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Familial neurodegenerative disorder associated with raised urinary vanillylmandelic acid

Urinary vanillylmandelic acid (VMA) is often raised in children with neuroblastoma (Voorhes and Gardner, 1962). It is sometimes transiently raised in infants in heart failure, after surgery, exchange transfusion, or during an acute asthmatic attack (Hakulinen, 1971).

Hirschberger and Kleinberg (1976) reported failure to thrive in an infant who had persistently raised urinary levels of VMA and in whom no neural crest tumour was found at necropsy. We report a child with a neurodegenerative disorder in whom hypertension and persistently raised urinary VMA were noted.

Case report

A 9-month-old baby boy was referred with a history of developmental delay and a possible neurodegenerative disorder. He is the third child of healthy, unrelated parents.

The baby's sister died at 2½ years. She had been well until 7-months old, and then regressed. During

the next year she became progressively more spastic, had recurrent bouts of vomiting, and at 2 years required tube feeding. At this time episodes of eye rolling, fever, and profuse sweating were noticed during which she emitted an offensive aroma. She died in coma at 2½ years. No necropsy was performed, and regrettably there is no information about her blood pressure. There is a healthy male sibling aged 3½ years.

Our patient had been well until 6 months when he began to show signs of regression with delayed milestones. He was noted to have brief cyanotic episodes, during which he would stiffen, sweat profusely, and emit a musty smell similar to his sister. During the next 9 months frequent short generalised convulsions were noted. Sweating continued and during the summer months he often required rehydration in hospital.

When examined at 9 months his height, weight, and head circumference were all around the 10th centile. Socially he was very responsive. The cranial nerves were normal but limbs were hypertonic with brisk reflexes. He had poor head control with marked head lag on pulling to sit, and he was unable to sit unsupported. The liver and spleen were just palpable. His blood pressure was consistently raised at 120/80 mmHg, with paroxysms of up to 180/110, often associated with intense irritability and sweating.

Examination at 18 months showed evidence of further regression. His liver remained just palpable and his blood pressure was persistently raised with a diastolic of 90–95 mmHg.

On a low tyramine diet, introduced because of the similarity of some of the clinical features of this syndrome to those occurring in adverse reactions to monoamine oxidase inhibitors, his neurological status remained virtually unchanged, with fewer episodes of irritability and paroxysmal hypertension. There was no further regression.

Investigations

Routine haematology and biochemistry, blood ammonia, creatine phosphokinase, copper, zinc, renin and aldosterone, and white cell lysosomal enzymes were all normal. There were no vacuoles in the lymphocytes, no abnormal storage cells in bone marrow, and no metachromatic granules in the urine. Examination of urine for amino and organic acids failed to show any consistent abnormality. Loading diets of leucine, isoleucine, and valine had no effect clinically or biochemically. ECG showed left ventricular hypertrophy although the chest x-ray was normal.

A skeletal survey showed generalised demineralisation with a possible compression fracture in the

8th thoracic vertebra. Radioisotope bone scan and intravenous pyelogram (IVP) were normal. Computerised tomography (EMI scan), electroretinography, visually evoked responses, and nerve conduction studies were all normal.

Urinary VMA was raised on 4 separate occasions and during a pyrexial illness associated with profuse sweating it was over twice the upper limit of normal (Table).

Platelet monoaminoxidase levels were normal as were urinary normetadrenaline, metadrenaline, and 3-methoxytyramine. An intradermal histamine test was normal.

Table Urinary VMA excretion*

Age (months)	Urinary VMA ($\mu\text{mol}/24\text{h}$)†	Remarks
19	21	
19½	16	
20½	16	
21½	26	Paroxysm of sweating and irritability
22	6	Low tyramine diet
23	13.5	"
24	8	"

*Using the method of Pisano *et al.* (1962).

†Upper range of normal—13 $\mu\text{mol}/24\text{h}$.

Discussion

We were unable to make a specific diagnosis in this child. The similarities between our patient and his sister suggest a hereditary condition.

Catecholamine metabolism is known to be disturbed in several familial disorders. Raised VMA is found in familial neuroblastoma and pheochromocytoma (Chatten and Voorhess, 1967), and raised homovanillic acid (HVA) may be present in the Riley-Day syndrome (Gitlow *et al.*, 1965), when the VMA is often low. We are unaware of any other familial disorder in which VMA is raised.

Extracts of banana, ice cream, and walnuts were excluded from this child's diet before and during collection of samples. After a low tyramine diet had been established, the urinary VMA tended to fall. This diet appeared to lower his blood pressure slightly and although there was little improvement in his neurological status he stopped regressing. The normal IVP and the renin and aldosterone values exclude renal disease or Conn's syndrome.

The combination of raised VMA excretion, hypertension, and sweating in this child is suggestive of a defect in catecholamine metabolism or excretion although the exact nature remains uncertain. Such disturbances of catecholamine metabolism or excretion have not been known to occur in children with a progressive neurological disorder or other

neurological insult, and we therefore wonder whether our patient has a disorder in which this abnormality is a specific feature.

Summary

We report a child who presented with a progressive neurological disorder associated with hypertension and paroxysms of irritability and sweating in whom an abnormality of catecholamine metabolism or excretion was demonstrated. An elder sister died at the age of 2½ years with similar clinical symptoms but without blood pressure or catecholamine excretion being recorded.

The exact mechanism of the disturbance of catecholamine excretion was not identified in our patient but some slight improvement in hypertension and arrest of his neurological deterioration was noted when he was put on a low tyramine diet.

It is suggested that our patient may well suffer from a familial neurodegenerative disorder in which an abnormality of catecholamine metabolism or excretion is a feature.

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