

Early Diagnosis of Familial Dysautonomia

Case Report with Special Reference to Primary Patho-physiological Findings

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The symptoms and signs of familial dysautonomia were first gathered into a clinical entity by Riley *et al.* in 1949. A review by Riley and Moore published in 1966 reveals how much has since been elucidated about the condition and how much still remains obscure. Most of the cases reported come from the USA, though the majority of the patients are of Jewish extraction and have ancestors who come from Eastern Europe (P. Brunt, 1967, personal communication; publication pending). It, therefore, seems likely that the paucity of reports in the British literature (McKendrick, 1958; Hutchison and Hamilton, 1962; Russell and Avery, 1963) reflects a failure to recognize or report rather than a scarcity of such immigrants in the United Kingdom.

This report concerns an English child diagnosed as having the condition at the age of 6 weeks. Apart from the 24-hour-old sib of a known case described by Geltzer *et al.* (1964), recognition of the condition at an earlier age has not been documented. The early diagnosis allowed a distinction to be made between those pathological changes that were primary features of the condition and those that occurred secondarily.

Case History

The patient is the second child of London-born, Jewish parents, of Eastern European origin. A maternal uncle died of cerebral haemorrhage at the age of 11 years; otherwise the family history is unremarkable. Pregnancy and delivery were normal, and the birthweight was 2948 g. at full term. Within 4 days there was difficulty in feeding, and she sometimes breathed heavily and looked grey. At 4 weeks, opisthotonus and abdominal distension developed, and she was transferred

to the care of Dr. Dennis Cottom at The Hospital for Sick Children, Great Ormond Street.

Clinical features. An ill baby with dilated pupils, she lay in opisthotonus which increased with crying. There was marked abdominal distension with visible peristalsis, though frequent amounts of stool were being passed. Tone was poor and the tendon reflexes were not elicited. The skin was grey and cool but became mottled when she cried. She was afebrile. Subsequently, it was noted that though she could suck and swallow, these two actions were not synchronized, and as a result food was repeatedly aspirated.

This last observation suggested the diagnosis, and provoked a search for confirmatory evidence. It was noted that she had no fungiform or circumvallate papillae on her tongue. Salivation and sweating were normal but overflow tears were not produced, even after 2 months of age. Corneal reflexes were absent and there was no response to pin-prick. The blood pressure was extremely labile, and if she were disturbed it rose sharply.

At 6 weeks the administration of 2.5% methacholine eye-drops produced conjunctival injection, and rapid constriction of the pupil. There was no change in pupil size in a normal control matched for age and eye colour. Intradermal injection of 0.01 ml. of 1 : 10,000 histamine sulphate produced little sign of pain, a circumscribed wheal, and no axon flare. When her oesophageal function was assessed by a barium swallow, pharyngeal incoordination was shown, with reflux of the medium into the nasopharynx at each gulp and some overflow into the trachea. Chest x-ray showed shadowing in the right upper lobe and the initial x-ray of the abdomen showed fluid levels which subsequently disappeared spontaneously. No haematological or serum biochemical abnormalities were found, and urinary amino acid and sugar chromatographic patterns were normal. Skull x-ray, CSF, EEG, and EMG were normal.

At 11 months the urinary excretion of vanillyl-mandelic acid (VMA) was 0.6 mg./24 hours and of

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homovanillic acid (HVA) 0.8 mg./24 hours, these results being normal, as is the HVA : VMA ratio.

Subsequent progress and treatment. The initial stay in hospital was prolonged owing to feeding difficulties which were still persisting at 2 years of age. The developmental milestones were delayed: she first rolled over at 9 months, at 10 months she was just reaching out and grasping objects, and she did not sit unsupported until 15 months.

