FAMILIAL DYSAUTONOMIA

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'Son of man, behold, I take away from thee the desire of thine eyes . . . , neither shall thy tears run down.'
Ezekiel, ch. 24, v. 16.

'Mine eyes do fail with tears, my bowels are troubled, . . .'
Lamentations, ch. 2, v. 11.

On 21 September 1959 I examined a 4½-year-old boy who was losing weight and had severe emotional difficulties.

He was the first child of young healthy parents and was born in a nursing home after an uneventful full-term pregnancy. Because of premature rupture of the membranes and an impression of a large foetal head, Caesarian section was performed and a healthy male infant of 6 lb. 8 oz. delivered. Two years later a full-term brother of 6 lb. 3oz. was delivered *per vaginam*.

The patient was difficult to rear and was delayed in the acquisition of motor skills. He walked alone at about 2 years 4 months. He was an unhappy child, often restless and crying. At 20 months ulcerations on both corneae were cauterized. At 2½ years he was rather chubby, weighing about 30 lb., but he was inordinately restless and the possibility of retardation was mooted by a physician. As a consequence, he was taken to 'every doctor in town' and there was general agreement that he had suffered an undetected encephalitis in infancy which had left him with some retardation and with the emotional and hyperactive responses of the brain-damaged child. An attempt at I.Q. testing at 3 years suggested that he was 'about one year behind'. Various medications had little effect on his restlessness and excitability.

His best weight had been 34 lb. but in the last 6 months he had lost 4 lb. During these months he had been subject to episodes of diarrhoea and frequent upper respiratory infections.

Physical examination was virtually impossible. A small thin child, he would not lie down and would not stand still or sit for more than a few seconds. He darted hither and thither, restlessly energetic, compulsively touching everything new he saw—spatula, stethescope, ophthalmoscope and various objects round the room when he broke free. Yet he answered intelligently and to the point when questioned, though his own inquiries were more urgent and frequent. 'What's that?' he asked of everything new he saw. He saw with difficulty, for there were corneal opacities over both pupils, and he had to put his face close to an object in order to identify it, feeling it with both hands at the same time. The retinae were momentarily seen and seemed normal.

The skull appeared rather large for the boy's size, and was asymmetrical. There were no other physical signs considered to be of significance, and it was agreed that he presented the typical picture of the brain-injured child as commonly seen after an episode of encephalitis. If for no other reason than that his head appeared unduly large, a diagnosis of prenatal toxoplasmosis was entertained and an X-ray of the skull suggested. This showed no calcifications. Urinalysis and patch test were negative.

It seemed that the loss of weight was due to the recent upper respiratory infections. The use of benadryl was suggested for curbing his hyperkinetic behaviour. Despite his ceaseless activity and odd appearance and manner he nevertheless gave the impression that his intelligence was probably reasonably normal.

Some weeks later, far into the evening, my thoughts idly and unaccountably wandered to a day in 1952 when I had seen an unusual case on the wards of the Babies' Hospital in New York City, and in a flash it was clear that my patient had the same condition. Early the next morning two questions were put to the mother over the telephone, and the diagnosis was established:

'Is it correct to say that your little boy never produces tears?'

'That is so, doctor, he never has tears, no matter how much he cries. The eye doctor always asked me that question. Once he even tried to make him cry, but he still did not shed any tears. His eyes are moist, but tears are absent. In this respect he is quite different to my other child.'

'And is it true to state that he is somewhat insensitive to pain?'

'Pain? He doesn't know what pain is. It is amazing what he can endure. Last week he fell and dislodged four teeth: not a murmur. He is always falling and cutting and bruising himself, but somehow he doesn't seem to feel anything. I get the impression that he has been hurt and injured so often that he has become immune to pain. Mind you, he hates to have an injection, but the ordinary pains from injuries don't bother him a bit.'

