Presenting features of thoracic neuroblastoma

G R MCLATCHIE AND D G YOUNG

Royal Hospital for Sick Children, Glasgow

SUMMARY In a retrospective study carried out at the Royal Hospital for Sick Children, Glasgow, for the period 1952-79, 7 cases of primary thoracic neuroblastoma were identified. The average age at presentation was 2 years. Respiratory symptoms were the modes of presentation in 2 patients, neurological symptoms in 4, and urinary tract symptoms in 1 patient. Dilatation of the urinary tract was present in 2 cases, and a third had a normal urinary tract but previous infections. After a maximum of 27 years and a minimum of 20 months, 5 of the patients remain well. One child died as a direct result of her tumour, the other from an unrelated tumour 25 years after partial excision of his neuroblastoma. The better prognosis of primary thoracic neuroblastoma and the variability of presentation compared with neuroblastoma in other sites are stressed.

Thoracic neuroblastoma accounted for about 7% of all primary neuroblastoma treated at this hospital during the 27-year period 1952-79. Neuroblastoma is a tumour of particular interest because it is known to arise from cells of the neural crest which possess the potential for maturation.¹⁻³ It has also the capacity to secrete substances capable of producing autonomic effects but the mechanism by which this tumour produces diarrhoea is not understood.⁴⁻⁶

Although most children with neuroblastoma seek medical care because of the presence of an abdominal mass, bone pain, or orbital proptosis in addition to the general malaise, weight loss, fever, and failure to thrive,⁷ a number present with neurological signs. Weakness or paralysis of the lower limbs may be secondary to cord compression by tumour.⁸ However, myoclonic jerks which may be of abrupt onset are now recognised as part of a syndrome with

hidden neuroblastoma.⁹ It was suggested too that this was an effect of the primary tumour itself and not due to secondary spread. The cases admitted to this hospital over the last 27 years have been reviewed to define the presentation and outcome of patients with primary intrathoracic neuroblastoma as this particular group is not well documented.

Materials and methods

The clinical and pathological case records were reviewed for 1952-79 and 7 cases of primary thoracic neuroblastoma were identified (Table 1). As the patients had no single pattern of signs or symptoms brief clinical summaries of each patient are presented. The 4-hydroxy-3-methoxy mandelic acid (HMMA or VMA) excretion in the urine has been tabulated (Table 2).

Table 1 *Presentation and outcome of patients with thoracic neuroblastoma*

Case	Age	Sex	Year of presentation	Presenting features	Duration of symptoms	Outcome
1	16 months	M	1952	Progressive paraplegia	6 months	Died 1977 (unrelated cause)
2	6 months	F	1964	Respiratory infection. Respiratory distress	1 month	Symptom-free
3	4½ years	F	1969	Horner's syndrome. Urinary tract infection	3 months	Died, December 1969
4	3½ years	M	1976	Urinary tract infection. Ataxia	3 weeks	Symptom-free
5	2 years	M	1976	Gross ataxia. Myoclonic jerks	2 months	Symptom-free
6	2 years	M	1976	Pupil asymmetry. Facial oedema. Persistent watery diarrhoea.	1 year	Symptom-free
7	8 months	M	1978	Urinary tract infections Clinical pneumonia	1 week	Symptom-free

Table 2 Urinary catecholamine levels before and after the operation

Case	Urinary 4-hydroxy-3-methoxy mandelic acid (HMMA, VMA) (mg/g creatinine)	
	Preoperative	Postoperative
1	Within normal limits	Within normal limits
2	138.9	23.2
3	12.0	Within normal limits
4	27.0	9.5
5	11.0	6.6
6	Within normal limits	Within normal limits
7	17.0	3.1

Normal levels, up to 10 mg/g creatinine.

Case reports

Case 1. Presenting feature: progressive paraplegia. In April 1952 a 16-month-old boy was admitted to a neurosurgical unit for investigation of paraplegia which had progressed over 4 months. He was known to have congenital defects of D11 and D12 with scoliosis at birth and lower limb weakness. Myelography confirmed a block at D7 level and chest x-rays showed a left intrathoracic mass. He was transferred to this hospital for removal of his chest mass. At thoracotomy a large dumb-bell tumour adherent to the vertebrae and compressing the spinal cord, with pleural secondaries, was encountered. An extensive resection and decompression were performed but the secondaries were too widespread for removal. The tumour was confirmed histologically to be a neuroblastoma. He received local megavoltage radiotherapy. Subsequently he regained some of the power of his limbs and when the family moved to Leeds in 1962 after several orthopaedic procedures he was mobile with calipers. He died in 1977 from an unrelated intra-abdominal tumour.

