Orthostatic hypotension and the Holmes-Adie syndrome

A study of two patients with afferent baroreceptor block

R. H. JOHNSON, D. L. McLELLAN, AND D. R. LOVE

From the University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, and the M.R.C. Blood Pressure Unit, Western Infirmary, Glasgow

SUMMARY Two patients who presented with symptoms due to orthostatic hypotension were found on examination to have the Holmes-Adie syndrome. Physiological investigation suggested that they both had an afferent block from baroreceptors in contrast to the efferent autonomic block found in most other cases of idiopathic orthostatic hypotension, including the cases of multisystem disease, now often called the Shy-Drager syndrome.

Patients presenting with 'idiopathic' orthostatic hypotension are often found to have degenerative disease of the central nervous system. This association was emphasized by Shy and Drager (1960) and has been confirmed in subsequent reports, including those of Bannister, Ardill, and Fentem (1967) and Hughes, Cartledge, and Millac (1970). The clinical findings in this disorder have been analysed by Thomas and Schirger (1970) who reviewed 57 patients and found evidence of Parkinsonism together with degeneration of the corticobulbar-corticospinal, extrapyramidal and cerebellar motor tracts. Johnson, Lee, Oppenheimer, and Spalding (1966) studied two patients with 'idiopathic' orthostatic hypotension, one of whom had multisystem degeneration, and found physiological evidence of a lesion of the preganglionic efferent autonomic pathways. They were able to correlate these results with degeneration of the intermediolateral columns of the spinal cord subsequently found at necropsy.

Croll, Duthie, and MacWilliam (1935) found orthostatic hypotension in a patient with the Holmes-Adie syndrome and a number of other such patients have been described. We report two patients with this association who can be further contrasted with cases of multisystem disease on the basis of physiological investigations which have indicated a block of *afferent* nerves from arterial baroreceptors.

CASE 1

P.T. (Killearn Hospital N.28,555), a male, presented in June 1968 at the age of 50 years with six months' history of giddiness on standing up from the sitting or stooping

positions. He also became giddy on walking briskly and could abolish this symptom by sitting down or pretending to tie his shoe laces. He also complained of impotence of six months' duration. In 1965 he had had a number 'nocturnal seizures' in which he waved both arms and was incontinent of urine. An EEG was normal, but nevertheless he was treated with phenytoin and had no further attacks until the drug was withdrawn six months later. A further six months' course of phenytoin again abolished the attacks, which did not recur when medication was discontinued in 1967. He was otherwise in good health and of normal intelligence. His father died of a heart attack at 55 years, but his mother was aged 80 years and in good health. He had one healthy adult son. On examination his height was 176 cm and weight was 85 kg. His supine blood pressure was 125/90 mm Hg, and fell to 60/30 mm Hg after standing for five minutes. The left pupil was larger than the right and both reacted sluggishly to light. Biceps and triceps tendon reflexes were diminished symmetrically, and supinator, knee, and ankle reflexes were unobtainable. There was also moderate pitting oedema of both ankles. No other clinical abnormality was found.

CASE 2

K.C. (Killearn Hospital N.31,314) a female, presented in April 1970 at the age of 20 years complaining of six months' dizziness, which most commonly occurred on rising from the sitting to the standing position. She had noticed that the dizziness was worse after she had been sitting near a fire and she sometimes became dizzy while standing at her job of towel packing. Some episodes of dizziness were accompanied by widespread sweating. Previously she had attended a dermatologist and a diagnosis of dermatitis artefacta of the hands and wrists had been made. The youngest of her three siblings was

known to have phenylketonuria. A positive test for phenylalanine in the urine had been obtained in this patient in 1965 and a negative test in 1969. No treatment had been prescribed in view of her age. Her verbal IQ was 72 and performance IQ was 46 (Wechsler Adult Scale). On examination her height was 154 cm and weight was 39.1 kg. The blood pressure was 210/145 mm Hg when she lay supine, falling to 140/80 mm Hg after two minutes when she stood up. There was obvious sweating in the axillae. Patches of skin abrasion were present on the fingers and thighs. Tendon reflexes of the biceps and triceps muscles were reduced, tendon reflexes at the ankles were absent, and plantar responses were flexor. The right pupil was larger than the left and both reacted very slowly to light, the right pupil requiring several minutes' dark adaptation before any response could be seen. The response of the pupil to accommodation was normal on the left and sluggish on the right. No other clinical abnormality was found, and in particular there was no evidence (apart from mental retardation) of the neurological abnormalities that have been reported to occur in association with phenylketonuria (Wolff, 1968).

