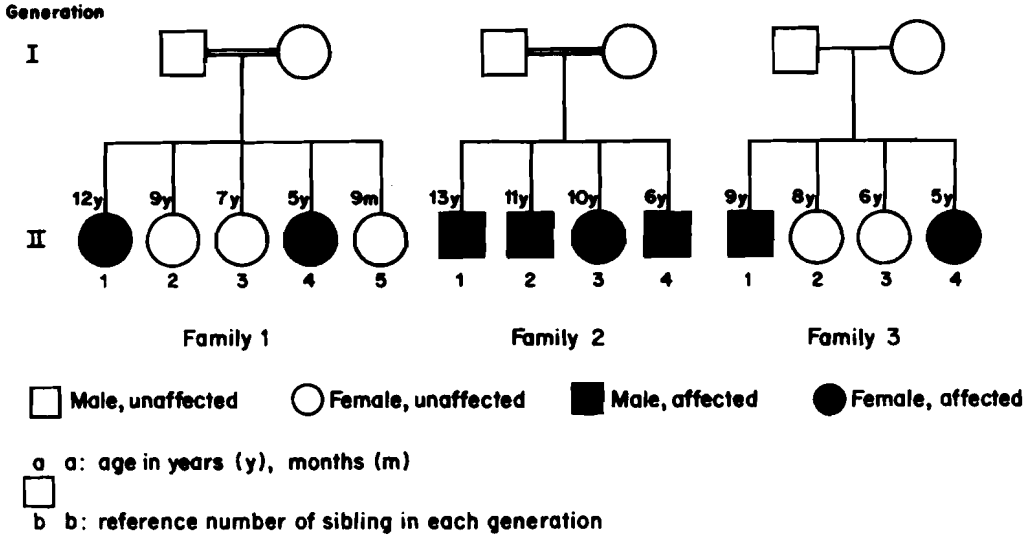

Fig. 1. Pedigree of families with severe childhood autosomal recessive muscular dystrophy. Families 1 and 2 were Saudis and family 3 was Syrian.

TABLE I
Severe childhood autosomal recessive muscular dystrophy in patients studied

Patient no	*Family no*[1]	*Pedigree no*[1]	*Sex*	*Age (yrs)*	*Age at Onset (yrs)*	*Age when last walked (yrs)*	*Overall disability grade*[2]	*Serum creatine kinase*	*Adhalin*
1	1	II.1	F	12	5	11	7	2453	Not done
2	1	II.4	F	5	3	–	2	13 770	Negative
3	2	II.1	M	13	3	–	3	903	Positive
4	2	II.2	M	11	3	–	2	414	Not done
5	2	II.3	F	10	3	–	2	477	Not done
6	2	II.4	M	6	3	–	1	249	Not done
7	3	II.1	M	9	4	–	5	2772	Not done
8	3	II.4	F	5	3	–	2	12 888	Not done
9	–	–	F	4	3	–	2	972	Not done
10	–	–	F	6	5	–	3	17 480	Not done
11	–	–	F	11	5	10	7	2681	Negative
12	–	–	F	12	9	–	3	4044	Not done
13	–	–	M	13	5	12	5	5454	Negative
14	–	–	F	16	6	12	10	66	Not done

[1]For families 1–3 in Figure 1; others are isolated cases.
[2]According to Walton (1981).

Fixed spinal deformities consisting in very mild scoliosis – less than 10°, as assessed by the method of Cobb (1948) – were observed in patient 11 at 11 years. Hyperlordosis (Fig. 2) was a remarkable feature in these patients.

No systematic psychometric tests were done for the patients, but informal assessment revealed normal language function. They attended normal school at appropriate ages. However, patients 13 and 1 left school (based on family decision) at 10 and 12 years of age, respectively, because of their progressive motor disabilities.

Symptomatic cardiac involvement was evident in a 16-year-old girl (patient 14) whose investigations revealed congestive cardiomyopathy.

Investigations

Electromyography revealed a myopathic pattern in all patients. Serum CK ranged from 66 to 17,480 i.u./L (Normal<232 i.u./L). The lowest value was in a 16-year-old girl (patient 14) who was bedridden. The mean CK for the group was 20 times the upper reference limit.

