Short reports

Leukoencephalopathy after prophylactic radiation for leukaemia in ataxia telangiectasia

J A EYRE,* D GARDNER-MEDWIN,† AND G P SUMMERFIELD‡

**Department of Child Health, Medical School, University of Newcastle upon Tyne, †Department of Paediatric Neurology, Newcastle General Hospital, and ‡Department of Haematology, Middlesbrough General Hospital*

SUMMARY Children with ataxia telangiectasia have a high probability of developing acute lymphoblastic leukaemia, and have increased sensitivity to chemotherapy and irradiation. We report a 5½ year old boy who had undiagnosed ataxia telangiectasia when he presented with acute lymphoblastic leukaemia. He subsequently developed a chemoradiation induced leukoencephalopathy after conventional central nervous system prophylaxis.

In ataxia telangiectasia there is a high incidence of neoplasia and an increased sensitivity both to radiation and to chemotherapeutic agents. We present a case report of a boy with undiagnosed ataxia telangiectasia who developed an acute leukoencephalopathy after prophylactic cranial irradiation and intrathecal methotrexate for acute lymphoblastic leukaemia.

Case report

A 4½ year old boy initially presented with clumsy gait. His gestation, delivery, and early development were normal. From 2 years his speech was noted to be poorly formed, he dribbled constantly, and his gait was unsteady. On examination he had mildly dysarthric speech and his gait was clumsy but there were no signs of ataxia, oculomotor apraxia, nystagmus, or telangiectasia. Muscle tone and power were normal, his reflexes were brisk, but his plantar responses were flexor. A provisional diagnosis of mild cerebral palsy was made.

One year later he represented with acute lymphoblastic leukaemia. Treatment following the UKALL VIII 'A' protocol was given. This included prophylactic cranial irradiation of 1800 rads given in 10 fractions and six intrathecal injections of 12 mg of methotrexate. Persistently low white cell counts and

anaemia during maintenance treatment led to chemotherapy being withheld for a total of 16 weeks and a dose reduction to 75% of that appropriate for his surface area for the remainder. During this time there began a subacute deterioration in his neurological condition. There was an appreciable deterioration in his higher mental functions. He had choreiform movements of his face and upper limbs, a positive glabellar tap sign, moderate ataxia and dyspraxia of gait, and signs of a spastic tetraparesis. A computed tomogram showed extensive areas of very low attenuation of the white matter in both cerebral hemispheres with several areas of dense calcification.

A full blood count was normal; bone marrow aspiration showed no evidence of a recurrence of the leukaemia. In the cerebrospinal fluid the concentrations of protein and glucose were normal and there were no leukaemic cells. Tests of liver function, and the concentrations of serum copper, caeruloplasmin, and lysosomal enzymes were within normal limits. Early morning plasma cortisol concentrations were low (120 µmol/l; normal range 145–610 µmol/l); however, a tetracosactrin test was normal. Peripheral nerve conduction studies and a nerve biopsy specimen were normal. Viral titres were negative as were cultures of cerebrospinal fluid, blood, and urine. The neurological deterioration continued and a brain biopsy was performed. Histological examination showed features diagnostic of a chemoradiation induced leukoencephalopathy.

In view of these findings a diagnosis of ataxia telangiectasia was considered. A chromosomal analysis showed a generally normal 46 XY karyotype but two cells had a translocation of parts of chromosomes 14 and 15. Cultured blood cells showed an increased sensitivity to radiation when compared with a control, the serum α-fetoprotein concentration was >246 µg/l and the concentration of IgG was 0.65 g/l, IgA was 0.90 g/l, and IgM was

1.07 g/l (all within the normal range); IgE, however, was very low at 0.4 µg/ml. The diagnosis of ataxia telangiectasia was further confirmed when at the age of 8 years conjunctival telangiectasia appeared.

