Short report

Acute dysautonomia associated with Hodgkin's disease

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SUMMARY A patient is described with acute dysautonomia associated with Hodgkin's disease. Testing of cardiovascular reflex control showed that this patient had a rare manifestation of autonomic cardiovascular neuropathy, namely intact parasympathetic heart rate control in combination with a sympathetic postganglionic lesion affecting the control of the vascular tree.

Cardiovascular reflex activity is commonly used to assess the extension and localisation of the damage in acute dysautonomia. It is generally held that the dysfunction in the cardiovascular system is predominantly parasympathetic.¹ An isolated sympathetic cardiovascular lesion has never been reported to our knowledge. In this case-report we describe a patient with acute autonomic dysfunction, associated with Hodgkin's disease and, as an especially unusual feature, severe orthostatic hypotension with intact vagal heart rate control.

Case report

In July 1983 a 22-year-old female student visited her family doctor with a supraclavicular lymph node swelling. The following week she started complaining of postural dizziness. Severe orthostatic hypotension was diagnosed. Afterwards she developed complaints of a dry mouth, constipation and urinary retention. On neurological examination, 6 weeks after the onset of her complaints, a dilated left pupil with a sluggish reaction to light and a diminished right sided Achilles tendon reflex were found. Electromyographic investigation revealed no abnormalities. Following a biopsy of the right supraclavicular lymph node and clinical staging Hodgkin's disease stage II A was diagnosed. For five months she was treated with a combination of mechlorethamine,

vincristine, procarbazine, prednisone and mantelfield radiation (40 Gy), resulting in a complete remission of Hodgkin's disease. During treatment bowel movements and bladder function almost normalised and the complaints of a dry mouth disappeared. The orthostatic hypotension was treated with 100 µg fludrocortisone daily with slight improvement.

On re-examination in June 1984 a dilated left pupil and diminished right sided Achilles tendon reflex were still present. Instillation of 0.125% pilocarpine hydrochloride produced miosis of the left pupil, but had no effect on the diameter of the normal right pupil. The combination of these abnormalities indicated the existence of Adie's syndrome.²

Cardiovascular reflex control was investigated on two occasions: on admission in August 1983, six weeks after the start of her complaints and again in June 1984. At the first examination heart rate (HR) variations during forced breathing expressed as the inspiration-expiration (I-E) difference were normal (I-E difference 20 beats/min (BPM)).³ After atropine, HR increased from 54 to 92 BPM. Supine values for systolic blood pressure (104-120 mmHg) and diastolic blood pressure (70-76 mmHg) were normal. On standing blood pressure dropped to 76/56 mmHg after half a minute. Heart rate increased instantaneously from 58 to 95 BPM in 15s. In spite of a progressive fall of arterial pressure HR did not increase further. She could not remain standing for more than one minute without fainting. Supine values for noradrenaline and adrenaline were abnormally low⁴ and on repeated examinations there was virtually no change in plasma catecholamines on standing (table). After administration of 10 mg of acetylcholine intradermally on the medial side of the calf muscle half way between the knee and ankle^{2,4} no piloerection was observed.

At the second examination: her orthostatic tolerance had slightly improved; she could stand 2 to 5 minutes. Changes

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Table Pharmacological investigations

Plasma catecholamines values ⁴ (in pg/ml; mean $\pm$ SD)	August 1983	June 1984	Reference
<i>Supine</i>			
Noradrenaline	43 $\pm$ 9 n = 9 (range 30–55)	93 $\pm$ 12 n = 6* (range 80–115)	145–575 pg/ml†
Adrenaline	12 $\pm$ 5 n = 9 (range 5–20)	42 $\pm$ 12 n = 6* (range 30–60)	10–150 pg/ml†
<i>Standing</i>			
Noradrenaline			
1–2 min standing	65	90	
5 min standing		60‡	
Adrenaline			
1–2 min standing	23	25	
5 min standing		60	
<i>After 6 mg tyramine</i>			
Noradrenaline		85	
Adrenaline		30	

*Unpaired Student *t* test $p < 0.001$ vs August 1983.

