

DIABETES MELLITUS IN A CHILD SHOWING FEATURES OF REFSUM'S SYNDROME

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This paper describes a diabetic child showing most of the features of a condition described by Refsum (Refsum, 1945, 1946a and 1946b, 1948, 1952; Refsum, Salomonsen and Skatvedt, 1949) under the name of heredopathia atactica polyneuritiformis. The malady is thought to be a recessive condition and is usually referred to as Refsum's syndrome. Only six other cases have so far been reported (Reese and Baretta, 1950; Clark and Critchley, 1951; Kjellson, 1953; Fleming, 1957; Olesen, 1957) and, as far as we are able to ascertain, no case has previously been described of this syndrome in association with diabetes mellitus. In view of the rarity of this association, we think that publication of this case is of interest.

Case Report

The patient, a girl, was first seen in the out-patient department in August, 1952, when she was 4½ years old. At that time she was the elder of two children, the other being a boy aged 7 months. Since then the mother has had a further child, a girl now aged 3 years. The patient had had anorexia for one month with weight loss, and also photophobia for a similar period. She had previously been quite well apart from an operation for intussusception at the age of 8 months. She was a thin girl, small in stature for her age. There was a left-sided concomitant squint and marked photophobia. Her urine was noted to contain sugar (2% Clinitest). She was admitted to the Sunderland Children's Hospital for further investigation, and particularly in order to determine whether she had diabetes mellitus. While in the ward she remained well and ate adequately. She had intermittent glycosuria, many specimens being free of sugar. During her stay in hospital she had marked photophobia and she was seen by Mr. A. Smith, consultant ophthalmic surgeon, Sunderland, who reported 'multiple epithelial erosions on both corneae'. It was thought that these could have been produced by sand when the child was playing on the beach one month previously. Her eyes were treated with 10% albucid drops and ung. atropine ½% twice daily. On this regimen the eyes became apparently normal within two weeks. A fasting blood sugar test was carried out, the result of which was 85 mg. per 100 ml.

She was discharged home but continued to lose weight and had persistent glycosuria; she was therefore readmitted to hospital in November, 1952. On this occasion her general condition was satisfactory, and her photophobia was not so obvious, but she had polyuria and persistent glycosuria. A blood sugar curve was typical of diabetes mellitus. The patient was given a 200 g. carbohydrate diet daily and soluble insulin was started in a dosage of two units twice daily. Following each injection, she became disorientated and drowsy. In view of this hypoglycaemic response an attempt was made to control her diabetes on diet alone but she continued to lose weight, and polyuria and polydipsia continued. Insulin was therefore recommenced and was now well tolerated; her diabetes appeared to be stabilized on a daily 200 g. carbohydrate diet with soluble insulin, seven units twice daily. She remained well on this regimen and, apart from a short admission to hospital for treatment of a left lower lobe pneumonia, she remained well though unusually small for her age until February, 1955.

In February, 1955, nearly three years after the start of her illness, the mother noted that the child was becoming increasingly deaf. She was seen by Mr. Rhys Evans, consultant ear, nose and throat surgeon, Sunderland, who reported that she had considerable, but not complete, bilateral hearing loss of perceptive type.

In April, 1956, nearly four years after the diabetes had been recognized, the mother noticed a progressively worsening tremor of both arms. Later titubation of the head began and in November, 1956, she began to be unsteady and to have difficulty in walking. She had to hold on to furniture to get round a room and her arms and legs became progressively weaker. She was seen by Dr. H. G. Miller, who diagnosed Refsum's syndrome and arranged admission to the Royal Victoria Infirmary, Newcastle-upon-Tyne.

On admission, aged 9 years, she was a pathetic figure, being totally deaf, dysarthric, small and underweight. She had an expressionless moon facies, and there was symmetrical wasting of the extremities of moderate degree. She had to be fed because of the severe tremor of her hands and preferred lying on pillows to sitting up. Her cardiovascular system was normal apart from a soft systolic murmur at the apex. Her skin was normal in texture and no rash or scaling was present. Abdominal palpation revealed enlargement of the liver about one and

a half inches below the costal margin. Her ears showed a circular depression in the centre of both drums, possibly old healed perforations. Her intelligence was not tested formally but was probably in the low average group for her age and there was no dementia. Her neurological condition was dominated by severe deafness, gross intention tremor, dysmetria and titubation made worse by exertion or emotional disturbance. She could not walk unaided. Her speech was grossly dysarthric, slow, scanning and slurred. There was symmetrical weakness of her whole face and bilateral ptosis with slight weakness of external rectus movement and occasional rotatory nystagmus. The pupils responded sluggishly to light and accommodation. The fundi showed atypical retinitis pigmentosa with right optic atrophy. The arms and legs were symmetrically wasted both proximally and distally and there was slight wasting of the hypothenar eminences, but no fasciculation was observed and there was no muscle tenderness. All four limbs were weak and flaccid. In the arms triceps and supinator jerks could just be elicited, whilst the biceps jerks and tendon reflexes in the legs were absent. The plantar responses were flexor; the abdominal reflexes were symmetrically brisk. Intention tremor, dysmetria and dysdiadochokinesia were severe in the upper limbs and the legs were also very ataxic. It was difficult to be sure of her cooperation in the appraisal of sensation. She could recognize and differentiate between touch and prick, though in view of the docile way in which she submitted to venesection, but not to certain other procedures, we regarded pain sensation as possibly diminished. The vibration sense was impaired in the lower limbs.

Investigations. The urine showed marked glycosuria without albumen or cells. Paper chromatography confirmed the presence of glucose with normal amino-acid excretion and no evidence of indican or other indoles in the urine. Twenty-four-hour urinary 17-ketosteroid excretion was 1.7 mg.