ECG revealed features compatible with congestive cardiomyopathy in a 16-year-old girl (patient 14). Changes in the others included sinus tachycardia of 100 to 126/min in patients 7, 11 and 13, but all of the group had normal axes. Patients 3 and 4 showed M-shaped QRS complex in lead III. Patients 7 and 11 had Rsr′ and RSr′ configuration in lead V1 which was associated in patient 7 with plane depression of ST segment in II, III and AVF. ST segment depression was confined to II and III in patient 4. The T wave was flat, biphasic or inverted in III and AVF in three children (patients 1, 7 and 13) and in II, III and AVF in another patient (11).

Muscle histology showed features consistent with MD that varied in severity according to the stage of the disease. Histochemistry revealed Type I fibre predominance with clear distinction between type I and type II fibres on the routine (pH 9.4) ATPase reaction.

Patients 1, 2, 3, 5, 11 and 13 showed a normal staining pattern of dystrophin with each of the three antibodies used in Riyadh. All four muscle specimens for patients 2, 3, 11 and 13 that were examined in Iowa were also positive for dystrophin. However, a specific deficiency of adhalin (Fig. 3) was detected in three: two Saudis, patients 2 and 13, and a Yemeni, patient 11. The fourth, patient 3, had normal adhalin (family 2, II.1, Fig. 1). All four of these patients also had normal levels of syntrophin (59 kDa dystrophin-associated protein) and b-dystroglycan (43 kDa dystrophin-associated glycoprotein) (data shown only for patients 3 and 13, Fig. 3).

Fig. 2. Saudi boy (patient 13) at 10 years showing tendency to spontaneous equinus posture of feet and masked hyperlordosis. Muscle biopsy was dystrophin positive but showed selective deficiency of adhalin.

Discussion

The clinical features of SCARMD as seen in Saudi Arabia are remarkably similar to those described previously in communities with high consanguinity rates in Sudan (Salih 1980, 1982; Salih *et al.* 1983), Tunisia (Ben Hamida and Fardeau 1980, Ben Hamida *et al.* 1983), Libya (Dubowitz 1980), Kuwait (Farag and Teebi 1990) and Qatar (Dubowitz 1980). Age at onset, the symmetrical distribution of muscle weakness (associated with pseudohypertrophy) and rate of disease progress follow the same pattern as that seen in Duchenne MD, but differentiate it from the milder autosomal recessive MD of childhood as seen in Europe, North America and Australia (Salih *et al.* 1983). The latter entity is characterized by a later date of onset (usually above 5 years) and affected patients are still ambulant after 14 years (Stern 1972, Ionasecu and Zellweger 1974, Shokeir and Kobrinsky 1976). In the kindred reported by Jackson and Strehler (1968), mean age at loss of ambulation was 24 years and age at death ranged between 41 and 67 years.

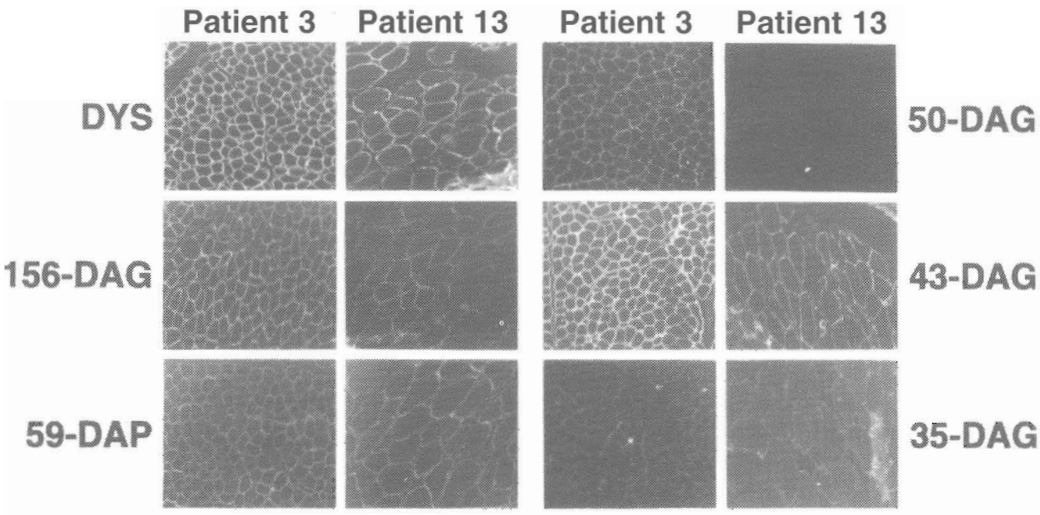

Fig. 3. *Immunofluorescence analysis of dystrophin-associated proteins in skeletal muscle of two 13-year-old patients with SCARMD. Patient 3, with milder form of SCARMD, had normal levels of dystrophin and all dystrophin-associated proteins. Patient 13, with more severe form of SCARMD, had severe deficiency of adhalin (50-DAG) but normal levels of dystrophin and all other dystrophin-associated proteins.*