At 5 months, long-term treatment was attempted with pilocarpine 0.125 mg. q.d.s. Before starting this treatment, a ciné swallow (taken in the supine position to avoid the effects of gravity, as recommended by Linde and Westover, 1962) demonstrated pharyngeal incoordination, with reflux of the contrast medium into the nasopharynx with each swallow. No good oesophageal stripping wave was seen, and there was some oesophageal residue. When repeated at 11 months while on pilocarpine, normal pharyngeal function was found, but the oesophagus was virtually non-contractile. Stopping pilocarpine at this stage made no difference to the film, and it is possible that the improvement was due to the child's having learned trick swallowing, rather than as a response to the drug. Pilocarpine similarly made no discernible difference to the other clinical features of the condition, and little success was achieved by this attempt at therapy. Methyl-cellulose drops were used as artificial tears, and antibiotics for recurrent aspiration pneumonia, but otherwise her anticipated progress has not been altered by treatment.

At 11 months she was readmitted in a moribund state, with a temperature of 42.1° C. for which no cause could be found. During this episode she became immobile and unresponsive but eventually recovered spontaneously.

Special investigations. The lability of the blood pressure in familial dysautonomia is well documented (Riley, 1957; Riley and Moore, 1966; Aronson, Stern, and Cohan, 1951; Fellner, 1964), but all cases, other than that described by Geltzer *et al.* (1964), have been in older children. Elsewhere, the response to infusions of methacholine (Smith, Hirsch, and Dancis, 1965) and noradrenaline (Smith and Dancis, 1964) have been described, and are now regarded as diagnostic (Riley and Moore, 1966). Recording the blood pressure in a baby is difficult and inaccurate, and the flush method may be misleading as it relies on vasodilatation as a guide to the end-point. It was, therefore, thought legitimate to record the pressure directly.

At the age of 4 months, using local anaesthesia, but without premedication, a small needle was inserted into the right femoral artery and the saphenous vein was cannulated with fine polythene tubing. During the procedure spontaneous variations in diastolic pressure from between 35 and 135 mm. Hg were recorded.

Slow intravenous infusions of 1.5 mg. methacholine produced hypotension and bradycardia. The blood pressure fell from 80/35 to 60/20 mm. Hg and from 115/65 to 60/20 mm. Hg on the 2 occasions that the

drug was given. The heart rate simultaneously fell from 160 and 168/min. to 60/min. When 2 µg. noradrenaline were given over a period of a minute, the pressure rose from 120/75 to 155/115 mm. Hg, and the heart rate from 180/min. to 204/min. These changes in blood pressure are quantitatively greater than expected, but perhaps more significant are the heart rate responses. Normally, when pressure rises, the aortic and carotid sinus baroreceptors are stimulated and cause reflex bradycardia, whereas hypotension induces reflex tachycardia. These reflex changes were absent in this patient.

General response to methacholine. Infusion of methacholine was also accompanied by alterations in the clinical state. Tone improved, and her ocular response to methacholine eye-drops was repeated. The patient also sweated, salivated, micturated, and defaecated. An intradermal injection of histamine, before the infusion of methacholine, had only produced a wheal, but after the infusion a flare developed around it. Weakly positive knee-jerks were also obtained within 5 minutes of the injection.

Skin and rectal biopsies. At 2 months, biopsy of abdominal skin, and at 4 months, under general anaesthesia, full thickness rectal biopsy including parasympathetic ganglia were taken, and compared with control material from surgical patients of the same ages. Unlike the experience of others (Kritchman, Schwartz, and Papper, 1959), general anaesthesia was tolerated without incident. The specimens were snap frozen, sectioned in a cryostat, and stained for acetylcholinesterase, using Gomori's (1952) modification of Koelle's method.

Under light microscopy the architecture, histology, and staining reactions of the ganglia were seen to be normal. In our patient the enzyme was present in a network around the sweat glands of the skin, and in neurones and nerve fibres contained in the rectal biopsy. Skin biopsies from control cases aged 2 months showed the same staining intensity, whereas those aged 3 months and over showed a somewhat greater intensity. The staining in the rectal biopsy was exactly comparable with the controls.

Discussion

Because of the paroxysmal nature of many of the symptoms and signs of familial dysautonomia, such as intermittent fever, skin blotching, sweating, and hypertension, earlier workers have postulated an imbalance between the activity of the sympathetic and parasympathetic nervous systems (Hutchison and Hamilton, 1962; Smith, Taylor, and Wortis, 1963). The observed responses to local and intravenous methacholine have given substance to this idea.

