Cockayne's syndrome and emphysema

MARY CUNNINGHAM, S. GODFREY, AND W. M. V. MOFFAT

From the Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London

SUMMARY A 5-year-old boy with Cockayne's syndrome is described. In addition to the recognised clinical features, he presented with severe fixed airways obstruction, and investigations confirmed clinical and physiological emphysema. In a disorder associated with many of the features of ageing, it is probable that the presence of relative α -1-antitrypsin deficiency (1.5 g/l) in a child with Patau's phenotype, contributed to his severe lung disease.

The progressive nature of Cockayne's syndrome was well illustrated by the first 2 cases he described (Cockayne, 1936). Ten years later (Cockayne, 1946) the predominant clinical features had changed from cachectic dwarfism with a scaly erythematous dermatitis and a 'pepper-salt' choroidoretinitis, to blindness caused by optic atrophy and cataracts, severe mental retardation, and joint contractures. The striking wizened appearance has been likened to progeria (Neill and Dingwall, 1950) and necropsy findings have included extensive atheroma, vascular calcification, and other evidence of ageing—such as excessive collagen in the meninges (Crome and Kanjilal, 1971). We report a child with Cockayne's syndrome who additionally had clinical and physiological features of emphysema—a degenerative condition of the lung usually seen in old age.

Case report

History. This boy was a normal delivery at term with a birthweight of 2.7 kg (3rd to 10th centile). The neonatal period was normal; the mother was uncertain of his early milestones but at 22 months he was referred to hospital by his family doctor because of failure to thrive. At that time, his weight (8.6 kg) and length (72 cm) were well below the 3rd centiles and his head circumference was just below the 3rd centile. He was walking with help and spoke single words.

After preliminary outpatient investigations including a chest x-ray which was normal, he came twice to follow-up and then failed appointments until January 1976, aged 4½, when he was admitted to hospital with signs of a chest infection. The mother said he had been unwell with a cold for a month, but the admitting doctor described him as 'emaciated, dehydrated, and desperately ill'. He was said to have

completed immunisation and had had no previous chest illness but the history was considered unreliable. After initial clinical studies he was transferred to Hammersmith Hospital for further investigations.

Family history. There was no history of chest disease in either parent or his two siblings. The patient's 3-year-old brother, whom we examined, was of normal body proportions and taller than the patient (Fig. 1 and Table 1).

Examination. The child was emaciated and pinnae, with a wizened appearance (Fig. 1). The facies showed enophthalmos, prominent cheekbones, and large ears; the teeth were carious. The hands and feet were large in proportion to the size of the child. He was pigeon-chested with an overinflated chest, and was using accessory muscles of respiration and the alae nasae. The respiratory rate varied from 20 to 30 per minute but there was no cyanosis or clubbing. The chest percussion note was hyperresonant and there were coarse crepitations at the right base with generalised rhonchi.

Examination of the CNS revealed a child of low intelligence who spoke in sentences of only 2 or 3 words. The fundi showed extensive abnormal pigmentation but no optic atrophy and there were

Table 1 Anthropometry

	Patient (5 years 1 month)			Brother (3 years 8 months)		
	Measured value	Expected mean	Centile	Measured value	Expected mean	Centile
Head circumference (cm)	49.0	52.0	3	50.5	51	50
Height (cm)	92.0	109.0	<<3	101.0	99	50-70
Weight (kg)	10.75	18.75	<<3	15.5	16	25-50

Patient: span 100 cm; crown to pubis 45.0 cm; upper/lower ratio 0.9

Received 13 January 1978

Fig. 1 Patient on right with brother, 17 months younger. Difference in crown/pubis length can be seen, as well as the relatively large hands, and the barrel-shaped chest deformity in the patient.

no cataracts. The eye movements were full and there was no nystagmus. His hearing was not fully assessed. In the peripheral nervous system, there was no gross muscle wasting, the deep tendon reflexes were not exaggerated, and the plantar responses flexor. His activity was limited by exertional dyspnoea but unsteadiness was noted in the upper limbs. He showed normal withdrawal response to pin prick but full sensory testing was not possible.

