Familial neuroblastoma: report of two sib pairs

Although neuroblastoma accounts for 6 to 7% of all childhood malignancies, it has very rarely been reported in more than one member of a family. So far only 4 families have been reported in which sibship aggregation of neuroblastoma has been conclusively proved. We describe 2 further families.

Case reports

First family.

Patient 1. A female was the first of 3 children. Her mother had had pulmonary tuberculosis in childhood and her father later developed Crohn's disease. There were no miscarriages or stillbirths.

She was well until 3½ years of age, when she developed intermittent fever, occasional vomiting, and progressive pain in the right hip and sacroiliac joints. On examination in April 1945, she was pale and ill, with pain on pressure over the iliac crests, tenderness over the spinous process of T12 and a slight kyphosis at this level. Other systems were normal on clinical examination. X-ray of the spine showed 6 lumbar vertebrae, with some evidence of disease or maldevelopment of L1. In view of the prevalence of tuberculosis at that time and in the knowledge that the child's mother had had pulmonary tuberculosis, a diagnosis was made of tuberculous osteomyelitis of the spine, and she was accordingly treated. After 2 weeks she developed a swelling in the left flank which was considered to be a psoas abscess. Following this her condition rapidly deteriorated and she died 2 months after the onset of symptoms.

Necropsy showed that the liver was diffusely infiltrated by tumour. There was a mass about 8 cm in diameter in the left flank, surrounding great vessels and the left kidney, and infiltrating the lumbar vertebrae. On section it was found to be extensively haemorrhagic with central necrosis. The left adrenal gland could not be located. The right adrenal and the right kidney were both healthy. There were no secondary deposits in the peritoneal cavity, and the other abdominal organs were unremarkable.

Histologically, the primary tumour mass and the

![Image](http://adc.bmj.com/ on July 7, 2017 - Published by group.bmj.com)
secondary deposits in the liver showed appearances characteristic of neuroblastoma (Fig. 1A).

Patient 2. A male, was the second child of the family. He was well until the age of 9½ years, when he developed intermittent pain in the left upper abdomen, with anorexia. On examination in June 1958 he was found to have a tender mass in the left hypochondrium. IVP showed the left kidney to be displaced downwards and the upper calyces rotated. The pelvis of the kidney had a flattened upper limit, and there was a dense retroperitoneal mass above it. Laparotomy showed a large retroperitoneal mass with numerous secondary deposits in the liver, from which a biopsy was taken. During the operation the child’s systolic blood pressure rose to 200 mmHg on several occasions, in spite of profuse bleeding.

Despite intensive treatment his condition deteriorated steadily and he died 3 months after the onset of symptoms. There was no necropsy.

Sections of biopsy material taken at the time of laparotomy showed features of typical neuroblastoma (Fig. 1B).

Family studies. The third child, A.B., of this family is alive and well, now aged 21. He is married and has a healthy 2-year-old daughter. He is normotensive and his HMMA excretion is within normal limits. His thoracic and lumbar spine is radiologically normal and no abdominal calcification was seen during intravenous pyelography. He has, however, a bifid renal pelvis and double ureter on the left side.

The father of the two affected children is normotensive and his HMMA excretion is also within normal limits. He shows no evidence of disease of the autonomic nervous system. The mother is under investigation for hypertension. There is no evidence of café-au-lait pigmentation in this family, nor is there any family history of neurofibromatosis, Hirschsprung's disease, or phaeochromocytoma.

Second family.