The response to methacholine eye-drops is one of the simplest and most reliable of the tests for familial dysautonomia, but it is not pathognomonic.

A similar response was seen in a child with congenital rubella syndrome, who presumably had a defect in the parasympathetic control of the pupil. The intradermal injection of histamine is also a useful diagnostic test but fails to produce an axon flare in atopic dermatitis (Cooper, 1950) and in peripheral neuritis (Kierland, 1965), as well as in familial dysautonomia. Once, unexpectedly, a faint flare was obtained in our patient, but it was then realized that the pupillary response to methacholine had been tested within the previous half hour, and small amounts of the drug must presumably have been absorbed through the conjunctiva. Care is thus needed in the interpretation of even the simplest tests, and the diagnosis is still largely clinical.

In our patient the pupillary responses to phenylephrine, ephedrine, and physostigmine, as well as to methacholine, have already been described elsewhere in a preliminary communication (Shinebourne, Sneddon, and Turner, 1967), and indicated denervation of both sympathetic and parasympathetic receptor sites. Intravenous infusion of methacholine stimulates other activities under parasympathetic control, such as tear production and peristalsis. Tone and tendon jerks as well as sensitivity to pain are partially or completely restored, as is the axon flare. This is harder to understand as methacholine would be expected only to exhibit the muscarine-like actions of acetylcholine.

The fact that the end-organs are capable of response suggested that in familial dysautonomia the basic fault was in synthesis or release of the neurohumoral transmitter. An indirect way of assessing acetylcholine activity is to stain histological specimens for acetylcholinesterase. This was done by Hutchison and Hamilton (1962) who described excess enzyme activity in the skin biopsy of an affected patient, and by Winkelmann, Bourland, and Smith (1966). Our findings agree with the latter workers who demonstrated normal histochemistry. The observation that the amount of this enzyme varies with age emphasizes the need to use controls of the same age, and may explain why our findings differ from those of Hutchison and Hamilton.

In our patient the ganglia in the rectal biopsy were anatomically and histologically normal, suggesting that the vacuolar cytoplasmic changes in Auerbach's plexus, described in a necropsy specimen by Solitare and Cohen (1965), were secondary developments rather than primary lesions of familial dysautonomia.

The biochemical assay which has most frequently been reported as abnormal is a high urinary HVA : VMA ratio (Smith *et al.*, 1963). HVA is

derived from dopa or dopamine, precursors of noradrenaline and adrenaline, whose breakdown product in turn is VMA. Impaired production of dopamine from dopa, or of noradrenaline from dopamine would have explained the urinary findings, but the ratio was normal in this patient.

In familial dysautonomia, local axon and spinal reflexes, common sensation, and special sensation, i.e. taste and smell, are disturbed, in addition to the impaired autonomic function. This indicates a widespread abnormality in neurotransmission, perhaps at synaptic junctions or at the neuronal membrane itself.

The negative resting intracellular potential of nerve cells depends principally on the selective cation permeability of the cell membrane. If this were abnormal, or if ionic flux and hence propagation of the action potential were impaired, then a widespread disturbance of nervous function would result. The release of acetylcholine at the motor nerve terminal is at least partly under the control of local calcium and magnesium levels (Feldman, 1965), and Burn and Gibbons (1965) have shown that the effectiveness of sympathetic stimulation depends on calcium concentration. Similarly, acetylcholine has been shown to exert its secretory effect on catecholamine release from the adrenal by promoting calcium influx into the chromaffin cells (Douglas and Rubin, 1963). The patho-physiological basis of familial dysautonomia could lie at the cell membrane, where calcium ion flux is disturbed.

Summary

The features and diagnosis of familial dysautonomia have been illustrated by observations on an English child diagnosed at 6 weeks of age. Under light microscopy normal ganglia and nerve endings were demonstrated in skin and rectal biopsies. There was presumptive evidence of acetylcholine production at nerve endings, and catecholamine metabolism was normal. Neurological findings show impairment of common and special sensation, and of local axon and spinal reflex arcs, as well as of autonomic function. These findings would be compatible with a functional defect at the cell membrane.

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