INVESTIGATIONS

The following estimations were made on both patients with normal results: serum electrolytes, alkaline phosphatase, thymol and zinc sulphate turbidities, SGPT, plasma proteins, B₁₂, WR; blood count and film; CSF protein, microscopy and WR; oral glucose tolerance test; mid-stream urine microscopy and culture. The urinary metadrenaline excretion in case 1 was 0.4 mg/24 hr. In case 2 it was 0.6 mg/24 hr. The urinary 17-ketosteroid excretion was 18 mg/24 hr in case 1, and 7.2 mg/24 hr in case 2. Urinary 17 hydroxycorticosteroid excretion in case 1 was 22 mg/24 hr; in case 2 it was 6.9 mg/24 hr.

Case 1 in 1968 had a consistently raised blood urea varying from 42 to 62 mg/100 ml. The serum creatinine varied from 1.2 to 1.7 mg/100 ml. An intravenous pyelogram (IVP) was normal. In 1970 the blood urea varied between 40 and 65 mg/100 ml. A repeat IVP in August 1970 was normal. The creatinine clearance was 3 ml./min in the erect position, but rose to 140 ml./min when he lay supine. These findings are in accord with the observation that renal blood flow is severely reduced in the erect position in patients with orthostatic hypotension (Wagner, 1959). No phenylalanine was detected in the urine. The EEG was normal at rest, on hyperventilation, and while standing.

Plasma cortisol was 16.0 µg/100 ml. at 2100 hr, and 22 µg/100 ml. at 09.30 hr, rising to 41.0 µg/100 ml. 30 minutes after an intramuscular injection of tetracosactrin 0.25 mg (Synacthen).

Case 2 had a blood urea of 23 mg/100 ml. Urinary alpha-amino-nitrogen excretion was 126 mg/24 hr, and creatinine excretion was 1.38 g/24 hr (normal). Chromatographic studies of the urine and plasma indicated phenylketonuria. An EEG showed symmetrical 8 Hz alpha rhythm with occasional central rhythmical 6 Hz activity with some phase reversal in the left mid-temporal area. A sleep record was obtained but no new features appeared.

INVESTIGATIONS OF HOLMES-ADIE SYNDROME

METHACHOLINE TEST In each patient instillation of 2 drops of 2.5% methacholine into the conjunctival sacs caused slow constriction of both pupils. This response does not occur in normal people and is pathognomonic of the tonic pupil (Sproffkin, 1953).

ELECTROMYOGRAPHY Motor conduction velocity of the left lateral popliteal nerve was: case 1, 47.9 m/sec; case 2, 51.7 m/sec. Distal motor latency was: case 1, 5.0 msec; case 2, 5.5 msec. No H response (Hoffmann, 1918) could be obtained on electrical stimulation of both medial popliteal nerves in each case. Needle electrode studies of the left tibialis anterior, left first dorsal interosseous, and extensor digitorum brevis muscles were also within normal limits. These results are consistent with the Holmes-Adie syndrome.

MUSCLE BIOPSY A biopsy was taken from the soleus muscle of case 2. No abnormalities were found on histological examination and in particular there was no evidence of a rodlet myopathy.

INVESTIGATIONS OF AUTONOMIC FUNCTION

BLOOD PRESSURE TESTS On the day of investigation the patient stayed in bed and was taken to the laboratory on a stretcher. The arterial blood pressure was recorded with a catheter in the brachial artery connected to a strain-gauge manometer recording system (Elema-Schönander). The manometer was fixed at the mid-sternal level. Its calibration was checked before and at the end of each investigation, and when the patient's posture was changed. The blood pressure and heart rate were observed while the following tests were performed:

Change in posture Each patient was moved from the supine to the erect position on a tilting table for two to five minutes, repeated four to five times within one hour. A marked fall in systolic and diastolic blood pressure occurred in both patients in the upright position (Fig. 1). When they were restored to the horizontal position the systolic and diastolic pressures not only rose again but significantly exceeded the original resting levels and remained high until the procedure was repeated. There was no change in heart rate with change of posture in case 1, and the heart rate change was very small in case 2. Arterial blood was sampled for estimation of plasma renin concentration by the method of Brown, Davies, Lever, Robertson, and Tree (1964) before the first tilt and between each subsequent tilting. Plasma renin concentration increased considerably in response to changes of posture (Fig. 2).

