Kocher-Debré-Semelaigne Syndrome in Presumed Identical Twins

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Summary

Abdurrahman, M. B. and Gassmann, L. (**1976**). *Nigerian Journal of Paediatrics*, **3** (**2**), 57. **Kocher-Debré-Semelaigne Syndrome in Presumed Identical Twins.** Two male twins, presumed to be identical, and having the unusual combination of cretinism and generalised muscular hypertrophy (Kocher-Debré-Semelaigne syndrome) are described. Diagnosis of cretinism was based on clinical, radiological and laboratory criteria. Primary muscle disease was excluded by histopathological features of muscle biopsy. Response to thyroid therapy was satisfactory. Evidence suggests autosomal recessive mode of inheritance in this family. Pathogenesis of this syndrome remains uncertain.

KOCHER-DEBRE-SEMELAIGNE (KDS) syndrome is the unusual combination of hypothyroidism and apparent muscular hypertrophy in children. The term "hypertrophy" is used only in the descriptive sense, without implications as to the histologic picture of the muscle. Though the first case was reported by Kocher as early as 1892 (Najjar and Nachaman, 1965; Cross, *et. al.*, 1968), less than 50 cases have been reported up to-date. Debré and Semelaigne (1935) emphasised the relationship between the muscular hypertrophy and the hypothyroidism. It occurs in different forms of hypothyroidism including athyreosis and enzymatic defects in thyroid hormonogenesis. Cross *et al.* (1968) described the syndrome in two sisters, and Najjar's (1974) report of 23 cases from Lebanon included at least two siblings. This report concerns the occurrence of the syndrome in a pair of presumed identical twins.

Case Report

Two 22-month old male siblings were first seen in the Department of Paediatrics, Ahmadu Bello University Hospital, Kaduna, at the age of 13 months. They were delivered after 8 months gestation. At birth, the first twin weighed 2.1 kg and the second one, 3.kg. Both were well until about the age of 5 weeks when they began to cry excessively and had an episode of acute respiratory distress. Their tongues were, at about the same time, noticed to be getting bigger. The parents' main concern was the delay in the children's psychomotor development and their general appearance. Two siblings who had similar symptoms and signs, died. At 13 months, the patients were only able to sit unsupported for a few minutes; they could neither crawl, nor vocalise. No tooth had erupted. These milestones were said to be markedly delayed compared with

those of the normal older siblings. Prominence of the limb muscles was noticed when the children were only a few months old.

Physical Examination

The most striking features in both twins were the typical cretinoid facies, large tongue, protuberant abdomen, umbilical hernia, and generalised muscular hypertrophy (Fig. 1). The hypertrophy was maximal at the calves. The muscles were firm on palpation, but were of normal tone; there was no myotonic reaction on percussion. The weight of the first twin (7.5 kg.) and his height (63 cm) were below the 3rd percentile for the age; the head circumference (45 cm) was within normal range. The upper/lower segment ratio was 2.32 (normal for age—1.54). Anthropometric measurements in the second twin were essentially the same. The thyroid gland was not palpable in either of the patients. Both responded to sound, but their mental and locomotor functions were grossly defective.

Laboratory Data

The clinical diagnosis of cretinism was supported by the radiological finding of delayed bone age, and confirmed by a high T_3 uptake and low serum thyroxine level. Histology of the gastrocnemius muscle biopsy showed the muscle fibers to be relatively normal in size and cellular orientation, but there was a slight increase of interstitial fibrous tissue.

Course

The patients were treated with thyroid extract, 60 mg daily. When seen again 5 months later, there was definite improvement; they were more active and livelier and the muscle hypertrophy had subsided. The first twin had grown 5 cm in length, but gained only 0.4 kg in weight. The second twin, on the other hand, measured 5 cms more in length, but lost 0.7 kg in weight. The body measurements of the twins are shown in Table. The upper/lower segment ratio was now 1.83 (normal—1.51). At $2\frac{1}{2}$ months old, the thyroid extract was replaced with equivalent