†95% confidence limits in healthy subjects.⁴

‡The lower limit of 95% confidence interval for the difference between standing and supine noradrenaline values in healthy subjects amounts to 120 pg/ml.⁴

in blood pressure induced by standing and the Valsalva manoeuvre were typical for autonomic failure (fig). On standing HR increased from 62 to 137 BPM within one minute and to 149 BPM maximally. Supine values of noradrenaline and adrenaline were higher than during the first examination, but noradrenaline was still abnormally low and there was virtually no change in catecholamines on standing (table). No changes in HR or blood pressure were observed after hand immersion in ice water for 1 minute.⁵ A low dose of phenylephrine (25 μ g) induced a 30 mmHg rise in systolic pressure with an inverse blood pressure HR relation; HR decreased from 55 to 47 BPM.⁵ Administration of a high dose of tyramine (6 mg) was not followed by an increase of plasma-noradrenaline (table).⁵ Acetylcholine induced an area of piloerection of 3 cm, a value still below normal.⁴

Discussion

The findings of an isolated autonomic neuropathy associated with Hodgkin's disease without signs of involvement of other parts of the nervous system appear to be extremely rare.^{6–10} There were symptoms of parasympathetic impairment of several organ systems, namely Adie's pupil, a dry mouth and disturbed bladder and bowel function. Sympathetic involvement was indicated by the severe orthostatic hypotension. During the follow up period we observed, like others,¹² partial regression of the acute dysautonomia. Nevertheless orthostatic hypotension persisted, as well as an Adie's syndrome. The origin of the pathophysiological defect remains a matter of conjecture. Altered immunology has been considered, but the underlying mechanism has not yet been defined.⁸

The cardiovascular dysfunction we found in this patient is unusual. The afferent, central and vagal efferent baroreceptor reflex pathways were functionally normal as indicated by a reflex bradycardia after the phenylephrine induced rise in systolic pressure, the marked HR variations during forced breath-

ing, the instantaneous large HR increase on standing and the atropine induced tachycardia.^{2 3 5 11 12} It appeared, therefore, that the lesion was located in the

Fig Blood pressure responses induced by the Valsalva manoeuvre (upper panel) and standing (lower panel). Both records show the typical responses generally seen with severe failure of sympathetic circulatory control. Blood pressure was measured noninvasively.¹³

effluent sympathetic vasoconstrictor fibres.^{2 5} This was confirmed by a negative cold pressor test, abnormally low noradrenaline levels at rest and virtually no change in noradrenaline on standing (table).^{4 5} Super-sensitivity to phenylephrine, no release of noradrenaline after a high dose of tyramine and no pilomotor responses after intradermal acetylcholine (table) imply a lesion in the postganglionic sympathetic nerves.^{1 2 4 5} Cardiac vagal denervation is common in acute dysautonomia and in diabetic autonomic neuropathy as well, whereas overt sympathetic circulatory impairment appears to be rare.^{1 2 4 12} The form of autonomic neuropathy in this patient with the unusual combination of intact parasympathetic HR control and a sympathetic lesion affecting the control of the vascular tree may be interpreted as the mirror image of the common pattern.

Severe orthostatic hypotension persisted; nevertheless the much more pronounced increment in HR after 1 minute standing at the second examination (75 BPM vs. 38 BPM), the partial recovery of pilomotor function and perhaps the increase in supine catecholamines suggest improvement of sympathetic cardiovascular control. The combination of hypoadrenergic orthostatic hypotension (fig, table)^{4 5} and a marked postural tachycardia has to our knowledge not been described before.

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recommended that, in elderly patients at least, it would be prudent to perform an ECG prior to starting carbamazepine therapy.³¹

All nine cases described so far, have been elderly and only one patient has had epilepsy. No fatalities have been reported, and in the two detailed post-mortem studies on sudden death in epileptics,^{8,9} only one was taking carbamazepine, but not in the therapeutic dosage.⁸ We suggest, however, that carbamazepine was responsible both for the syncopal attacks and the death of our young epileptic probably by causing ventricular asystole.

The lesson to be drawn would seem to be that any patient on carbamazepine, for whatever reason, who complains of syncope or a change in seizure type, should be admitted for investigation of this atrio-ventricular conduction system.

The differentiation of cardiac and epileptic loss of consciousness can often be difficult and the temptation to increase the dose of carbamazepine in an epileptic who complains of loss of consciousness should be resisted until assessment of their cardiovascular status is complete. If in doubt, it is probably best to stop the drug and substitute an alternative. It may be prudent to perform an ECG in the elderly, before commencing treatment with carbamazepine but, in the absence of further data on death related to the drug, no further precautions can be justified.

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Correction

In the paper "Acute dysautonomia associated with Hodgkin's disease" (J Neurol Neurosurg Psychiatry 1986;49:830-2) reference 13 was incomplete. It should have read: Ref 13. Wesseling KH, Wit B de, Settels J, Klawer WH, Arntzenius AC. On the indirect registration of finger blood pressure after Penaz. *Funkt Biol Med* 1982;1:245-50.

Notice

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