The salient features of autosomal recessive MD of childhood (as observed in Europe) have recently been outlined by Gardner-Medwin and Johnston (1984), who studied 14 cases (12 girls and two boys) in a national survey in the UK. Although the clinical picture in these children was superficially similar to that of Duchenne MD, certain features served to distinguish it from the Duchenne type. These included the pattern of onset, which is characterized by early toe-walking (at the age of 1 to 5 years) before signs of difficulty in walking, a relatively milder muscle involvement, ability to walk retained to 11 to 15 years or later and normal intelligence. In the present series, and in contrast with the previous observations (Gardner-Medwin and Johnston 1984), toe-walking was seen in two boys (aged 9 and 10 years) and in none of the girls. This is similar to what has been observed in Sudan (Salih 1985), where toe-walking had not been seen in girls at any stage of the disease and was observed to start late in boys (at about 10 years). Also similar to findings in the Sudanese children (Salih 1985), fixed spinal deformities (following the wheelchair stage) consisted in very mild scoliosis in the present cohort, in contrast to the severe rotational kyphoscoliosis seen in Duchenne MD. Conversely, marked hyperlordosis was a feature similar to the situation in the Sudanese patients. Marked lumbar lordosis, which is seen in only a minority of Duchenne cases, seems to offer some protection against the disfiguring rotational and lateral deformities (Wilkins and Gibson 1976).

Although no formal psychometric tests were performed in this study, intelligence seemed to be normal in these children with SCARMD, since they could perform well at public schools and the decision to discontinue their course was based on their physical disability. Similarly, SCARMD patients from Tunisia (Ben Hamida *et al.* 1983) were found to have normal intelligence, in contrast to the decreased intelligence observed in Duchenne MD, which is known to affect verbal ability most severely (Billard *et al.* 1992).

ECG in this cohort did not show the tall right precordial R waves in the lateral and left leads characteristic of Duchenne MD (Perloff *et al.* 1967). Instead, ST segment depression and T wave changes showed the tendency to occur in fixed leads, remarkably similar to what has been observed in Sudanese patients (Salih *et*

al. 1983), and pointing to the possibility of myocardial involvement with the dystrophic process (Armstrong 1985). This is especially interesting given that cardiomyopathic hamsters have a specific deficiency of adhalin in skeletal muscle and a deficiency of mutiple dystrophin associated glycoproteins (DAGs) in cardiac muscle (Roberds *et al.* 1993). Thus the molecular pathogenesis of SCARMD patients and cardiomyopathic hamsters may be very similar, and cardiac involvement in SCARMD patients would be expected. The changes seen in QRS configuration in four patients suggest intraventricular conduction delay similar to what has been observed in Tunisian patients with SCARMD in whom partial right or left atrioventricular heart blocks were reported (Ben Hamida *et al.* 1983).

Of special interest in the muscle biopsies of children with SCARMD in this study was the predominance of type I fibres, similar to that observed in Tunisian (Ben Hamida *et al.* 1983) and Sudanese (Salih *et al.* 1983) patients. There was also good differentiation of the major fibre types in the routine ATPase test (pH 9.4), similar to the findings in Sudanese children (Salih *et al.* 1983) and in contrast to the poor differentiation of fibre type in Duchenne MD (Dubowitz 1985). The muscle biopsies depicted in a study of SCARMD from Tunisia also showed this clear distinction between the fibre types (Figs. 6A, 7A and 7C in Ben Hamida *et al.* 1983). The normal dystrophin staining in the present cohort excluded the possibility that this patients sample included female carriers of Duchenne MD, who may present with severe myopathy (Minetti *et al.* 1991). It also helped to identify an isolated case: that of a 13-year-old boy whose disorder resembled Duchenne MD phenotypically but who had normal intelligence. The detection of selective deficiency of adhalin in this boy and in another two girls tallies with findings in cases of SCARMD from Algeria (Matsumura *et al.* 1992). This provides further evidence that the cases reported previously from the Arabian Peninsula (Dubowitz 1980, Farag and Teebi 1990), Sudan (Salih *et al.* 1983) and northwestern Africa (Ben Hamida *et al.* 1983) are likely to belong to the same disease entity, as has been speculated on the basis of the available clinical and laboratory data in previous communications (Salih *et al.* 1983, Salih 1985).