Investigations. Hb 11.4 g/dl; WBC $11.6 \times 10^9/l$ ($11.6 \times 10^3/mm^3$) (neutrophils 65%, lymphocytes 25%, monocytes 9%, eosinophils 1%). Blood chemistry, including liver function tests and lipids: normal. Chest x-rays, overdistended lungs with flattened diaphragm, and relative translucency of both lower zones, patchy shadowing in both lungs. ECG: normal. Virology screen, including adenovirus and influenza titres, negative. Bacteriology, nose and throat swabs negative. Sweat Na, 24 mmol/l (weight 0.444 g). Normal growth hormone response to hypoglycaemia.

Arterial blood gas measurements (Table 2) were made using local anaesthesia breathing air and 100% O₂ by facemask. The child was hypoxic at rest and although this was corrected by breathing O₂, PCO₂ rose considerably. Regional lung function studies using radioactive N₂ (Ronchetti *et al.*, 1975) showed gross ventilation-perfusion imbalance in all areas, with underventilation and underperfusion of both lower zones (Fig. 2).

Fig. 2 Radioisotopic lung function tests after inhalation (a) and infusion (b). Lungs are divided into 4 zones and shaded areas represent the range of normal washout curves. Low peak counts in lower zones for both studies indicate underventilation and underperfusion of these regions, and the grossly delayed washout of radioactivity by breathing after the infusion indicated severe ventilation-perfusion imbalance, again worse in the lower zones.

Motor nerve conduction, right ulnar—26.5 m/s, right posterior tibial 30.0 m/s (both slow).

IQ assessment, retarded language development (3½ years); perception of form with normal limits.

α -1-Antitrypsin levels and phenotype status of the patient and his close relatives (Table 3) showed them all to be heterozygotes (Pi_{MZ}) and relatively deficient in the enzyme with levels ranging from 0.9 to 2.0 g/l (normal range 2.0–4.0 g/l, homozygotes <0.5 g/l).

Discussion

This boy shows the cardinal features of Cockayne's syndrome as first described in 1936—cachectic dwarfism with microcephaly, mental subnormality, and a pigmentary retinopathy. Earlier reports of the syndrome have likened it to progeria (Moossy, 1967) but the progressive intellectual deterioration seen in Cockayne's syndrome is not a feature of the latter. More recent reports (Norman and Tingey, 1966; Rowlatt, 1969; Crome and Kanjilal, 1971) have shown that patchy demyelination is a feature of brain necropsies, and Moosa and Dubowitz (1970) confirmed peripheral neuropathy in a patient who also had evidence of segmental demyelination on a sural nerve biopsy. These findings, supporting progressive demyelination, are evidence for Cockayne's syndrome being a form of leucodystrophy, but despite extensive study no consistent biochemical abnormality has been found. Reports of several affected members in a family (Paddison *et al.*, 1963) and consanguinity in the parents, suggest autosomal recessive inheritance.

Chest illness has rarely been reported in Cockayne's syndrome except as a terminal event. Pigeon-chest deformity is, however, common and one such patient was reported at necropsy to show emphysema and changes of acute on chronic bronchitis (Riggs and Seibert, 1972). Another patient at necropsy

showed overdilation of the lungs but there was no mention of chest deformity (Rowlatt, 1969). Review of the literature shows 14 cases of Cockayne's syndrome with chest deformity (out of a total of 36) and 8 necropsy reports, but apart from those mentioned above the only pulmonary abnormalities noted were bronchopneumonia and pneumonia.

Our patient presented with major respiratory difficulties. The wizened appearance and dyspnoea even at rest were reminiscent of an elderly patient with emphysema of the type A 'pink puffer' (Burrows *et al.*, 1964). However, although his blood gases and air were consistent with this type of disturbance, he showed the pattern more commonly seen in patients with chronic bronchitis in whom the PCO_2 rises to dangerous levels when given high O_2 concentrations to breathe. Because of the child's poor co-operation it was not possible to get a reliable measurement of lung mechanics, but a trial of corticosteroids and high dose theophylline produced no clinical improvement.