Patient 1. A male was the third child of the family; 2 sisters, at that time aged 9 years and 3 years, were both well. At the age of 9 months he became pale and lethargic, with anorexia, occasional vomiting, and rapid loss of weight. On examination in January 1964, aged 10 months, he was pale and dyspnoeic, and there was a large, hard, smooth lobulated mass filling the left side of the abdomen. An IVP showed displacement of the left kidney downwards, laterally, and forwards. There was a large, smooth, rounded mass about 13 cm in diameter in the left hypochondrium posteriorly; no calcification was seen. The right kidney showed some lateral displacement. X-ray of the chest showed a mass in the left paramediastinal region, and some evidence of a paravertebral mass on the right side at a level of T10-L1. His HMMA excretion was 1.2 mg/24 hr. At operation a huge inoperable tumour was found

![Fig. 2.—Second family. (A) Patient 1, poorly differentiated neuroblastoma. (H. and E. × 250.) (B) Patient 2, neuroblastoma showing a moderate degree of differentiation. (H. and E. × 250.)](image-url)
in the left retroperitoneal region, displacing kidney, pancreas, and duodenum, and extending across the midline towards the right kidney. A biopsy was taken. His general condition steadily deteriorated despite intensive treatment. 3 weeks later x-ray showed a destructive lesion in the lower left femur, typical of secondary neuroblastoma. He died about 2 months after the onset of his symptoms.

Necropsy showed a large retroperitoneal mass evidently arising from the left adrenal; only a small part of the left adrenal cortex could be identified. The right adrenal was normal. Both kidneys were normal apart from some displacement and distortion. The pancreas was invesited by tumour tissue. The liver contained a number of small metastatic deposits. There was widespread involvement of the abdominal lymph nodes, and tumour tissue extended along the spermatic cord towards the left scrotum. In all these sites the cut surface of the tumour was soft, fleshy, and greyish but with many tiny haemorrhagic necrosis. There was a large metastatic deposit in the upper left mediastinum. Haemorrhagic deposits were found near the costochondral junction on the internal aspect of the second and third ribs, and similar deposits were present on the internal aspect of the vault of the skull.

Histological sections taken from the retroperitoneal mass, liver, mesenteric lymph nodes, and the mediastinal mass all showed appearances typical of neuroblastoma (Fig. 2A).

**Patient 2.** A female, the youngest of 4 children, was well until she was 17 months old when she developed an abdominal swelling with dilated abdominal veins. On examination (June 1966) a large fixed swelling was found in the right flank. Chest x-ray was normal. Laparotomy revealed a large tumour occupying the right flank, adherent posteriorly to muscle and superiorly to the diaphragm. Histologically the tumour (Fig. 2B) proved to be a neuroblastoma. Postoperatively she was treated with actinomycin D, but her general condition remained poor. She died less than 1 month after the first signs of illness. There was no necropsy.

**Family studies.** In the second family both parents are healthy and normotensive. The father is a non-identical twin and there are no other sibs. His sister is married but has no children. The mother has one sister who has 2 normal children. The maternal grandparents are well. The paternal grandmother died in childbirth. The paternal grandfather is well; he has married again and the 2 sons of his second marriage are normal and they themselves have normal children. There is no family history of Hirschsprung's disease, neurofibromatosis, or neuroblastoma.

There are 2 remaining sibs in the second family, both girls. P.B., the eldest, was born in 1957. She is subject to eczema but is otherwise healthy. Clinical examination revealed one *café-au-lait* mark measuring 2·5 cm × 1 cm over the left scapula. There were no subcutaneous nodules and in general no other abnormalities were noted. The blood pressure was 140/80 mmHg.

![Image](http://adc.bmj.com/)

The second sib, C.B., born in 1960, is also subject to eczema but is otherwise healthy. She too had a *café-au-lait* mark 1 cm in diameter on the left thigh. No other abnormalities were noted. Her blood pressure was 110/60 mmHg. The urinary excretion of HMMA and metadrenaline over 24 hours are normal in the parents and children. These are shown in the Table.

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**Discussion**

It is curious but evidently coincidental that both of the families described here possessed the same surname, but a full documented pedigree for each family over 6 generations has proved that there is no interrelationship. The first indisputable sib pair was reported by Dodge and Benner (1945) in which neuroblastoma was satisfactorily proved to occur in a brother and sister. In the second family, described by Zimmerman (1951), the common father of 2 half sibs with confirmed neuroblastoma had a benign mass in his posterior mediastinum which may have been a ganglioneuroma. A further kindred was reported by Hardy and Nesbit in 1972 in which 2 sibs and their paternal aunt had proven neuroblastomas in infancy.