Blood examinations showed: haemoglobin, 16.3 g./100 ml.; W.B.C. 6,250/cu. mm.; the peripheral blood film appeared normal. The erythrocyte sedimentation rate was 3 mm. in one hour. Glucose tolerance curve was typically diabetic with a fasting blood sugar of 160 mg./100 ml. Serum calcium, 9.0 mg./100 ml.; diffusible, 4.1 mg./100 ml. (Greenberg, Larson and Tufts); serum protein: total, 6.6 g./100 ml.; albumen, 4.9 g./100 ml.; globulin, 1.7 g./100 ml. (by difference); plasma phosphate, 3.4 mg. phosphorus/100 ml.; plasma iron, 127 µg/100 ml.; serum cholesterol, 260 mg./100 ml.; plasma amino acid, 3.3 mg. α amino acid nitrogen/100 ml.; plasma bilirubin, total, 0.2 mg./100 ml.—directly reacting absent; zinc sulphate turbidity, 2 units; thymol turbidity, 3 units; thymol flocculation, 0; cephalin cholesterol, +; plasma alkaline phosphatase, 6.9 units (Jenner and Kay); plasma prothrombin, 80% of normal average (one-stage Quick technique). The Wassermann reaction was negative.

Radiographs of the skull, thoraco-lumbar spine and the hands and feet revealed no abnormality. An electrocardiogram showed abnormally flat and diphasic T

waves; Q-T at upper limit of normal. Audiometry showed severe inner-ear deafness (70 decibels at 1,024 cycles per second). Vestibular function was normal as judged by caloric testing at 44 degree F. Perimetry was attempted, but the patient was not sufficiently cooperative to make the result worth while. Lumbar puncture (twice): normal pressure, 1 lymphocyte per cu. mm.; protein, on the first occasion, 120 mg./100 ml., on the second, 95 mg./100 ml.

On this admission the patient's diabetes was treated by giving a free diet and increasing her soluble insulin to 20 units twice a day. Several weeks later because of several hypoglycaemic attacks insulin was reduced to 15 units twice a day. At the present time the child is at home and is walking short distances with support.

The Family History. The paternal grandmother died of diabetes mellitus. There was no history of nervous disease in the two preceding generations. The parents and two siblings were clinically normal. The optic fundi, electrocardiograms and urine of the two siblings were also normal.

Discussion

The salient features of hereditary ataxia polyneuritic form (Refsum, 1952) are (1) Atypical retinitis pigmentosa with hemeralopia and concentric constriction of visual fields. (2) A picture of chronic polyneuritis with progressive pareses of distal parts of limbs and decreased or absent reflexes. (3) Ataxia and other cerebellar signs. (4) Increased cerebrospinal fluid protein with normal cell count. (5) In some cases abnormal electrocardiographic changes have been noted, in others neurogenic hearing loss, pupillary abnormalities and skin changes resembling ichthyosis.

The condition of the child we have described resembles Refsum's syndrome although there are several unusual characteristics, chiefly, photophobia rather than night blindness and the presence of dysarthria. We have not demonstrated parental consanguinity or a hereditary tendency, but this does not exclude recessive inheritance; on the other hand the disease may be the result of a mutation.

Differential Diagnosis. The differential diagnosis from such diseases as toxoplasmosis and neurosyphilis presents no real difficulty.

Other heredo-familial degenerations, Friedreich's disease, cerebellar ataxias, familial spastic paraplegia, bear some resemblance to the case described but features such as nerve deafness and retinitis pigmentosa are not usually present in these conditions.

Peroneal muscular atrophy (Charcot-Marie-Tooth) and hypertrophic neuritis (Dejerine and Sottas) were deemed unlikely on account of the gross ataxia and dysarthria.

As far as metabolic disorders were concerned, there was no evidence of nutritional deficiency in this

child and there was no significant response to oral therapy with vitamin B complex. There was no abnormal amino aciduria; this would tend to exclude such conditions as hepatolenticular degeneration and the condition due to abnormal indole metabolism described by Baron, Dent, Harris, Hart and Jepson (1956).

In our patient the relationship between the diabetes mellitus and the degenerative condition of the central nervous system was obscure. The clinical picture was quite distinct from that of diabetic myelopathy (Garland and Taverner, 1953). Although the cerebrospinal fluid protein is elevated in both conditions, our patient's disease was insidiously progressive and quite unaffected by control of the diabetes. The family history suggests that the diabetes may have been independent.

There are many similarities between the degenerative conditions of the central nervous system in our patient and those of Friedreich's ataxia and other hereditary cerebellar ataxias and familial spastic paraplegia. It has been found that there is a higher incidence of diabetes in patients suffering from Friedreich's ataxia than in the comparable general population (Ashby and Tweedy, 1953). It now seems to be apparent that many of the heredo-degenerative diseases of the central nervous system are inter-related and that transitional cases occur. Refsum's syndrome may be another member of the hereditary ataxia group, along with Friedreich's ataxia, hereditary spastic paraplegia and peroneal muscular atrophy. It would therefore be of interest to know

the incidence of diabetes mellitus in patients suffering from these degenerative conditions, and the incidence in members of affected families, as it might subsequently be possible, with adequate information, to demonstrate linkage or crossing-over between the gene or genes responsible for diabetes and those which produce the various hereditary ataxias.

Summary

A description is given of a child having many of the features of Refsum's syndrome together with diabetes mellitus.

The possible significance of the diabetes in this disease and other degenerative diseases of the central nervous system is briefly discussed.

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