Case 2. Presenting features: respiratory infection and respiratory distress. In late 1964, a 6-month-old girl was transferred from a neighbouring hospital in respiratory distress. She had been admitted with a cold and nasal discharge of 1 week's duration. However, chest x-rays showed a left spontaneous pneumothorax with a large opacity in the upper mediastinum. Urinary VMA levels were 138.9 mg/g (79.3 $\mu\text{mol}/\text{mmol}$) of creatinine. This lesion was excised through a right thoracotomy and confirmed to be a neuroblastoma. Urinary VMA levels immediately dropped to 23.2 mg/g (13.4 $\mu\text{mol}/\text{mmol}$) of creatinine. Her postoperative follow-up included 3000 rad of local radiotherapy over a 5-week period in conjunction with weekly intravenous injections of vincristine. She remains well on no further treatment.

Case 3. Presenting features: Horner's syndrome and urinary tract infection. A 4½-year-old girl presented with a left-sided Horner's syndrome worsening over a 3-month period. She also had a urinary infection on admission which was successfully treated with co-trimoxazole (Septrin). Intravenous pyelogram was normal but chest x-rays showed a large opacity in the left upper field which suggested a neuroblastoma. Her preoperative VMA level was 12 mg/g (6.9 $\mu\text{mol}/\text{mmol}$) of creatinine, which was slightly raised. A large neuroblastoma was removed at thoracotomy in April 1969. There was no evidence of metastases. She then received local radiotherapy and combination chemotherapy—cyclophosphamide, prednisolone, and vincristine which she tolerated poorly. In October 1969 she was readmitted with abdominal pain, nausea, and bruising. Her liver was now enlarged and marrow biopsy confirmed extensive infiltration with neuroblastoma cells. Skull x-ray suggested that secondary deposits were present in the frontal region. Despite further chemotherapy including methotrexate she died in late December 1969. A necropsy examination was not carried out as consent was refused.

Case 4. Presenting features: urinary tract infections and ataxia. A 3½-year-old boy presented with a urinary tract infection in September 1976 and at that time an abnormality of his gait was noted. The urinary tract infection was treated but when he returned for follow-up a left thoracic tumour was found. By this time he had marked staggering which was worsening. Myelography showed a complete obstruction at the upper border of the 7th thoracic vertebra with the cord displaced to the right. A skeletal survey confirmed partial collapse of the upper lobe of the left lung with destruction of the necks of the 5th and 6th ribs on the left side. There was also destruction of the neural arches of the 4th and 5th thoracic vertebrae on the left side. In view of the rapid growth an initial trial of vincristine was given but the neurological signs progressed. It was then decided that decompression of his cord and, if possible, removal of the mediastinal lesion be attempted. At operation spinal decompression was performed initially and extended to thoracotomy. The large thoracic tumour which had encircled the trachea and aorta and displaced the oesophagus to the right was excised. The deformed ribs were removed and histological examination showed small nests of neuroblastoma within the marrow. Postoperatively his HMMA level fell to 14.5 mg/g (8.3 $\mu\text{mol}/\text{mmol}$) of creatinine after 3 weeks from 27 mg/g (15.4 $\mu\text{mol}/\text{mmol}$), and to 9.5 mg/g (5.4 $\mu\text{mol}/\text{mmol}$) of creatinine after 4 weeks. His further

management consisted of chemotherapy in the form of vincristine, adriamycin, and cyclophosphamide for 1 year. He remains well, having made an almost complete neurological recovery.

The investigation of his urinary tract showed that there was pronounced dilatation of both upper renal tracts with bilateral hydronephrons and hydroureter. Because of the appearances of uretero-vesical obstruction he underwent ureteric reimplantation after resection of the distal ureters in March 1977.

Case 5. Presenting features: gross ataxia and myoclonic jerk. A 2-year-old boy presented with a 2-month history of irritability and unsteadiness on his feet as a consequence of which he preferred to remain lying down. It was also noted that he had nystagmus, several left-sided myoclonic jerks, and that he was ataxic to such a degree that he was now unable to walk or stand. After full neurological investigation including computerised tomography scans, myelography, and lumbar puncture he was noted to have a slightly enlarged 4th ventricle, but no other positive findings were shown at this time. The myoclonic jerks were becoming worse. On his transfer to this hospital he was found to be grossly ataxic with peculiar eye movements 'dancing eyes'. Routine chest x-rays showed a thoracic neuroblastoma in the left lower chest. On 10 June 1976 this was excised with the para-aortic glands which were shown to be unaffected. He received a post-operative course of radiotherapy to the lower thoracic region. After the operation his HMMA level fell from 11 mg/g (6.3 μ mol/mmol) to 6.6 mg/g (3.8 μ mol/mmol) of creatinine and his general response to excision of the tumour was also remarkable. His myoclonic jerks decreased and his motor control improved. He was able to sit and subsequently to walk again. His initial striking improvement was not maintained and he required treatment with corticosteroids to control his neurological sequelae. The prednisolone was gradually reduced during the next 3 years and he has no residual problems.

