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Letters to the Editor

Development of the anterior cingulate syndrome in a child due to delayed necrotising methotrexate leukoencephalopathy

Delayed necrotising leukoencephalopathy may occur after intrathecal, intraventricular, or intravenous treatment with methotrexate (MTX) mostly in combination with radiotherapy.1 A clinical picture dominated by pyramidal pareses, ataxia, dysarthria, seizures, and deterioration of consciousness is reported. In one adult case of delayed necrotising leukoencephalopathy, akinetic mutism as a key symptom of one of the frontal syndromes has been reported previously.1 In adults three types of frontal syndromes are discerned: the dorsolateral frontal syndrome, the orbitofrontal syndrome, and the anterior cingulate syndrome.2 Anterior cingulate syndrome is characterised by profoundly apathetic behaviour and severe loss of initiative. Personality and picture of response inhibition on go-no go tests, do not speak spontaneously, and answer questions in monosyllables, if at all. They move little, are incontinent, and eat and drink only when fed. They display no emotion, even when in pain, and are indifferent to their circumstances. The most severe form of anterior cingulate syndrome is akinetic mutism.2

We had the rare opportunity to study the development of anterior cingulate syndrome in a 13 year old boy with delayed necrotising leukoencephalopathy. In this previously healthy and normally developed right handed boy, acute lymphocytic leukaemia was diagnosed at the age of 11 years. He was treated according to the current acute lymphocytic leukaemia protocol, vincristine, corticosteroids, and L-asparaginase. The CNS prophylaxis consisted of 24 Gray irradiation in 12 fractions and intrathecal injections of MTX delivered in three weeks (total dose 68.75 mg). Subsequently the patient received intrathecal MTX and intravenous MTX during the consolidation phase and on recurrence of acute lymphocytic leukaemia in the testis 18 months after diagnosis. When he was 13 years old he developed a left peripheral facial nerve paresis due to a second recurrence of acute lymphocytic leukaemia. The patient was treated according to a CNS recurrence protocol including intrathecal sandwich therapy of MTX in combination with cytisine-arabinoside (ARA-C) up to a total dosage of 132 mg MTX and 240 mg ARA-C.

Three weeks after the last intrathecal MTX infusion he was admitted because he had changed within four days from a talkative boy of superior intelligence into a child that only answered questions after strong stimulation. Neurological examination showed a diminished facial expression, eye blinking, and extensor plantar reflexes in addition to a slight left peripheral facial nerve paresis.

Brain CT showed hypodense slightly swollen white matter bilaterally in the frontal-parietal part of the centrum semiovale with a slight preponderance on the right side (figure, A). Repeated CSF examinations showed normal cell counts. Immunophenotyping did not show lymphoblasts.

Sponantaneous speech was almost absent. When stimulated he answered in a telegraphic style. By contrast, he could repeat long sentences and read aloud a difficult text, monotonously but without language and articulatory problems. The token test did not show language comprehension problems. No signs of apraxia were present. On a standardised memory test (15 words test) he obtained a very low score (first decile). His IQ was 76 (Groninger intelligence test1). One week later he became severely hypokinetic and developed a paralysis of the left arm and leg and was unable to make voluntary orofacial movements. Involutionary movements such as yawning and swallowing remained intact. He also became mute, but he communicated by yes or no questions by lifting the right hand.

Two weeks after admission CT showed extension of the hypodense white matter lesions into the parietal regions. Desmazethane treatment was started and steroids were reduced. The hemiparesis ameliorated and voluntary orofacial movements were again possible.

Four weeks after admission he showed a slight left peripheral facial nerve paresis and a slight bilateral pyramidal paresis more so on the left than on the right side. Grasp reflexes could be easily elicited in both hands. He was able to walk independently. He did not attempt to speak and could not be stimulated to talk spontaneously, repeat words, or read aloud. By contrast, he could name objects and answer questions by writing. He obeyed written and spoken commands. He remained in this condition for the next five weeks. Finally he died from an acute subdural haematoa, a sequela of the acute lymphocytic leukaemia.

An extensive recurrence of the acute lymphocytic leukaemia was found with lymphoblast cells in the subarachnoid spaces and in the perivascular spaces, especially of the frontoparietal regions. Large, sharply demarcated necrotic areas were seen bilaterally in the frontal central white matter, not involving the U fibres (figure, B). The cere-
bral grey matter was normal. The posterior borders of these lesions were formed by the caudate nuclei, the anterior parts of the internal capsules being spared. The lesions reached the parietal periventricular areas. The necrotic areas were characterised by extensive loss of myelin with myelin laden gitter cells. Both sides included a substantial number of neurons in the ventromedial parts of the putamen and in the nuclei accumbens showed central chromatolysis. No signs of neuronal degeneration were found in the rostral parts of the putamen or in the caudate nuclei on both sides.

The extensive coagulative necrosis of central white matter with spongiosis, sparing the U fibres, is in agreement with the diagnosis of delayed leukoencephalopathy. The presence of gitter cells and reactive glialis is compatible with onset of the disease about six to eight weeks before the patient’s death. The absence of CSF pleocytosis at the onset of delayed necrotising leukoencephalopathy suggests that a CNS leukaemic relapse was not important in its evolution.