The onset of symptoms and the severity of disease course have been noticed to vary in Tunisia from one family to another (Ben Hamida *et al.* 1983). This is demonstrated in the Saudi families 1 and 2 in the present study (see Fig. 1 and Table 1). Whereas a 12-year-old girl (who had lost the ability to walk at 11 years) had an advanced disability grade of 7 (patient 1), a 13-year-old boy from family 2 (patient 3) was still mobile and showed a much milder disability (grade 3). The muscle biopsy of the younger affected sister (5 years) in family 1 (patient 2)) revealed a specific deficiency of adhalin, suggesting a causal relation to the severe variant of SCARMD. Adhalin (Roberds *et al.* 1993) is an integral part of the dystrophin–glycoprotein complex that spans the sarcolemma of skeletal muscle and provides linkage between the subsarcolemmal cytoskeleton and the extracellular matrix (Matsumura and Campbell 1993). Recently, severe SCARMD with the deficiency of adhalin was found to map the chromosome 13q12 (Azibi *et al.* 1992, Ben Othmane *et al.* 1992). However, other families with SCARMD and adhalin deficiency have been excluded from linkage to markers on chromosome 13q12 (Passos-Bueno *et al.* 1993, Romero *et al.* 1994). Following cloning of human adhalin cDNA, the adhalin gene was mapped to chromosome 17q12-q21.33 (Roberds *et al.* 1994). Thus, defects in at least two genes can cause SCARMD. The cause of the milder variant of SCARMD (family 2, Fig. 1), remains to be identified.

The prevalence of SCARMD in Tunisia was reported to be equivalent to that of Duchenne MD and consanguinity was found in 76% of affected families (Ben Hamida and Marakchi 1980). We observed similar findings in Saudi Arabia where consanguineous marriages are also high. In a review of 84 childhood neuromuscular disorders seen between 1982 and 1992 at KKUH in Riyadh (unpublished data), SCARMD was more common than Duchenne MD (30% *vs* 25%,

respectively, of 40 cases with different types of MD). Conversely, the prevalence of Duchenne MD was estimated to be about 12 times higher than SCARMD in Europe (Emery 1991). In other parts of the world, it has been estimated that around 2.5 to 4% per cent of isolated males diagnosed as having X-linked MD may in fact have SCARMD (Zatz *et al.* 1989). The contrary may be true in the Arabian Peninsula and North Africa, where SCARMD is likely to be underdiagnosed in isolated male cases. A vivid example of this is the 13-year-old isolated male (patient 13) in whom Duchenne MD had been provisionally diagnosed. Subsequent investigations showed normal dystrophin staining in his muscle specimen but also the deficient adhalin that characterizes SCARMD.

In conclusion, SCARMD with adhalin deficiency must be considered when diagnosing muscular dystrophies in populations of Arab descent who live either within the Arabian Peninsula (Kuwait, Qatar, Saudi Arabia, Syria and Yemen), in Sudan or in North Africa (Algeria, Libya, Morocco and Tunisia).

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SUMMARY
The clinical, biochemical and histochemical features of 14 patients (nine females and five males) with severe childhood autosomal recessive muscular dystrophy (SCARMD) seen at a tertiary hospital in Riyadh from 1982 to 1993 are described. Onset was at 3 to 9 (median 3) years and four of five children aged >12 years lost ambulation. Five of the eight pairs of parents were closely consanguineous. The mean creatine kinase was 20 times the upper normal limit. Histochemistry of muscle showed dystrophic features in all cases, and dystrophin was positive in all cases examined (N=6). Three patients (two girls and a boy) were deficient in adhalin, the 50-kDa dystorphin–associated glycoprotein. A boy aged 13 years had rapidly progressing disease. Another boy of the same age (from a family characterized by early onset and slower progression) had normal dystrophin and adhalin. The clinical features conformed with previous observations from Sudan, North Africa and Qatar in the Arabian Peninsula. The disease is common in Saudi Arabia and seems to be more prevalent than Duchenne muscular dystrophy.