VALSALVA'S MANOEUVRE After a deep inspiration the subjects attempted a forced expiration for at least seven seconds through a face mask connected by a thick-walled rubber tube to strain gauge and mercury manometers. They were asked to maintain a constant pressure of 30-40 mm Hg during the period of increased intrathoracic pressure (phase 2). In a normal subject the blood

FIG. 1. The effect of change of posture from the horizontal to the standing position upon arterial blood pressure in case 1 (P.T.) and case 2 (K.C.).

FIG. 2. Arterial blood pressure, heart rate and plasma renin concentration of case 1 (P.T.) during successive changes of posture from horizontal to standing position in 110 minutes. Systolic pressure ●, and diastolic pressure ○. During the period of time marked 'A' the patient was tilted to only 30° from the horizontal.

pressure falls initially and then rises slightly. The heart rate also rises. When the pressure is released there is a rise of blood pressure above the resting level (the 'overshoot'). In both patients the blood pressure fell progressively and there was no overshoot after the manoeuvre (a 'blocked' response). The heart rate fell during phase 2 (Fig. 3).

Sudden noise and mental arithmetic A biscuit tin was thrown to the floor immediately behind the patient. A rise of blood pressure occurred in case 1, and a less consistent rise in case 2 (Fig. 4). A simple test of addition and subtraction produced a definite rise of blood pressure in case 1 and a less consistent rise in case 2 (Fig. 4). These results suggest the presence of intact efferent nerve fibres subserving vasomotor function (Sharpey-Schafer, 1956; Sharpey-Schafer and Taylor, 1960).

Infusion of noradrenaline Intravenous infusion of noradrenaline at measured rates of between 5 and 10 $\mu\text{g}/\text{min}$ raised the blood pressure in both patients. No bradycardia occurred (Fig. 5). An excessive hypertensive response would have indicated autonomic denervation (Cannon and Rosenbluth, 1933) but was not obtained.

TESTS OF SWEATING AND PILOERECTION *Sweating in response to heat* The ability to sweat normally was tested by heating the patients for 30 minutes with a

radiant heat cradle over the trunk while they lay on an electric blanket. The presence and the anatomical distribution of sweating was demonstrated by the application of 1-4 dihydroxyanthraquinone (Quinizarin) powder as an indicator (Guttman, 1940). Both patients sweated normally in all areas, indicating normal efferent sudomotor pathways.

Intradermal injection of acetylcholine Acetylcholine (5-10 mg) was injected intradermally at several sites on the trunk, arms, and legs and always produced piloerection in an area of 3 to 5 cm diameter. Sweating also occurred in this area. This normal response is mediated by an axon reflex in intact postganglionic sympathetic fibres (Lewis and Landis, 1929; Janowitz and Grossman, 1950; Bárány and Cooper, 1956).

TESTS OF VISCERAL INNERVATION *Heart rate* No change of heart rate occurred with change in posture in case 1, but there was a small change in case 2 (Fig. 6). Neither patient showed any change during infusion of noradrenaline (Fig. 5). However, intravenous injection of atropine 0.65 mg caused an increase in heart rate (Fig. 7A). A standard insulin test meal (Hollander, 1946; Bachrach, 1953) produced normal amounts of gastric acid in case 1 (Fig. 7B), but case 2 was unable to tolerate a Ryle's tube. These observations are consistent with normal efferent vagal activity.

FIG. 3. The effect of Valsalva's manoeuvre upon arterial blood pressure in case 1 (P.T. A) and case 2 (K.C. B). In case 2 intrathoracic pressure was also recorded and the heart rate change is shown, B.

FIG. 4. The effect of noise and mental arithmetic (serial sevens test) upon arterial blood pressure in case 1 (P.T.).