The diagnosis was familial dysautonomia. Further inquiries revealed the following additional information:

Both parents are Jewish and unrelated, with no known familial traits. The mother became pregnant at an inconvenient time and half-hearted attempts were made to interrupt the pregnancy at 6 weeks by the use of an ergot preparation. The mother still feels guilty about this episode. Pregnancy proceeded normally and his birth by Caesarian section took place on 2 June 1955. Breast feeding was abandoned after a few days; he would not feed well, but the bottle was a poor substitute. His feeding was a great struggle; he often took more than an hour to swallow but a few ounces. When solids were added he was even worse. Throughout infancy he was fussy, unhappy, crying, refusing to feed despite evident hunger. It says much for the mother's perseverance that he weighed about 30 lb. at 2½ years.

The routine immunizations did not upset him unduly, and he has not yet suffered any of the 'inevitable' infections.

Teeth appeared at 7 months, he sat alone at 9 months, crawled at 14 months, attempted to walk with assistance at 18 months and walked alone at 2 years 4 months.

He was born with a squint in the left eye, which was corrected by operation at 2½ years. At 8 months ulcerations appeared on both corneae. These cleared and reappeared repeatedly, and at 20 months he was admitted to hospital, where the ulcerations were cauterized, after which the corneal scars did not progress, although they seriously interfered with his vision. At the time of his admission to hospital a number of investigations were performed as follows:

Hb. 12·7 g.%; w.b.c. 10,700 per c.mm. (polymorphs 62%, lymphocytes 32%); platelets normal; ESR 38 mm./hour. No pyrexia. Tuberculin test (PPD) negative. Numerous modifications of WR test, all negative. Serum albumin 2·8 g.%, globulin 2·7 g.%, gamma globulin 0·99 g.%. X-ray of hips (done because of odd gait) normal.

Home again, his behaviour was a sore trial. He had inexhaustible energy, never sat still, touched everything within sight, never finished a job, had no continuity of attention, and demanded an inordinate amount of parental affection and expressions of love. He could say 2 consecutive words ('I'm hot') at a year, but the mother feels that he did not really understand what he was saying until well after 2 years. At present he knows colours, can count up to 20, sings, recites nursery rhymes, is shrewd, thinks intelligently.

He eats well, usually sleeps well, has had no episodes of unexplained fever, no fits, is not prone to vomiting, but he drools excessively. His hearing and 'balance tubes' have been tested by an otologist and pronounced normal. His sense of smell is good. As an infant he was prone to long sessions of head banging, and he still indulges in head rolling, but was never given to thumb-sucking. There has been no difficulty with his sphincters. He walks with an unsteady gait. He is said not to sweat excessively, though 2 years ago he had an episode of fever associated with copious perspiration, and in the past month a nursery school teacher reported that his socks were wet with perspiration, and this on a cool day. His extremities have always been cold ('hands are like blocks of ice').

He was re-examined—again with some difficulty—and a number of additional features noted, as follows:

He is distinctly small (height 39 inches) and thin (his legs look like chicken-bones). The slightly asymmetrical skull measures 19¾ inches. A small patch of partial baldness is present in the right parietal region. The pulse is 90 per minute and regular. The blood pressure is 100/70 mm. Hg in the supine position, and falls to 96/64 mm. on standing up, but promptly jumps 10 mm. (systolic and diastolic) when anything distracts or excites him—which is pretty often. His eyes are pale blue and have corneal opacities over both pupils, the right opacity being rather larger and denser. The corneae are totally anaesthetic; he fails to blink no matter how long cottonwool is rubbed over them. There were 2 or 3 healed scars on his thin bird-like face. His voice lacked the crisp clear tones of childhood. Despite the warmth of the day his hands were remarkably cold and the skin on the arms and legs was blue and mottled. Peripheral pulses normal. There was no scoliosis, no pes cavus, no dermographism. Knee jerks were brisk and equal. The gait was unsteady but he had no spasticity or undue flaccidity. Gag reflex present. He was drooling.