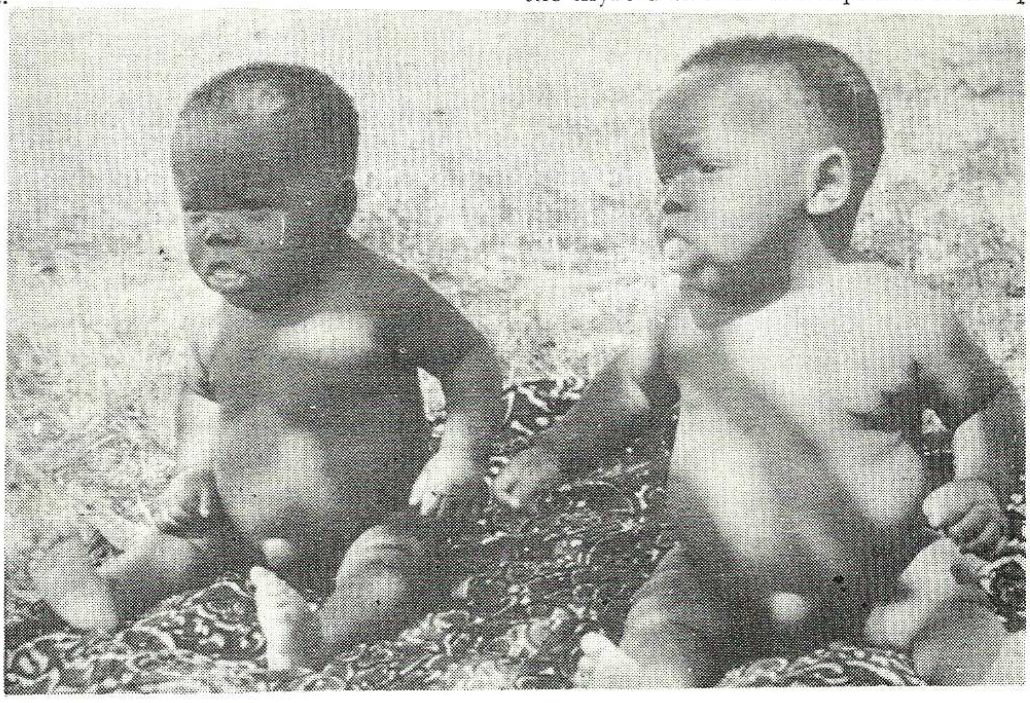

Fig. 1 Photograph of twin brothers, aged 13 months, with KDS Syndrome. Note the large tongue, cretinoid facies, protuberant abdomen and umbilical hernia. Both patients had generalized muscular hypertrophy.