FIG. 5. The effect of an infusion of noradrenaline upon arterial blood pressure and heart rate in a patient with cervical cord transection, A, case 1, B, and case 2, C. The rate of infusion in A was $0.10 \mu\text{g/kg/min}$, in B $0.12 \mu\text{g/kg/min}$, and in C $0.125 \mu\text{g/kg/min}$. The response in the patient with cord transection was greater than in our cases in spite of a bradycardia. The difference indicates that there is no denervation sensitivity in our cases.

FIG. 6. The effect of standing for two minutes upon arterial blood pressure and heart rate in a normal subject, A, a patient with cervical cord transection, B, and in case 1 and case 2, C. Both B and C show orthostatic hypotension which is related to a marked tachycardia in the patient with cervical cord transection (normal vagus), whereas case 1 and case 2 have a lower response indicating failure of vagal inhibition.

DISCUSSION

The Holmes-Adie syndrome (Adie, 1931; Holmes, 1931) comprises the 'tonic pupil' and reduced or absent phasic stretch reflexes. It usually occurs in women and in most patients only one pupil is affected. The pupil reacts slowly on convergence, dilating slowly when accommodation is relaxed. The reaction to light is reduced or absent, but a slow constriction may be seen if the pupil is exposed to light after dark adaptation. Areflexia is not a consistent finding in patients with the tonic pupil, and in only three of Adie's five original cases were phasic stretch reflexes absent. Adie also drew attention to the occurrence of an 'atypically reacting tonic pupil' associated with areflexia, which he regarded as being a partial or early expression of the same condition. When one pupil is affected, the consensual light reflex from the affected eye is normal, indicating a lesion in the efferent pathway or its central connections. The increased sensitivity of the sphincter pupillae to methacholine and of the ciliary muscle to pilocarpine (Russell, 1958) implies peripheral denervation. Gross degeneration of neurones in the

ciliary ganglion has been found at necropsy by Ruttner (1947) and Harriman and Garland (1965).

The pathogenesis of the lack of phasic stretch reflexes is uncertain. Sympathectomy has no clinical effect on phasic stretch reflexes and it is unlikely that the absent tendon reflexes of the Holmes-Adie syndrome result from disturbance of the autonomic system. Levy (1962) interpreted his electromyographic reflex studies as indicating withdrawal of facilitation from spinal motoneurones. From their electromyographic and clinical studies on three patients and a review of the literature, Hardin and Gay (1965), noting the association of autonomic system disturbances with the Holmes-Adie syndrome concluded that the cause of the areflexia was a lesion either of the presynaptic terminals of group 1a dorsal root fibres, or of interneurones facilitatory to anterior horn cells in the spinal cord. They favoured the latter because such neurones may derive from the same stem cells (in the basal lamina of the neural tube) as autonomic system neurones. Harriman and Garland's case (1965) had slight neuronal degeneration in a sacral dorsal root ganglion, but they doubted whether it was significant and emphasized

FIG. 7. Tests of vagal function. A. The effect of atropine (0.65 mg intravenously) on heart rate in case 1 and case 2 indicating a tachycardia resulting from vagal blockade. B. The effect of soluble insulin (10 i.u. S/C) upon gastric acid secretion and blood sugar in case 1. The rise in heart rate and the increase in gastric acid secretion both indicate vagal activity. The absence of tachycardia with change in posture is, therefore, not a consequence of vagal block but is probably due to an afferent block from baroreceptors.

the pathologically more striking feature of changes of rodlet myopathy in the soleus muscle, although these changes were not found in sections from the gluteus maximus, hamstrings, or extraocular muscles. According to Matthews (1970), the H-wave is unobtainable in the Holmes-Adie syndrome if the reflexes are clinically absent. McComas and Payan (1966) investigated patients with a tonic pupil whose phasic stretch reflexes were depressed but still present, and demonstrated marked reduction in H-wave amplitude on stimulation of the medial popliteal nerve. The H response recovered its excitability more slowly than normal and they suggested that 'synaptic transmitter substance' formed by the afferent fibre might be reduced. The H responses and ankle tendon reflexes were absent in our patients, and no evidence of a peripheral motor neuropathy was obtained. A soleus muscle biopsy in case 2 failed to show any evidence of a myopathy as suggested by Harriman and Garland (1965).