It is well known that patients with severe α -1-antitrypsin deficiency (the homozygote Pi_{ZZ}), have a high incidence of early panacinar emphysema (Eriksson, 1964) which particularly affects the lower lobes (Welch *et al.*, 1969), but whether the heterozygous state Pi_{MZ} is a significant risk factor in the development of emphysema is still under discussion. Morse *et al.* (1975) reported a community study in Arizona measuring trypsin inhibitory activity (but not analysing phenotypes) and found no difference in the incidence of pulmonary disease among those with an intermediate level of α -1-antitrypsin (assumed heterozygotes) and normal people. A more recent study of 1995 workers over the age of 35 in Northern Ireland (Cole *et al.*, 1976) showed no increased respiratory symptomatology or higher incidence of airways obstruction in Pi_{MZ} individuals than the Pi_{MM} members of the population. However, Cooper *et al.* (1974) looking at lung function in more detail found lower arterial PO_2 values, a lower maximum expiratory flow, and loss of elastic recoil in the heterozygote, more pronounced in heavy smokers with Pi_{MZ} phenotype.

Even in Pi_{ZZ} individuals, respiratory symptoms do not usually occur until the 3rd decade. Talamo *et al.* (1971) reported a child in whom dyspnoea began at age 18 months and whose lungs on biopsy showed panacinar emphysema. Serum α -1-antitrypsin levels were 0.1 and 0.2 g/l, and later phenotyping showed Pi_{ZZ} . It was postulated that measles bronchopneumonia may have contributed to the early onset of her pulmonary disease. The child reported in this paper had no previous respiratory illness, nor had he had measles.

Obstructive lung disease has also been reported in

Table 2 Arterial blood gases

	Air		100% O_2	
pH	7.41		7.23	
	kPa	(mmHg)	kPa	(mmHg)
PO_2	7.5	(56)	32.0	(240)
PCO_2	4.4	(33)	7.0	(53)

Table 3 α -1-Antitrypsin levels and phenotype of patient, parents, and siblings

	α -1-Antitrypsin (g/l)	Phenotype
Patient	0.9 (repeat 1.5)	Pi_{MZ}
Father	1.4	Pi_{MZ}
Mother	2.0	Pi_{MZ}
Brother	1.8	Pi_{MZ}
Sister	1.3	Pi_{MZ}

two siblings with homozygous α -1-antitrypsin deficiency, who also had perilobular cirrhosis on liver biopsy (Glasgow *et al.*, 1973). Houštek *et al.* (1973) reported a 13-year-old child with x-ray changes of bullous emphysema in the left lower lobe, in whom the trypsin inhibiting capacity was in the homozygous range. There are no reports of intermediate α -1-antitrypsin levels being associated with lung disease in children.

Although bronchopneumonia may be the terminal illness in patients with Cockayne's syndrome, chest illness is not a common feature of the disorder. Most necropsy material confirms patchy demyelination in the brain but lung pathology has not been looked at in detail. The one case reported by Riggs and Seibert (1972) who had post-mortem evidence of emphysema, was a boy who died at age 7. No mention is made of previous chest illness, but as most patients with Cockayne's syndrome survive beyond the first decade, respiratory illness may have contributed to this child's earlier death. Until further data are available on lung disease in these patients, the relevance of emphysema to Cockayne's syndrome in our patient remains uncertain. However, as in adult cases of α -1-antitrypsin deficiency, the lower lobes were most affected and it is interesting to speculate that in a disorder associated with some of the pathological features of the aging process, the associated relative α -1-antitrypsin deficiency in this child has produced the features of an aging lung.

Measurements of α -1-antitrypsin and phenotype were made at the Hallamshire Hospital, Sheffield. M.T.C. was in receipt of a grant from Action Research for the Crippled Child.