RÉSUMÉ
Caractéristiques pathologiques cliniques et moléculaires de dystrophies musculaires autosomiques récessives graves de l'enfance en Arabie saoudite
Les caractéristiques cliniques, biochimiques et histochimiques de 14 patients (neuf filles et cinq garçons) avec une dystrophie musculaire autosomique récessive grave de l'enfance (SCARMD) vus dans un hôpital tertiaire de Riyad de 1982 à 1993 sont précisées. Le début était entre 3 et 9 ans (médian à 3 ans) et quatre de cinq enfants âgés de plus de 12 ans avaient perdu la marche. Cinq des huit paires de parents étaient fortement consanguines. Le taux moyen de créatine kinase était de 20 fois au dessus de la limite normale. L'histochimie des muscles révélait des caractéristiques dystrophiques dans tous les cas et la recherche de dystrophine était positive dans tous lex cas examinés (N=6). II y avait une déficience en adhaline, la 50-kDa glyco-protéine associée à la dystrophine chez trois patients (deux filles et un garçon). Le garçon âgé de treize ans avait une forme rapidement évolutive. Un autre garçon de même âge venant d'une famille où la maladie était à début précoce et progression lente avait une dystrophine et une adhaline normales. Les données cliniques étaient en accord avec les observations antérieures venant du Soudan, de l'Afrique du nord et du Qatar. La maladie est commune en Arabie Saoudite et semble avoir une prévalence supérieure à celle de la dystrophie musculaire de Duchenne.

ZUSAMMENFASSUNG

Klinische und molekular-biologische Merkmale der kindlichen autosomal rezessiven Muskeldystrophie in Saudi Arabien

Es werden die klinischen, biochemischen und histochemischen Merkmale von 14 Patienten (neun weiblichen und fünf männlichen) mit schwerer kindlicher autosomal rezessiver Muskeldystrophie (SCARMD) beschrieben, die in einem tertiären Krankenhaus in Riad in der Zeit von 1982 bis 1993 behandelt wurden. Die Krankheit begann mit 3 bis 9 (im Mittel 3) Jahren und vier von fünf Kindern, die >12 Jahre alt waren, verloren ihre Gehfähigkeit. Fünf der acht Elternpaare waren nahe Blutsverwandte. Der mittlere Kreatinkinasewert war 20 mal höher als der obere Normalwert. Die Muskelhistochemie zeigte in allen Fällen dystrophe Merkmale und in allen untersuchten Fällen (N=6) war das Dystrophin positiv. Drei Patienten (zwei Mädchen und ein Junge) hatten einen Mangel an Adhalin, dem 50-kDA Dystrophin assoziierten Glycoprotein. Der Junge, 13 Jahre alt, hatte eine sehr rasch fortschreitende Erkrankung. Ein anderer Junge in deselben Alter (aus einer Familie, bei der die Erkrankung durch frühen Beginn und langsames Fortschreiten charakterisiert war) hatte ein normales Dystrophin und Adhalin. Die klinischen Merkmale stimmten mit früheren Beobachtungen aus dem Sudan, aus Nord Afrika und Katar auf der arabishcen Halbinsel überein. Die Erkrankung kommt in Saudi Arabien oft vor und scheint häufiger zu sein als die Duchenne'sche Muskeldystrophie.

RESUMEN

Características patológicas, clínicas y moleculares de la distrofia muscular progresiva infantil grave en Arabia Saudita

Se describen las características clínicas, bioquímicas e histoquímicas de 14 pacientes (nueve hembras y cinco varones) con distrofia autosómica recesiva muscular grave de la infancia (DMARI), vistos en un hospital terciario de Riyadh desde 1982 a 1993. El inicio tuvo lugar entre los 3 y 9 años (promedio 3). Cuatro de cinco niños de más de 12 años habían perdido la deambulación. Cinco de los ocho pares de padres eran consanguíneos próximos. El promedio de creatinquinasa era de 20 veces el límite alto de lo normal. La histiquímica muscular mostró características distróficas en todos los casos y la distrofina era positiva en todos los casos examinados (N=6). Tres pacientes eran deficientes (dos chicas y un chico) en adalina, la glicoproteina 50-kDa asociada a la distrofina. El varón, de 13 años, tuvo una enfermedad rápidamente progresiva. Otro chico de la misma edad de una familia caracterizada por el inicio precoz y la progresión más lenta tenía normales la distrofina y la adalina. Las características clínicas estaban de acuerdo con previas observaciones hechas en el Sudan, Norte de Africa y Qatar en la península arábiga. La enfermedad es corriente en la Arabia Saudi y parece que es más corriente que la distrofia muscular de Duchenne.

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