Kocher-Debré-Sémélaigne syndrome and congenital nystagmus

K. RADHAKRISHNAN†
M.D., D.M., M.A.M.S.

K. VENKATESWARLU*
M.B.B.S.

B. N. S. WALIA*
M.D., D.C.H., M.A.M.S.

S. B. S. MANN‡
M.S.

Departments of †Neurology, *Paediatrics and ‡Otorhinolaryngology
Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India

Summary

A 11-year-old boy with hypothyroidism developed generalized muscle hypertrophy and proximal muscular weakness. Electromyographic findings were suggestive of myopathy. He had had congenital nystagmus (CN) since early infancy. Although the association of childhood hypothyroidism and CN has been documented before, the triad of hypothyroidism, hypertrophic myopathy and CN exhibited by the patient is believed to be unique.

Introduction

The uncommon association of muscle hypertrophy with childhood hypothyroidism has been referred to as the Kocher-Debré-Sémélaigne (KDS) syndrome (Najjar and Nachmann, 1965; Spiro *et al.*, 1970). Congenital nystagmus (CN) is an ocular movement disorder apparent at birth or shortly thereafter, characterized by bilateral pendular or jerk nystagmus with an eccentric neutral position in which the nystagmus slows or stops (Gay *et al.*, 1974). The present report describes a patient with KDS syndrome and CN. The occurrence of two rare abnormalities suggests that their association is more than a mere coincidence.

Case report

An 11-year-old male child was seen by us in September, 1980 with complaints of failure to grow, constipation, cold intolerance, loss of initiative and somnolence of 3-4 years duration. His school performance was poor and he took little interest in games. Developmental milestones up to the age of 3 years were normal, although the parents were aware of the abnormal eye movements he had had since early infancy. His younger brother, 4 years old, was normal and there was no history of dwarfism, goitre, or eye movement disorders in other members of the family.

He had an infantile look, dull facies and dry skin. His height was 101 cm (<3rd percentile) with upper/lower segment ratio of 1.2. The body weight was 16.2 kg (<3rd percentile) and the head circumference was 49 cm. All these parameters corresponded to the age of 3-4 years (Fig. 1). There was no thyroid swelling. He was slow to respond to questions and the IQ was 78. Muscles were bulky, especially in the calves. There was mild proximal weakness (power grade 4/5) at the shoulders. He had a waddling gait and was unable to get up from the sitting position unaided. Deep tendon jerks were slowed in contraction and relaxation, especially at the ankles. Neuro-ophthalmological examination disclosed normal visual acuity and a normal optic fundus in each eye. Ocular movements were full. Coarse horizontal nystagmus was evident in all directions of gaze and he did not have any oscillopsia. With gaze 10-20° to the left of primary position, the nystagmus diminished markedly and he had a constant head turn to the right side (Fig. 1). The nystagmus was absent on convergence and there was no vertical nystagmus. No other neurological deficit was demonstrable and the rest of the systemic examination showed no abnormality.

Laboratory findings

Normal investigations included urine analysis, haematocrit, blood biochemistry and radiographs of chest and skull. Serum cholesterol was 5.16 mmol/l. Electrocardiogram showed a low voltage graph with heart rate of 70/min. Skeletal X-rays disclosed normal upper femoral epiphyses and only three carpal bones (Fig. 2), which corresponded to the retarded bone age of 3 years. Thyroid function tests showed: PBI 228.5 nmol/l (normal 315-630 nmol/l), serum thyroxine (T_4) 20.6 nmol/l (normal 87.5-148 nmol/l), serum triiodothyronine (T_3) 0.6 nmol/l (normal 0.9-1.2 nmol/l). Muscle enzymes:

FIG. 1. Patient before therapy. Dwarfism, disproportionately short limbs in relation to trunk, bulky muscles and the characteristic head posture are apparent.

FIG. 2. X-ray picture of the wrist. Shows three carpal bones only.

serum aldolase 15 SL units/ml (normal 2–8 SL units/ml), serum creatine kinase 11 Sigma units/ml (normal 3–13 Sigma units/ml).

Electromyography (EMG) was done with Medelec MS 6 Electromyograph under standard conditions with concentric needle electrodes. The calf muscles showed no spontaneous activity at rest, motor unit potentials of 50–100 μ V in amplitude and 2–4 msec in duration with 30% polyphasic potentials, and normal recruitment pattern on maximal voluntary activity. These findings suggested a myopathy. Electronystagmography confirmed the clinical features of the nystagmus and showed the null point 10–12° to the left of primary position (Fig. 3).

He was treated with L-thyroxine 50 μ g/day, gradually stepped up to 100 μ g/day. He was alert, attentive and relieved of the constipation when last seen in July 1981. Pulse rate was 92/min. There was decrease in calf muscle size and no girdle muscle weakness was demonstrable. The nystagmus persisted.