Croll *et al.* (1935) first described the occurrence of orthostatic hypotension in association with the

Holmes-Adie syndrome, and this was followed by Laufer's report (1942) of a similar patient in whom he postulated a post-encephalitic lesion of the central nervous system affecting hypothalamic function. Ross (1958) and Petajan, Danforth, D'Allesio, and Lucas (1965) each described a patient with the Holmes-Adie syndrome who had generalized sudomotor impairment with normal vasomotor reflexes, and the patients of Lucy, Van Allen, and Thompson (1967) and Esterly, Cantolino, Alter, and Brusilov (1968) had segmental sudomotor denervation. A further case with progressive generalized autonomic degeneration was reported by Bonnin, Skinner, and Whelan (1961) who concluded that all the physiological abnormalities in their patient, except the lack of tendon reflexes, could be explained by post-ganglionic lesions of the autonomic system.

Blood pressure studies on our patients confirmed orthostatic hypotension (Fig. 1), and Valsalva's manoeuvre failed to cause vasoconstriction, which also indicates interruption of circulatory reflexes. The slowing of the heart rate during Valsalva's

manoeuvre is an unusual finding and may be evidence of the effect of afferent stretch receptor activity of the lungs acting independently in the absence of other vascular reflexes (Corbett, 1969). Further evidence suggested that efferent vasomotor pathways were functioning normally, and normal sweating and piloerection indicated that other efferent sympathetic functions were active. It has been suggested (Chokroverty, Barron, Katz, del Greco, and Sharp, 1969) that the release of renin requires normal function of the sympathetic nervous system. As our patients showed a marked increase in plasma renin concentration in response to a change from the horizontal to the upright posture it is possible that renin release depends upon certain components of efferent pathways rather than the integrity of the complete reflex arc from baroreceptors. The rise in supine blood pressure after return of the patients from the vertical position may have resulted from the increase in plasma renin concentration. This may also explain a similar observation in patients with cervical cord transection (Johnson, Crampton Smith, and Spalding, 1969). These results are discussed in further detail in a paper now in press (Love, Brown, Chinn, Johnson, Lever, Park, and Robertson, 1971). Heart rate and insulin test studies indicated that efferent parasympathetic function of the vagus was present. Although case 1 complained of impotence, there was no evidence in either patient of any disturbance of micturition which might have indicated sacral parasympathetic failure.

These findings of intact efferent autonomic pathways suggest that the circulatory reflex arc was blocked on the *afferent* side of the reflex or its connections in these patients (Table). It is unfortunate that no test at present exists for examining the activity of afferent fibres separately, and therefore afferent baroreceptor block is a diagnosis by exclusion. Our tests do not exclude incomplete lesions of the efferent pathways, but it is clear that the predominant abnormality is a lesion of the afferent pathways or their central connections. The patients reported here are clinically and physiologically distinct from those with the 'Shy and Drager' type of idiopathic orthostatic hypotension.

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TABLE
TESTS OF AUTONOMIC NERVOUS SYSTEM FUNCTION

Test	Case 1 (P.T.)	Case 2 (K.C.)	Conclusion
Blood pressure studies			
Change of posture to vertical	Postural hypotension	Postural hypotension	Blocked baroreceptor vasomotor reflexes
Valsalva	Heart rate falls Blocked blood pressure response	Heart rate falls Blocked blood pressure response	
Noise	BP ↑	BP ↑ ±	Suggests normal function of efferent vasomotor pathways
Mental arithmetic	BP ↑	BP ↑ ±	
Noradrenaline infusion	BP ↑ normal	BP ↑ normal	
Sweating and piloerection responses			
Rise in central temperature	Normal sweating	Normal sweating	Efferent vasomotor pathway functioning
Intradermal injection of acetylcholine	Piloerection and sweating	Piloerection and sweating	Intact postganglionic sympathetic fibres
Visceral innervation			
Bladder	No symptoms Normal IVP—no residual urine	No symptoms	No abnormality demonstrated
Heart rate change with posture	None	Slight increase	Blocked vasomotor reflexes
Heart rate change with noradrenaline	None	None	
Heart rate change with atropine	Normal rise	Normal rise	Normal vagal efferent function
Insulin test meal	Normal	Not done	

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