Discussion

Ataxia telangiectasia is an uncommon condition with an estimated frequency of 1/40 000 live births. It is autosomal recessive in inheritance and is characterised by a progressive cerebellar ataxia, dystonia, oculomotor apraxia, oculocutaneous telangiectasia, a predisposition to upper and lower respiratory tract infections, and an increased incidence of malignancy.¹ Ataxia is virtually always the presenting symptom and it typically becomes apparent when the child begins to walk. The ataxia is, however, only slowly progressive and the normal development of motor skills between the ages of 2 and 5 years may mask its progression. In consequence an initial diagnosis of cerebral palsy is often made. The oculocutaneous telangiectasia usually appears later, at between 3 and 6 years. In our patient the presentation was not atypical, although none of the most specific features such as oculomotor apraxia, respiratory tract infections, or telangiectasia were apparent at the age of 4 years.

Children and adults with ataxia telangiectasia are known to be at high risk of developing a malignant neoplasm. The estimated incidence is between 10 and 15% with lymphoreticular neoplasms and acute lymphoblastic leukaemia predominating in patients aged less than 15 years.² Chromosomal instability, particularly of chromosome 14, and pronounced chromosomal sensitivity to radiation are accepted hallmarks of ataxia telangiectasia cell lines.³ The instability of chromosomes and the increased sensitivity to irradiation in ataxia telangiectasia may have important implications not only for the aetiology of the malignancies but also for their treatment. Patients with the disease may have an unexpectedly severe reaction to radiation and to chemotherapy. In children and adults with lymphoma who have been treated with standard radiotherapeutic protocols, it has been reported that severe ulcerative dermatitis and oesophagitis associated with extensive deep tissue necrosis, which sometimes culminates in fatal complications, may occur.^{4 5} Acute neurological deterioration after prophylactic cranial irradiation for acute lymphoblastic leukaemia has been reported only once previously.⁶ In this paper the outcome of 19 children with ataxia telangiectasia and acute lymphoblastic leukaemia was reviewed; central

nervous system prophylaxis was given to five and acute neurological deterioration was reported in three. Of these one child had received cranial irradiation of 1200 rads, the second cranial irradiation of 1800 rads and intrathecal methotrexate, and the third intrathecal methotrexate only. The two children who had central nervous system prophylaxis but no neurological deterioration died within three months of presentation; it is possible there was insufficient time for neurological deterioration to become apparent. No acute neurological deterioration was noted in the 14 children who did not have central nervous system prophylaxis.

We report this case to highlight both the difficulties of making a diagnosis of ataxia telangiectasia in children aged less than 5 years, and the potentially harmful effects in these children of standard chemotherapy and radiotherapy. Although ataxia telangiectasia is a rare disorder it must be expected to occur with a much higher frequency among children with lymphoreticular neoplasms and acute lymphoblastic leukaemia; it should therefore be considered if the child has a clumsy gait. If ataxia telangiectasia is confirmed the standard therapeutic dose of radiation should be reduced in those with lymphoma, and in children with acute lymphoblastic leukaemia prophylactic cranial irradiation and intrathecal methotrexate should be either withheld or given in reduced dosages.

We thank Mrs Val Davidson for measurements of cellular sensitivity to radiation. J A E is supported by the Wellcome Foundation.

References

- 1 Border E. Ataxia-telangiectasia: an overview. *KROC Found Ser* 1985;19:1-63.
- 2 Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency diseases. *Cancer* 1971;28:89-98.
- 3 McKinnon PJ. Ataxia-telangiectasia: an inherited disorder of ionising-radiation sensitivity in man. *Hum Genet* 1987;75:197-208.
- 4 Pritchard J, Sandland MR, Breatnach FB, Pincott JR, Cox R, Husband P. The effects of radiation therapy for Hodgkin's disease in a child with ataxia telangiectasia. *Cancer* 1982;50:877-86.
- 5 Abadir R, Hakami N. Ataxia telangiectasia with cancer. An indication for reduced radiotherapy and chemotherapy doses. *Br J Radiol* 1983;56:343-5.
- 6 Toledano SR, Lange BJ. Ataxia-telangiectasia and acute lymphoblastic leukemia. *Cancer* 1980;45:1675-8.

Correspondence to Dr JA Eyre, Department of Child Health, Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH.

Accepted 7 June 1988