Postradiation motor neuron syndrome of the upper cervical region—a manifestation of the combined effect of cranial irradiation and intrathecal chemotherapy?

CNS prophylaxis is now an integral part of the management of acute lymphoblastic leukemia and was treated according to the United Kingdom Acute Lymphoblastic Leukaemia Trial 4 (UKALL 4) (-intensive) schedule. This comprised induction with cyclophosphamide, cytosine arabinoside (ara-C), vincristine, prednisolone and intrathecal ara-C; consolidation with the same, together with adriamycin, asparaginase, 6-mercaptopurine, intrathecal methotrexate and cranial irradiation; and maintenance with vincristine, methotrexate, ara-C, 6-mercaptopurine and prednisolone. The total dose of irradiation was 2400 cGy (rads) and the field extended to the level of the C3 vertebral body.

Apart from an early bone marrow relapse in June 1977, he made a complete recovery. In particular, there was no evidence of CNS involvement at any time.

He received his last dose of vincristine in May 1979 and completed his chemotherapy by June 1979. The period of cranial irradiation spanned 19 days in April 1977.

In January 1981 he was referred to the neurology clinic with a three month history of progressive painless wasting and weakness of the shoulder girdle muscles. There was marked bilateral winging of the scapulae, left worse than right. The trapezius, rhomboids, supra- and infraspinati, deltoids, teres major and both sternocostal and clavicular heads of the pectoralis major muscles were wasted, more on the left, and power was reduced to grade 4 on the left and 4+ on the right. There was proximal weakness of the shoulder girdle muscles. Triceps muscles were spared as were the distal upper limb muscles and lower limbs. There was questionable weakness of the orbicularis oculi and failure of frontalis to maintain elevation of the eyebrows. Although his face was thin there was no focal wasting or demonstrable weakness of the other facial muscles. There were no sensory symptoms or signs. Tendon reflexes were well preserved and symmetrical. Plantar responses were flexor.

Investigations at this stage including muscle enzymes, thyroid function, cervical spine radiographs, haematological screen and bone marrow were normal. Electroencephalographic (EMG) studies revealed reduced amplitude and duration which was not felt to be of clinical significance. Muscles

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**Table: Serum Alpha-1-antichymotrypsin (ACT) and Inter-alpha-trypsin inhibitor (ITI) contents, CSF ACT contents and ACT/serum ratio in Alzheimer’s disease (AD) patients**

<table>
<thead>
<tr>
<th>Control groups</th>
<th>Serum</th>
<th>CSF</th>
<th>Serum/CSF ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT mean (SD)</td>
<td>0.67 (0.27) g/l</td>
<td>0.63 (0.22) g/l</td>
<td>1.07 (0.54)</td>
</tr>
<tr>
<td>ITI mean (SD)</td>
<td>0.71 (0.19) g/l</td>
<td>0.72 (0.29) g/l</td>
<td>1.07 (0.54)</td>
</tr>
</tbody>
</table>
sampled serially showed little change with time. Nerve conduction studies showed normal motor latencies, conduction velocities and F wave latencies. The ulnar sensory action potentials and mixed nerve potentials were of reduced amplitude but also had normal conduction times, suggesting an axonal degeneration. A biopsy of the deltoid and quadriceps muscles showed non-specific changes only and no dystrophic features.

In February 1989 an MRI scan of the cervical spine showed the upper cervical cord to be enlarged and increased signal intensity on the T2 weighted spin echo sequence, the significance of which was unclear.

This patient developed an asymmetrical and patchy wasting and weakness of the shoulder girdle muscles involving several myotonies from C3 to C7. The explanation for the symptoms minimal weakness of the orbicularis oculi and frontalis muscles is uncertain. It may reflect patchy involvement of the muscles. Similar to the symptomless involvement of the other cranial nerves such as the bulbar muscles would escape detection) or might merely be constitutional.

We propose that the neurological abnormalities in our patient are a manifestation of augmentation of irradiation by combination intrathecal and systemic chemotherapy with two potentially neurotoxic agents, metothrexate and cytosine arabinoside, in accordance with the intensive UKALL 4 regimen. The predominant features of this case are in keeping with a postirradiation motor neuron syndrome. The minor upper sensory abnormalities described on EMG and without associated clinical symptoms or signs were probably secondary to vincristine.