The most remarkable family is that reported by Chatten and Voorhess (1967). In this family the mother, who had no symptoms, was found to excrete abnormally high urinary levels of dopamine, noradrenaline, and VMA. She bore 5 children, only the second of which was healthy. The first child died early with long segment Hirschsprung's disease. At necropsy a microscopical neuroblastoma was found in one of the adrenal glands. The third child of the family presented with a left adrenal neuroblastoma and multiple secondary deposits. The fourth child, who had a persistent ductus arteriosus and pulmonary hypertension at 4 months of age, also died and at necropsy a mass 3 cm in diameter was found in the left thoracic chain at the level of T8. Both adrenals contained tumour masses, that in the left weighing 22 g
and in the right 10.5 g. All tumours were shown to be neuroblastomas. The fifth child was carefully followed prospectively because of the extraordinary family history. At the age of 5 months a tumour mass was detected radiologically in the thorax at the level of T8. This was resected and shown to be yet another neuroblastoma. This child was vigorously treated and is well, now aged 4 years (J. Chatten, personal communication, 1969).

In this family there was also evidence of neural crest anomalies on the father’s side, in that the father and 3 of his sibs had cafe-au-lait spots. This evidence makes it difficult to reject the idea that some genetic factor may play a part in the aetiology of at least some neuroblastomas.

**Summary**

Two families are reported in each of which 2 children developed neuroblastoma. These are only the fifth and sixth families in which neuroblastoma has been conclusively shown to occur in sibs.

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**References**


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**Primary endocardial fibroelastosis**

**An inherited condition**

The name endocardial fibroelastosis (EFE) was introduced by Weinberg and Himelfarb in 1943, though the condition had been described under other names. Gowing (1953) defined endocardial fibroelastosis as a 'congenital condition of unknown aetiology in which there occurs a diffuse thickening up of the mural endocardium associated in most cases with myocardial hypertrophy and leading to early death'. Andersen and Kelly (1956) divided their series of endocardial fibroelastosis into the common variety associated with other congenital cardiac anomalies and the rarer primary form without such anomalies, and found a familial incidence in 23% of the primary variety. Forfar et al. (1964), reviewing 72 cases of endocardial fibroelastosis, found multiple familial incidence only in the primary group which accounted for 22% of their cases. A familial incidence has also been described in the primary form by Dordick (1951), Winter et al. (1960), and Sellers, Keith, and Manning (1964).

The aetiology of primary EFE remains a mystery. Possible theories fall into 3 categories (1) inflammatory, (2) mechanical, and (3) hereditary. A recent and attractive view is that EFE is a secondary response in certain individuals either to an intrinsic inherited myocardial defect, which results in inefficient myocardial function, or to grossly abnormal haemodynamics associated with a congenitally malformed heart (Moller et al., 1964). This view accords well with the clinical and haemodynamic findings in the natural history of primary and secondary varieties.

Though a number of authors have dealt with the hereditary element in EFE, most have not assessed the two forms separately. Generally the mode of inheritance has been assumed to be an autosomal recessive type. Our experience in Edinburgh suggests a higher incidence in families with affected children than would be expected from recessive inheritance. This paper deals with 4 families having more than one child affected. In each family at least one child has been confirmed at necropsy as suffering from primary EFE.

**Case material**

The clinical, electrocardiographic, and pathological data are presented in the Table.

**Family I.** There were 3 children in this family. The first child (Case 1, female) had the typical clinical picture of EFE in infancy but remains well on digoxin, though with reduced exercise tolerance. Cardiac catheterization has not been carried out. The second child (female) is apparently normal. The third child (Case 2, male) died in infancy after a brief but typical illness, and primary EFE was confirmed at necropsy. There is no family history of heart disease.

**Family II.** There were only 2 children in this family. The first (Case 1, male) died suddenly and a procurator
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