In February 1959 an EEG was done while he had been put to sleep with barbiturates: 'There are a large number of scattered high-amplitude delta waves. This is probably due to moderate brain damage from an early age; in fact many of the waves resemble space-occupying lesion waves, non-focal and non-episodic, though there is some predominance in the left occipital area' (Dr. L. Sussman, Tara Hospital).

The X-ray of the skull which was done to exclude toxoplasmosis, though otherwise normal, indicated the presence of plagiocephaly. There was no suggestion of increased intracranial pressure. The parents declined to have air studies performed.

DISCUSSION

This patient has a hotch-potch of curious and seemingly unrelated symptoms and signs, and one may readily be excused for overlooking the fact that a symptom-complex exists. The most pronounced features of his syndrome are: Jewish origin, lack of tears with corneal anaesthesia and opacities, insensitivity to pain, poor motor coordination, emotional lability, difficulty with feeding in infancy, cold extremities.

These features apparently have no connection with each other, but Riley and his co-workers[1] (1949) recognized the presence of a specific entity, described the syndrome and gave it a name.

At the Babies' Hospital, New York City, they observed 4 children 'with symptoms so puzzling as to defy exact diagnosis yet so similar as to constitute a clinical entity'.[1] Since then (up to 1957) about 70 cases of the Riley-Day syndrome have been identified in North America, and one reported from Germany and one from England.[2,3]

Riley states[2] that the manifold symptomatology is clearly due to widespread involvement of the central nervous system—ranging from autonomic, through motor and sensory, to psychic disturbances, and that such widespread derangements can only be conceived of in terms of biochemical malfunction—possibly some enzymatic defect of metabolism within the central nervous system. He lists the signs and symptoms under 3 headings:

(*a*) *Probably present in all cases, though future experience may reveal exceptions:* Jewish origin (with very rare exceptions); reduced tears when crying; emotional lability; indifference to pain; postural hypotension; excessive perspiration; cold hands and feet; disturbed swallowing reflex; poor motor incoordination; dysarthria.

(*b*) *Often present:* Hypertension on excitement; skin blotching on excitement; erratic temperature control; drooling beyond the usual age; hypoactive or absent tendon jerks; corneal anaesthesia; mental retardation (in about half of all cases); breath-holding spells in infancy; episodes of vomiting; frequent bronchopneumonia; retardation in growth; abnormal EEG; occurrence in siblings (25% - 35% of cases).

(*c*) *Sometimes present:* Diarrhoea or constipation; scoliosis and other orthopaedic conditions; corneal ulceration; increased tendency to body injury; consanguinity of parents; occurrence in related families.

Children with dysautonomia that are prone to recurrent vomiting, bronchopneumonia and hyperpyrexia have a poor prognosis, and 13 of the described cases have come to autopsy, but have shown no consistent gross abnormalities of the central nervous system.[2] Air studies of the brain are generally unhelpful[4] and the blood chemistry normal,[5] but the EEG is non-specifically abnormal.[4] The diagnosis is thus entirely clinical.

The disease is virtually confined to Jews, though Riley believes that it has been satisfactorily defined in 4 non-Jewish children.[2] This might perhaps be due to unknown Jewish antecedents, genetic mutation, or prenatal phenocopy. Jews have their troubles, not the least of them being their genetic disabilities, and, since they intermarry, dysautonomia (recessive gene?) virtually remains confined to them. Its alleged presence in non-Jewish children should be viewed with much suspicion. In about a quarter to a third of the reported cases siblings have been affected.

The principal diagnostic feature is the lack of tears, which together with corneal anaesthesia is responsible for the occurrance of corneal ulceration and cicatrization. Biopsy of the lacrymal glands shows no abnormality.

All the children are dwarfed, and nearly all poorly nourished, with comparable delay in bone maturation, but puberty is not strikingly delayed. Their emotional and physical handicaps are responsible for the difficulty in accurately assessing their intellectual capacities, and their disturbances of behaviour are frequently the chief cause of concern within the family. They are slow to acquire motor skills and most begin talking late, and have a nasal and monotonous voice.