Case 6. Presenting features: pupil asymmetry, facial oedema, persistent watery diarrhoea, and urinary tract infections. A 2-year-old boy having previously suffered from recurrent urinary tract infections was admitted to this hospital in June 1976 for investigation of facial oedema and intermittent watery diarrhoea, both of which had been present for about 1 year. His parents also reported that his pupils had each been a different size for some considerable time and had had ophthalmological consultation. Although his diarrhoea settled from time to time his

stools were never formed. At routine chest x-ray a partially calcified mass was noted in his right upper chest. The report suggested a diagnosis of thoracic neuroblastoma with superior vena cava obstruction. Catecholamine excretion was normal and intravenous pyelogram confirmed a degree of bilateral hydroureter. The mass was removed completely at thoracotomy and confirmed to be a neuroblastoma containing numerous mature and nearly mature ganglion cells. During the excision the right sympathetic chain was divided.

His postoperative improvement was striking: his facial oedema subsided and his bowel motions immediately became normal. He received no radio- or chemotherapy, and remains well and symptom-free.

His right-sided Horner's syndrome is improving with time and his most recent pyelogram showed a normal renal tract.

Case 7. Presenting feature: clinical pneumonia. An 8-month-old boy presented with clinical pneumonia which resolved with appropriate treatment. The clinical suspicion had been confirmed radiologically but a fortnight later the films suggested a solid mass in the upper part of the right pleural cavity. This was confirmed at thoracotomy to be a neuroblastoma. The hard tumour mass was present in the upper posterior aspect of the pleural cavity close to the superior vena cava. After the operation his HMMA levels fell from 68 mg/g (38.8 μ mol/mmol) on the day of the operation to 6.0 mg/g (3.4 μ mol/mmol) of creatinine thereafter. The tumour was resected but small residual fragments may have been left at the apex of the pleural cavity. Postoperatively he had a satisfactory recovery although he developed a right-sided Horner's syndrome after division of the right sympathetic chain. Histology confirmed this to be a neuroblastoma and he received a course of radiotherapy. He remains well with no evidence of recurrence of his tumour. He continues to be followed up.

Discussion

Of 7 patients who presented during the 27-year period, neurological signs were present in 5 (Cases 1, 3, 4, 5, and 6). Some of these signs can be attributed to the physical presence of the tumour with the resultant pressures. Thus, Horner's syndrome or progressive paraplegia can result. However, the movement disorders—such as cerebellar ataxia, myoclonic jerks, and nystagmus—are thought, in the absence of metastasis, to be produced by the primary tumour itself. In two patients (Cases 4 and

5) the movement disorder either disappeared or improved when the primary tumour was removed but 2 patients with ataxia and nystagmus described by Senelick *et al.*⁹ continued to have exacerbations of their ataxia even after the tumours had been excised. The mechanism underlying the remote damaging effect of cancer on the nervous system is not clear and one can only speculate about the cause of such movement disorders. One theory suggests an antigen-antibody complex which damages the nervous system, and a second suggests excessive release of toxic metabolites from a neuroblastoma.¹⁰

Two children (Cases 2 and 7) presented with respiratory symptoms—Case 2 with respiratory distress, and Case 7 with an unresolved pneumonia. Routine chest x-rays confirmed the presence of a mediastinal mass in each.

Although the patient who presented with persistent watery diarrhoea had no biochemical studies performed to identify an increased concentration of vasoactive intestinal peptide we feel that the immediate change of bowel habit after operation lends weight to the suggestion that neuroblastoma can be an ectopic source of endocrine secretions.

Three patients (Cases 3, 4, and 6) had urinary tract infections at the time of their presentation and in 2 (Cases 4 and 6) the intravenous pyelogram showed bilateral hydronephrosis and hydroureter. Ureteric reimplantation was necessary in one patient; spontaneous resolution to normal occurred in the other. The urinary system can be affected in neuroblastoma by direct extension of the tumour or metastasis.¹¹ To our knowledge however, none of our patients had extension of tumour to the urinary tract. We therefore, suggest that dilatation of the urinary system may be a distant effect of neuroblastoma.

The most striking feature of this study of mediastinal neuroblastoma is the very low mortality rate. After a minimum of 20 months and a maximum of 25 years, 6 (86%) of the patients are alive and well. Five of these children were under 2 years at the time of diagnosis. It is a common experience in many centres that the overall survival rate is inversely proportional to age. The influence of age presents a paradox for which no adequate explanation is available since although cell maturation apparently occurs more completely with advancing age, spontaneous regression is virtually unknown in tumours appearing after the age of 2 years.^{7 12-13}

A better prognosis has also been observed in patients with mediastinal primaries.¹⁴ Our cases verify this observation but once again, the main factor may be age since 5 (71%) of the 7 patients reviewed were under 2 years old.