References

- Burrows, B., Niden, A. H., Fletcher, C. M., and Jones, N. L. (1964). Clinical types of chronic obstructive lung disease in London and Chicago. *American Review of Respiratory Diseases*, **90**, 14–27.
- Cockayne, E. A. (1936). Dwarfism with retinal atrophy and deafness. *Archives of Disease in Childhood*, **11**, 1–8.
- Cockayne, E. A. (1946). Dwarfism with retinal atrophy and deafness. *Archives of Disease in Childhood*, **21**, 52–54.
- Cole, R. B., Nevin, N. C., Blundell, G., Merrett, J. D., McDonald, J. R., and Johnston, W. P. (1976). Relation of alpha-1-antitrypsin phenotype to the performance of pulmonary function tests and to the prevalence of respiratory illness in a working population. *Thorax*, **31**, 149–157.
- Cooper, D. M., Hoepfner, V., Cox, D., Zamel, N., Bryan, A. C., and Levison H. (1974). Lung function in alpha-1-antitrypsin heterozygotes (Pi type MZ). *American Review of Respiratory Disease*, **110**, 708–715.
- Crome, L., and Kanjilal, G. C. (1971). Cockayne's syndrome, case report. *Journal of Neurology, Neurosurgery, and Psychiatry*, **34**, 171–178.
- Eriksson, S. (1964). Pulmonary emphysema and alpha-1-antitrypsin deficiency. *Acta medica Scandinavica*, **175**, 197–205.
- Glasgow, J. F. T., Lynch, M. J., Hercz, A., Levison, H., and Sass-Kortsak, A. (1973). Alpha-1-antitrypsin deficiency in association with both cirrhosis and chronic obstructive lung disease in two sibs. *American Journal of Medicine*, **54**, 181–194.
- Houštek, J., Copová, M., Zapletal, A., Tomášová, H., and Samánek, H. (1973). Alpha-1-antitrypsin deficiency in a child with chronic lung disease. *Chest*, **64**, 773–776.
- Moosa, A., and Dubowitz, V. (1970). Peripheral neuropathy in Cockayne's syndrome. *Archives of Disease in Childhood*, **45**, 674–677.
- Moossy, J. (1967). The neuropathology of Cockayne's syndrome. *Journal of Neuropathology and Experimental Neurology*, **26**, 654–680.
- Morse, J. O., Lebowitz, M. D., Knudson, R. J., and Burrows, B. (1975). A community study of the relation of alpha-1-antitrypsin levels to obstructive lung diseases. *New England Journal of Medicine*, **292**, 278–281.
- Neill, C. A., and Dingwall, M. M. (1950). A syndrome resembling progeria: a review of two cases. *Archives of Disease in Childhood*, **25**, 213–221.
- Norman, R. M., and Tingey, A. H. (1966). Syndrome of microcephaly, strio-cerebellar calcifications, and leucodystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **29**, 157–163.
- Paddison, R. M., Moossy, J., Derbes, V. J., and Kloepper, W. (1963). Cockayne's syndrome, a report of five new cases with biochemical, chromosomal dermatologic, genetic, and neuropathologic observations. *Dermatologia tropica*, **2**, 195–203.
- Riggs, W., Jr, and Seibert, J. (1972). Cockayne's syndrome: roentgen findings. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, **116**, 623–633.
- Ronchetti, R., Stocks, J., Freedman, N., Glass, H., and Godfrey, S. (1975). The clinical application of regional lung function studies in infants and small children using ^{13}N . *Archives of Disease in Childhood*, **50**, 595–603.
- Rowlatt, U. (1969). Cockayne's syndrome. Report of a case with necropsy findings. *Acta neuropathologica*, **14**, 52–61.
- Talamo, R. C., Levison, H., Lynch, M. J., Hercz, A., Hyslop, N. E., Jr, and Bain, H. W. (1971). Symptomatic pulmonary emphysema in childhood associated with hereditary alpha-1-antitrypsin and elastase inhibitor deficiency. *Journal of Pediatrics*, **79**, 20–26.
- Welch, M. H., Reineck, M. E., Hammersten, J. F., and Guenter, C. A. (1969). Antitrypsin deficiency in pulmonary disease: the significance of intermediate levels. *Annals of Internal Medicine*, **71**, 533–542.

Correspondence to Dr Mary Cunningham, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London W12.