Frequently they develop transient erythematous blotches, usually about the upper chest, and they invariably have profuse perspiration (but not in the case reported here). The electrolyte concentration of sweat is normal. Unlike what happens normally, in all cases reported the blood pressure (especially the diastolic) drops when the patient

stands up (in the case reported here this was not a striking feature). Sometimes there are massive swings in blood pressure, leading to suspicion of phaeochromocytoma. Knee jerks may be present, especially in older children. Routine immunization procedures sometimes produce major feverish reactions, and unexplained hyperpyrexia is common; so are frequent bouts of bronchopneumonia. At about 3 - 4 years of age recurrent episodes of severe and prolonged vomiting may make their appearance, frequently requiring the use of intravenous fluids.

Differential Diagnosis

According to which constellation of symptoms is most prominent, it may be necessary to exclude such conditions as fibrocystic disease, pink disease, hypogammaglobulinaemia, mental retardation, childhood schizophrenia, cerebral palsy, Sjorgen's syndrome, and phaeochromocytoma. In the full-blown case of dysautonomia the diagnosis presents but little difficulty.

Prognosis and Treatment

There is insufficient data for advice on prognosis, but certainly the death rate is higher in those prone to infections, hyperpyrexia and vomiting. The oldest recorded patient is now (1959) 25 years old. Up to 1957 the condition had not been described *de novo* in adults. The patients' emotional difficulties tend to subside with time and, if their intellect is reasonable, their adaptation to society may be adequate.

The risks inherent in anaesthesia have not yet been properly assessed; more data are needed. My patient had two uneventful operations on his eyes.

Treatment is entirely supportive. The child here reported is making progress in a nursery school for emotionally disturbed children. The psychiatric aspects of the condition have been considered by Freedman *et al.*[5] A society for the parents of afflicted children has been formed in New York and group therapy has proved helpful.

SUMMARY

The Riley-Day syndrome or familial dysautonomia has not yet been reported in this country. A case of this 'new disease' is now recorded in a 4-year-old Jewish boy, who illustrates the principal features of lack of tears with corneal anaesthesia and corneal ulcers, insensitivity to pain, cold extremities, pronounced feeding difficulties, motor incoordination, dysarthria and emotional instability—in particular, anxiety, restlessness, impulsiveness, irascibility, compulsive touching, and hyperkinesia, in fact the typical picture of the behavioural disturbances of the brain-injured child. The absence of marked postural hypotension and of constant excessive perspiration is not felt to be a bar to the diagnosis.

The diagnosis is entirely clinical, and no doubt *formes frustes* of the condition occur—all the way to normality. Until more definitive diagnostic criteria are established (e.g. one or other enzyme, yet to be isolated, in the plasma or cerebrospinal fluid), it would be difficult indeed to sustain a diagnosis of 'a mild case of dysautonomia'. The syndrome lends an interesting foundation to the possibility of organic brain damage (enzymatic defect?) as a basis of some disturbances of behaviour.

There is no treatment other than supportive and there are no consistent gross brain abnormalities to account for this conglomeration of curious symptoms. The syndrome is familial, and virtually confined to Jews.

My thanks are due to Dr. K. F. Mills, Superintendent of the Johannesburg General Hospital, for permission to quote from the patient's records at the Children's Hospital, and to Dr. H. Moross for allowing me to reproduce the EEG report from Tara Hospital.

POSTSCRIPT

I have since been informed by Dr. B. Senior, Johannesburg, that his firm of paediatricians have seen two or three children with dysautonomia in the past few years. The case reported here was also seen by one of them, and I am given to understand that the diagnosis of dysautonomia was entertained but was not communicated to the parents.

Since this report was submitted the mother has been delivered of another boy; he is breast feeding normally and is presumed to be well.

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