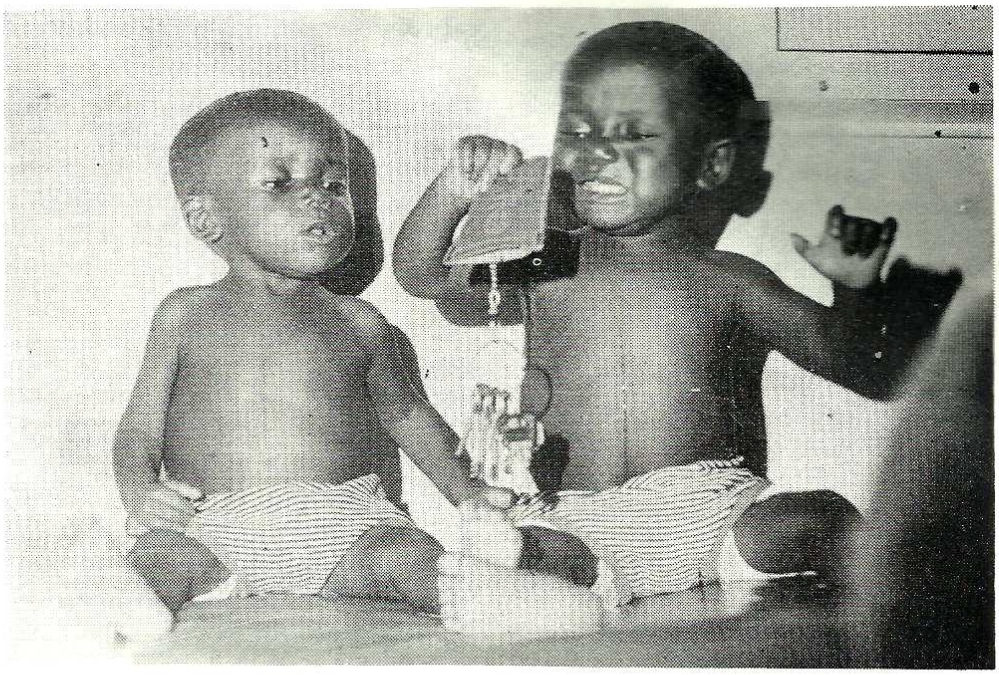

Fig. 2 The same twin brothers now aged 20 months. Photograph taken 7 months after therapy with thyroid extract (60 mgm daily). Note that the cretinoid facies have disappeared and there is no longer any evidence of muscle hypertrophy.

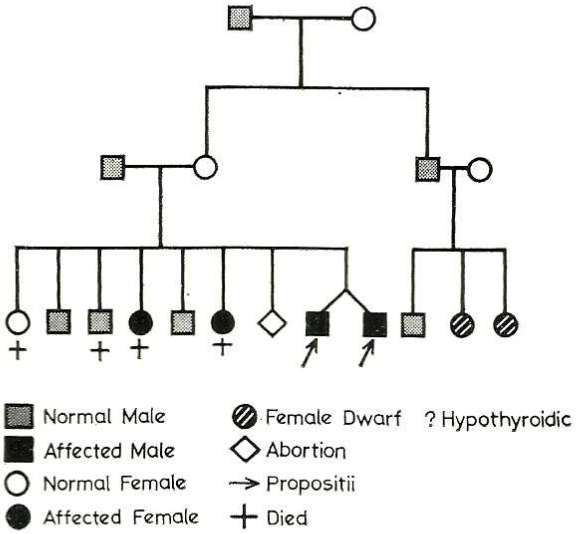

Fig. 3 Pedigree of family

TABLE

BODY MEASUREMENTS BEFORE AND AFTER THYROID TREATMENT IN TWINS WITH KDS SYNDROME

	Case 1		*Case 2*	
	Before (cm)	*After (cm)*	*Before (cm)*	*After (cm)*
arm	15	14	16	15
forearm	14.5	13	15	13.5
thigh	24.5	22	26	23
calf	18	15	18	15
chest	50	47	52	49
abdomen	50	44	50	48
head	45	47	47	47

dose of l-thyroxine, and this dose was gradually increased, so that at the age of 22 months, they were receiving 250 micrograms daily. Figure 2 illustrates the physical improvement achieved by the twins at the age of 20 months.

Family History

The pedigree of the family is shown in Figure 3. The parents of the propositi are origins of the Benue State of Nigeria. There is no history of consanguinity, nor any family history of deafness or goitre. The mother of the patients had eight pregnancies of which one terminated in abortion. The remaining seven pregnancies produced eight live born children (five males and 3 females) including the twins. Of the eight live born children, four (three females and one male) died. Two of the dead children were said to have had psychomotor retardation and generalized muscle hypertrophy similar to those of the twin siblings. The only other detected abnormality in the pedigree was the presence of dwarfism in two female first cousins.

Discussion

The occurrence of KDS syndrome in 4 out 8 of siblings including a pair of presumed identical twins suggests a familial tendency, favouring an autosomal mode of inheritance. The presumed identicalness of these twins was based on the phenotype and on the similarity of the blood group and haemoglobin genotype (AA).

Cretinism, like other thyroid disorders, shows a preponderance of girls over boys. Among the 37 children with KDS syndrome reported in the literature there were 21 boys and 16 girls, and the addition of our two cases brings the male/female distribution to 23/16. Though there seems to be a male preponderance, the total number of patients reported so far is too small to assign a definite sex ratio.

The incidence of KDS syndrome appears small in comparison with the incidence of cretinism. Whether this is due to actual rarity of the syndrome or that cases are missed or not reported is not quite clear. Among 222 cases of myxoedema seen in a 3-year period in Madras General Hospital, 38 were juveniles, and only one of these 38 had KDS syndrome (Annamalai and Fernandez, 1970). In contrast, Najjar (1974) reported 23 cases of the syndrome out of 118 children with hypothyroidism.