In the present case all symptoms of anterior cingulate syndrome as described by Cummings were present, but the clinical picture did not deteriorate to the most severe form of anterior cingulate syndrome—that is, the akinetomutism strikingly characterised by Cairns et al as “a state of motionless, mindless wakefulness”. In our patient verbal communication remained possible by writing and reading excluding global aphasia as the cause of his mutism.

In children mutism is a rather non-specific symptom, which may occur in a wide variety of neurological diseases. The present finding suggests that in children with anterior cingulate syndrome mutism is associated with an extreme loss of initiative. This selectively affects the modalities of communication of which spontaneous speech and spontaneous writing seem to be the most vulnerable.

We are grateful to Dr RM Egeler for critically reading the text and for helpful comments.

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Unilateral auditory hallucinations in a boy with ipsilateral conductive hearing loss

Unilateral auditory hallucinations in adults and adolescents are associated with contralateral CNS lesions and ipsilateral peripheral lesions.

A nine year old boy was admitted to the child psychiatric inpatient unit after exhibiting self destructive and aggressive behaviour for two weeks at school. He attempted to burn himself on a radiator and to jab a pencil into his skull. He begged his head, punched one teacher, and threw a chair at another without provocation.

Four years before admission he had tried to set a tree on fire. Two years before admission he had started to spit and to sit on his bedroom on fire. He often shopped from the neighbourhood store and often fought siblings and peers. One month before admission his mother’s intoxicated boyfriend hit him hard on the chest, leaving marks.

He was conceived when his father raped his mother. The umbilical cord was tightly wrapped around his neck at birth. His Appgar scores were 6 and 8. At birth he had a cleft soft palate, hyperuribilinaemia, and sepsis with Streptococcus viridans and diptheroids. At two and a half years of age his cleft palate was repaired. Two years later auditory brainstem-evoked potentials were placed to treat multiple episodes of otitis media. At four years of age a right hydrocele was repaired. At four and a half years of age audiological examination disclosed a right active hearing loss and a mild to moderate right conductive hearing loss. Both parents used street drugs. His father is a violent, abusive man who has not been living in the family for many years. His mother was abandoned by her own mother and was raised in orphanages. His mother had psychiatric admissions to hospital beginning in childhood, resulting in treatment with antipsychotic and antidepressant blocking drugs. No other family member was reported to have a hearing loss.

On mental status examination he had a moderately severe articulation deficit. He heard the voices of devils outside his head at night and during the day telling him to jump off the building and to kill himself. He heard the voices only in his right ear. He saw faces of devils, a rag doll that his mother had given him, Jason, a character in a horror movie, cockroaches that turned into red devils, and hell that looked like a fire surrounded by cockroaches.

His right myringotomy tube was disim- pacted from the cerumen and was removed. His left myringotomy tube was patent and in place. The visual and auditory hallucinations continued unabated. Audiograms showed normal left hearing and a mild right conductive hearing loss at 1 kHz and 4–8 kHz and improved to normal hearing at 1–5 kHz. His EEG was normal.

The visual and auditory hallucinations and suicidal and homicidal ideation stopped a few days after starting treatment with the antipsychotic drug molindone (5 mg twice daily). He denied having visual or auditory hallucinations during subsequent treatment with molindone and, later, with haloperidol. His discharge diagnoses were brief reactive psychosis and conduct disorder.

This case report is reminiscent of the occurrence of schizophrenia in elderly people with peripheral auditory disease. Typically, unilateral hearing loss is associated with auditory hallucinations in adults with severe hearing loss. Our case is novel because the patient is a child with a mild conductive hearing loss affecting only a portion of the acoustic frequencies which are significant in speech perception.

The disappearance of auditory hallucinations in our patient coincided with the resolu- tion of his psychosis when he received antipsychotic medication.

The occurrence of hallucinations has been considered to be caused by (1) stimulatory phenomena in the CNS—for example, electrical excitation by electrodes, seizures,2 pharmacological agents,1 or (2) release of inhibitory phenomena on sensory neurons—for example, sensory deprivation,2 the visual hallucinations in blindness (the Charles Bonnet Syndrome), and the phantom limb hallucinations after damage to peripheral nerves in amputees.3 We propose that mild conductive hearing loss, even if limited to only a portion of the acoustic frequencies which are significant in speech perception, may predispose vulnerable children to develop ipsilateral auditory hallucinations during psychotic episodes.

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MATTERS ARISING

Low dose interferon-α is safe in patients with myasthenia gravis

Piccolo and colleagues1 have recently reported that interferon-α (IFNα) could induce myasthenia gravis in patients with hepatitis C virus infection and briefly reviewed the incidence of patients with myasthenia gravis induced by IFNα. The therapeutic efficacy of IFNα treatment in myasthenia gravis has been shown in experimental studies.2 We performed a prospective study that aimed to evaluate the efficacy of IFNα (Roferon-2b, 3 μg subcutaneously three times a week, for six months) in seven myasthenic patients. No appreciable clinical deterioration or myasthenic crisis was noted during the IFNα treatment; clinical grading according to modified myasthenia gravis scoring showed improvement in four, no sig- 

ificant change in two patients, and the score was worse than that before treatment in one patient. Findings from single fibre

J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp.62.3.301 on 1 March 1997. Downloaded from http://jnnp.bmj.com/ on May 28, 2022 by guest. Protected by copyright.