Four types of radiation myelopathy have been described,2 the least common being lower motor neurone syndrome. The mechanism underlying this phenomenon is unclear but there is evidence from clinical and pathological studies that radiation injury to vascular endothelium produces ischaemia which leads to selective anterior horn cell degeneration.3,4 Greenfield and Stark observed this phenomenon in three patients, and Sadowsky et al reported it in a fourth.5 All four cases comprised a selective lower motor neurone disease confined to lower limb muscles starting three to eight months after radiation of the spinal axis. All followed a subacute and self-limiting course. In our patient the latent period was longer (2½ years), in keeping with other studies where the average symptom free interval was 14 months, but otherwise the disease followed a similar course. Unlike the other cases described, he did not receive direct irradiation to the spinal cord apart from that part of the upper cervical cord included in the field during cranial irradiation.

Byfield et al5 reported an infant who developed radiation myelitis of the cervical cord after receiving routine doses of vincristine and radiation therapy and postulated a synergistic effect.6 In 1975 a histopathological study by Price et al suggested a similar synergism between irradiation and intravenous methotrexate in the development of fatal leukoencephalopathy in children with ALL.7 Intrathecal has a greater neurotoxic effect ranging from a chemical arachnoiditis to transient/permanent paresis and encephalopathy.

Cytosine arabinoside, the other intrathecal agent given postoperatively, can cause disseminated multifocal coagulation necrosis of white matter and has been implicated in enhancing radiation induced congenital abnor- malities.8 A recent study has shown that intrathecal ara-C significantly reduces the dose-effect of irradiation for the development of radiation damage in rat spinal cord.

We are not aware of any previous reports describing an upper cervical cord motor neuron syndrome occurring following cranial irradiation and would be interested to hear if others have encountered this feature in leukemic patients treated similarly.

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Figure: CT scan shows thickened retrobulbar segment of right optic nerve with small area of low attenuation in the thickened portion.

Haematological and biochemical parameters were normal. The erythrocyte sedimen- tation (ESR) was 26 mm and the VDRL was negative. Skull radiographs of the optic foramen and superior orbital fissures were normal. CT scan of the head and orbit with contrast enhancement showed a retrobulbar segment of the right optic nerve thickened with a small area of low attenuation in the thickened portion of the optic nerve. Retrobulbar fat was preserved and the muscle cone was normal. The optic nerve at the orbital apex appeared to be of normal width. The brain parenchyma was normal as was the left optic nerve (Fig). Perimetry revealed superior altitudinal right hemianopia. Ultrasonography showed a mass in the region of the right optic nerve. The Casoni test was negative.

A diagnosis of optic nerve glioma or granulo- loma was considered. A right fronto- craniotomy and extradural frontal orbitotomy was performed. After incising the tenon's fascia normal retrobulbar fat protruded. The optic nerve was exposed by microdissection and was found to have fusiform thickening. A small portion of nerve just behind the optic globe was normal as was nerve near the apex. A small residual incision was made over the maximum bulge. There was intense fibrosis. On deeper incision a sago grain like cyst was found and excised. Histopathology revealed it to be cystercerosis. Postoperatively the patient's vision fully recovered but there was IIIId nerve paresis.

Cystercerosis is one of the most serious public health problems in the developing countries.9 Any part of the neuraxis can be involved, except the peripheral nerves, result- ing in protein features.10 Cystercerosis occurs in 3% of cases and may be single, unilateral or bilateral.11 Subretinal involve- ment of the eye usually occurs initially through the posterior ciliary arteries but migration of the parasite is common. The nasal side of the eye is more commonly involved than the lateral side. This is due to an anatomical peculiarity of the ophthalmic artery which after giving rise the lacrimal branch runs along the medial side of the orbit and divides into its terminal branches.12 The optic nerve obtains its blood supply from the branch of the central artery of the retina and retinal blood vessels may thus be involved.

The usual symptoms are of pain, irritation of the eyes due to iridocyclitis and dimness of vision. The eye may be involved alone or may be associated with other clinical features of neuro-cystercerosis when the brain is also involved.

Optic nerve involvement is rare in any kind of cyst or granuloma. As a result, in our
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