While both twins had significant growth in length five months after starting thyroid therapy, the first twin gained only slight weight during this period, and the second twin actually lost weight. This discrepancy between growth in length and that in weight following therapy has also been documented by Najjar and Nachman (1965), Cross *et. al.*, (1968). The lack of satisfactory weight gain or actual weight loss, as in the case of the second twin, may be explained by the disappearance of the muscle hypertrophy.

The pathogenesis of this syndrome remains uncertain. The disappearance of the hypertrophy with adequate thyroid therapy indicates a causal relationship between the hypertrophy and hypothyroidism. Apart from muscular hypertrophy these children do not differ clinically from other children with hypothyroidism. The hypertrophied muscle has been described by various authors as weak and hypotonic, firm,

normotonic, and hard. Description of histologic appearance of the muscles has not been consistent. In the patient reported by Najjar and Nachman (1965) there was variation in the size and shape of the muscle fibers, very few degenerating fibers and the presence of ringbinden of doubtful significance. Cross *et al.* (1968) and Poncher and Woodward (1936) found no abnormalities in the muscle biopsy. In our patients, there was slight increase of interstitial fibrous tissue which could not possibly account for the hypertrophy. Histochemical and ultrastructural study of skeletal muscle obtained from a $3\frac{1}{2}$-year old girl with the syndrome showed non-specific abnormalities (Spiro *et al.*, 1970). Thus, there are no consistent findings of any recognized factors namely: increase in size or number of muscle fibers, presence of adipose tissue, infiltrative process or oedema, that can possibly account for the apparent hypertrophy. The suggestion has been made that the muscular hypertrophy appears to be related to the severity and duration of the hypothyroid state (Najjar, 1974; Spiro *et al.*, 1970) as well as to the sex of the child (Najjar, 1974).

The authors wish to postulate the liberation of an "oedema factor" from the thyroid gland as a result of hypoactivity. The tendency of this "factor" to accumulate fluid in the interstitial tissue is aggravated by inactivity of the patient. If this fluid increases to a certain level and/or is under tension, the underlying muscle will be compressed, and its metabolic activity may be further compromised by pressure effect on the blood supply. Accumulation of osmotically active metabolites in the interstitial tissue will still further increase the oedema. With thyroid therapy, the "oedema factor" disappears, and the oedema fluid is absorbed into the cardiovascular compartment. The "oedema factor" may be released along with thyroid stimulating hormone and may be intimately related to the hormone.

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REFERENCES

Annamalai, A. L. and Fernandez, M. P. (1970). Muscular hypertrophy due to juvenile hypothyroidism, an unusual and curable complication. *Clin. Pediat.*, **9,** 368–371.

Cross, H. E., Hollander, C. S., Rimoin, D. L. and McKusick, V.A. (1968). Familial agoitrous cretinism accompanied by muscular hypertrophy. *Pediatrics*, **41,** 413–420.

Debré, R. and Semelaigne, G. (1935). Syndrome of diffuse muscular hypertrophy in infants causing athletic appearance. *Am. J. Dis. Child.*, **50,** 1351–1355.

Najjar, S. S. (1974) Muscular hypertrophy in hypothyroid children: The Kocher-Debré-Semelaigne syndrome. A review of 23 cases *J. Pediat.* **85,** 236–239.

Najjar, S. S. and Nachman, H. S. (1965). The Kocher-Debre-Semelaigne Syndrome: Hypothyroidism with muscular "hypertrophy", *J. Pediat.*, **66,** 901–908.

Poncher, H. E. and Woodward, H. (1936). Pathogenesis and treatment of myotonia congenita. *Am. J. Dis. Child.* **52,** 1064–1087.

Spiro, A. J., Hirano, A., Beilin, R. L. and Finkelstein, J. W. (1970). Cretinism with muscular hypertrophy (Kocher-Debré-Semelaigne syndrome). Histochemical and ultrastructural study of skeletal muscle. *Arch. Neurol.* **23,** 340–349.