Discussion

The KDS syndrome refers to the unusual symptom complex of muscle hypertrophy with childhood hypothyroidism (Najjar and Nachmann, 1965; Spiro *et al.*, 1970). The muscular involvement is generalized, prominent in the calf muscles, giving these children an athletic appearance (Najjar and Nachmann, 1965). EMG studies in hypothyroidism have shown normal to frankly myopathic changes (Waldstein *et al.*, 1958; Schwarz and Rose, 1963). Although there is an intimate relationship between thyroid function and muscle metabolism, the structural functional relationship is unclear and the pathogenesis of muscle hypertrophy in hypothyroidism is unknown. The changes on pretreatment biopsy have been shown to reverse completely with thyroid therapy (Spiro *et al.*, 1970). The clinical

FIG. 3. Electronystagmogram. Horizontal nystagmus on (A) centre gaze, (B) rightward gaze, (C) leftward gaze and (D) upgaze. Decrease or absence of nystagmus on (E) convergence and (F) at null point 10–12° to left of primary position.

features and hormone profile in our patient are diagnostic of sporadic thyroprivic hypothyroidism. The bulky muscles, proximal muscular weakness and EMG findings indicated hypertrophic myopathy. Decrease in muscle size and increase in muscle power on thyroid replacement therapy unequivocally establish its relation to hypothyroidism. Anthropometric and radiological findings date the onset of overt thyroid deficiency to around the age of 3 years.

A good account of the clinical characteristics of CN is given by Gay *et al.* (1974). Usually pendular in primary position, the nystagmus acquires a jerk-type character on lateral gaze and is markedly reduced or abolished on convergence. The nystag-

mus beats horizontally in all fields of gaze, and a horizontally beating nystagmus in upgaze is almost diagnostic of CN. There is an eccentric neutral position where the nystagmus slows or stops and most patients will develop a constant characteristic head posture. The nystagmus appears at birth or soon after and the patients usually have no visual symptoms. In the differentiation of congenital from acquired nystagmus, exploration of the three features (upgaze, null point and convergence effect) by electronystagmography may provide decisive information (Barber and Stockwell, 1976). The clinical features and electronystagmogram in the present patient are pathognomonic of CN.

The association of CN and hypothyroidism has

been documented possibly only once in the literature. Schulman and Crawford (1969) described 5 cases of hypothyroidism with CN. CN is usually hereditary (Gay *et al.*, 1974) but in patients with hypothyroidism no family history was obtained (Schulman and Crawford, 1969). Although prompt replacement therapy has been shown to result in the disappearance of the nystagmus in one of the cases reported by Schulman and Crawford (1969), the majority of their patients continued to manifest nystagmus despite adequate thyroid therapy. The patient under discussion exhibited no change in the nystagmus during the 10-month period of replacement therapy.

The basic pathology in CN is unknown; the classical motor-defect type may involve the corticopontine pathways, possibly the result of failure or delay in their maturation (Cogan, 1967). There is experimental evidence to indicate impairment in the development of the nerve cell processes and retarded myelination of the axon in the central nervous system in hypothyroidism (Greene, 1976). These changes are largely irreversible, a fact reflected in the poor response of the neurological impairment to delayed treatment of the human cretin (Man, Merkmann and Cooke, 1963). Although the onset of overt hormone deficiency in our patient was at about 3 years of age, vulnerable areas in the central nervous system might have been involved even in the subclinical stage. This might explain the isolated restricted involvement of the oculomotor system in the present patient. It is an established fact that deficiency of the postnatal concentration of thyroxine or inadequate replacement therapy in congenital

hypothyroidism may promote normal physical growth, but can leave irreparable imprints on the central nervous system development (Man *et al.*, 1963).

References

- BARBER, H.O. & STOCKWELL, C.W. (1976) *Manual of Electroneurophysiology*, p. 89. C.V. Mosby Company, Saint Louis.
- COGAN, D.G. (1967) Congenital nystagmus. *Canadian Journal of Ophthalmology*, **2**, 4.
- GAY, A. J., NEWMAN, N.M., KELTNER, J. L. & STROUD, M.H. (1974) *Eye Movement Disorders*, p. 66. C.V. Mosby Company, Saint Louis.
- GREENE, R. (1976) The thyroid gland: its relationship to neurology. In: *Handbook of Clinical Neurology*, Vol. 27 (Ed. by Vinken, P.J. & Bruyn, G.W.), p. 255. North-Holland Publishing Company, Amsterdam.
- MAN, E.B., MERKMANN, A.C. & COOKE, R.E. (1963) The development of children with congenital hypothyroidism. A note on early, temporary replacement therapy for 2 goitrous infants. *Journal of Pediatrics*, **63**, 926.
- NAJJAR, S.S. & NACHMANN, H.S. (1965) The Kocher-Debré-Sémélaigne syndrome. Hypothyroidism with muscular 'hypertrophy'. *Journal of Pediatrics*, **66**, 901.
- SCHULMAN, J.D. & CRAWFORD, J.D. (1969) Congenital nystagmus and hypothyroidism. *New England Journal of Medicine*, **280**, 708.
- SCHWARZ, G.A. & ROSE, E. (1963) Neuromyopathies and thyroid dysfunction. Some unusual associations. *Archives of Internal Medicine*, **112**, 555.
- SPIRO, A.J., HIRANO, A., BEILIN, R.L. & FINKELSTEIN, J.W. (1970) Cretinism with muscular hypertrophy (Kocher-Debré-Sémélaigne syndrome). Histochemical and ultrastructural study of skeletal muscle. *Archives of Neurology*, **23**, 340.
- WALDSTEIN, S.S., BRONSKY, D., SHRIFTER, H.B. & OESTER, Y.T. (1958) The electromyogram in myxedema. *Archives of Internal Medicine*, **101**, 97.