The presence of bone metastases also indicates a poorer prognosis.¹⁴ The single child in our study who had extensive bony secondaries succumbed, but other children with large primary tumours, Horner's syndrome, or erosion of ribs or thoracic vertebrae survived despite incomplete excision of the tumour. This child received more-intensive chemotherapy than the other children in this series without response and the possibility of chemical immunosuppression affecting endogenous defence mechanisms may be implicated.

Thoracic neuroblastoma is a rare tumour which can present in an unusual manner. Every infant and young child who exhibits a movement disorder or peculiar nystagmus that cannot be readily explained should be handled as though he had a neuroblastoma and careful estimations of VMA in urine samples should be carried out. Horner's syndrome, progressive paraplegia, and persistent watery diarrhoea in the absence of other symptoms also require this consideration. In our patients chest x-ray was the most useful investigation but a full physical examination with intravenous pyelography, bone marrow aspiration, and skeletal survey should also be carried out.

We thank the Records Department, Royal Hospital for Sick Children, for tracing the case reports of these patients, and Mrs K. Wright for preparing the manuscripts.

References

- Cushing H, Wolbach S B. Transformation of a malignant paravertebral sympathetic neuroblastoma into benign ganglio-neuroma. *Am J Pathol* 1927; 3: 203-16.
- Eyre-Brook A L, Hewer T F. Spontaneous disappearance of neuroblastoma with maturation to ganglio-neuroma. *J Bone Joint Surg* 1962; 44: 886-90.
- Haber S L, Bennington J L. Maturation of congenital extra-adrenal neuroblastoma. *Arch Pathol* 1963; 76: 121-5.
- Greenberg R E, Gardner L I. Letter: New diagnostic test for neural tumours in infancy: increased urinary excretion of 3-methoxy- 4 hydroxymandelic acid and norepinephrine in ganglioneuroma with chronic diarrhea. *Pediatrics* 1959; 24: 683-4.
- Mason G A, Hart-Mercer J, Millar E J, Stran L B, Wynne N A. Adrenaline secreting neuroblastoma in an infant. *Lancet* 1957; ii: 322-5.
- Robinson R, Ratcliffe J, Smith P. A screening test for pheochromocytoma. *J Clin Pathol* 1959; 12: 541-3.
- Pochedly C. *Neuroblastoma*. Massachusetts: Arnold, 1976; 60-5, 276-8, 285-8.
- Traggis D E, Filler R M, Druckman H, Jaffe N, Cassady J R. Prognosis for children with neuroblastoma presenting with paralysis. *J Pediatr Surg* 1977; 12: 419-25.
- Senelick R C, Bray P F, Lahey M E, Vandyk H J L, Johnson D G. Neuroblastoma and myoclonic encephalopathy: 2 cases and a review of the literature. *J Pediatr Surg* 1973; 8: 623-32.

- ¹⁰ Bray P, Ziter F A, Lahey M E, Myers G. Coincidence of neuroblastoma and acute cerebellar encephalopathy. *J Pediatr* 1969; **75**: 983-90.
- ¹¹ Varkarakis M, Bhanalaph T, Murphy A. Kidney involvement in neuroblastoma. *NY State J Med* 1972; **72**: 2753-6.
- ¹² Varkarakis M, Bhanalaph T, Albert D, Sinks L, Murphy G P. Current status of prognostic criteria in neuroblastoma. *J Urol* 1973; **109**: 94-7.
- ¹³ Breslow N, McCann B. Statistical estimation of prognosis for children with neuroblastoma. *Cancer Res* 1971; **31**: 2098-103.
- ¹⁴ Filler R, Traggis D, Jaffe N, Vanter G. Favorable outlook for children with mediastinal neuroblastoma. *J Pediatr Surg* 1972; **7**: 136-43.

Correspondence to D G Young FRCS, Department of Paediatric Surgery, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

Received 28 September 1979

Paediatric Cardiology 1981

A conference will be held on 16-18 September 1981 at the Royal College of Obstetricians and Gynaecologists, London. Further details from Conference Services Limited, 3 Bute Street, London SW7 3EY.

The following articles will appear in future issues of this journal:

Hepatic haemangiomata: diagnosis and management. *V F Larcher, E R Howard, and A P Mowat*

Immunological studies in cows' milk protein-sensitive enteropathy. *M Yadav and N Iyngkaran*

Depression in mothers of young children. *S Wolkind*

Screening for cystic fibrosis by a stool trypsin method. *D C Forrest, B Wilcken, and G Turner*

Disseminated eosinophilic infiltration of a newborn infant, with perforation of the terminal ileum and bile duct obstruction. *S M Murray and C J Woods*

Congenital hypothyroidism in Denmark. *B B Jacobsen and N J Brandt*