Letters

Akathisia following traumatic brain injury: treatment with bromocriptine

Sir: The efficacy of neuroleptic drugs in the treatment of schizophrenia is to a great extent limited by non-compliance. Perhaps the most important reason for non-compliance is akathisia, a highly disturbing motor restlessness unrelated to anxiety or psychosis, compelling the patient to move or pace constantly. The incidence of akathisia in neuroleptic-treated patients is quite high, estimates ranging as high as 40% in one study.1 Besides leading to non-compliance, akathisia is frequently misdiagnosed as increased psychosis and has also been implicated in several suicides.2

The pathophysiology of akathisia remains unclear. Previous authors have postulated a relative increase in dopaminergic activity in the striatum, possibly related to blockade of presynaptic autoreceptors. However, akathisia may be induced by reserpine, and it frequently coexists with neuroleptic-induced bradykinesia, arguing against this hypothesis.2

There is strong animal evidence that akathisia may be related to blockade of dopamine in the prefrontal cortex rather than the striatum. Catalepsy may be induced in rats with prefrontal injection of dopamine,3 and motor restlessness may be induced by medial prefrontal 6-hydroxydopamine (6-OHDA) lesions.4 A relationship between prefrontal dopamine and akathisia has not yet been demonstrated in humans, however.

We recently cared for a patient who developed severe motor restlessness following bilateral prefrontal brain injury. The restlessness responded dramatically to bromocriptine, lending further support to this hypothesis.4

A 61 year old, right handed white male was well except for bilateral cataracts until one year prior to initial consultation, at which time he fell off a ladder, striking his occiput. He lost consciousness for four minutes, and had minimal post-traumatic amnesia. Since the accident, both the patient and his wife reported a marked loss of motivation, social skills and personal hygiene. More significantly, however, they both reported profound motor restlessness, resulting in the patient spending his entire day pacing or rocking in a rocking chair.

On initial consultation, these symptoms persisted. The patient had been treated with alprazolam 2 mg day, with only minimal improvement of the restlessness. He specifically denied anxiety, describing himself as “fidgety but not nervous.” He likewise denied depressive symptoms. On examination, the patient was rather dishevelled. He was cooperative with the examination, albeit somewhat non-spontaneous. He was oriented and memory language function and visuospatial function were intact. Performance was quite poor on controlled work fluency, however, and he exhibited severe perseveration on copying figures. Motor examination revealed normal strength and tone throughout and a normal gait. Most striking, however, was a profound motor restlessness. The patient paced constantly in the office, only occasionally sitting down and rocking in the chair at those times. Computed tomographic (CT) scan at that time revealed a small right parieto-occipital area of encephalomalacia and much larger bilateral orbitofrontal lesions (fig).

Alprazolam was discontinued, and the patient was treated with diazepam 15 mg per day, resulting in a mild reduction in restlessness, although the patient reported subjectively feeling better. The following month, bromocriptine was added, and increased over one week to 7.5 mg per day. Both the patient and his wife reported complete resolution of the restlessness within several days. On return visits, the patient was able to sit in a chair for up to 45 minutes, and no trace of restlessness could be noted. The patient has been maintained on both bromocriptine and diazepam for the past twelve months, and continues to do well. Both the patient and his wife remain reluctant to withdraw the medications.

This case lends further support to the hypothesis that akathisia is related to decreased dopaminergic activity in the prefrontal cortex. To our knowledge, this is the first case reported in which akathisia can be directly related to a prefrontal lesion.

Perhaps the best animal model for akathisia is the so called ventral tegmental area (VTA) syndrome, characterised by motor restlessness, decreased attention, and increased reactivity to stimuli, but normal sleep, following radio-frequency lesions to the VTA,6 the origin of the mesocortical dopamine system that terminates in the prefrontal cortex. In these animals, the severity of the restlessness produced correlates well with the magnitude of dopamine loss in the prefrontal cortex but not elsewhere,7 suggesting that mesocortical dopamine is implicated in the pathogenesis of the restlessness. In addition, the VTA syndrome is treatable with dopamine agonists, such as dextroamphetamine and apomorphine.8 Although a true VTA syndrome has not been demonstrated in man, there is a loss of dopamine in the VTA in Parkinson’s disease and Lang and Johnson have reported that akathisia-like symptoms are fairly frequent in this illness.9 Finally, this VTA syndrome bears some resemblance to human Attention Deficit Disorder.10 Both, in terms of symptoms and “paradoxical” response to dextroamphetamine. In fact, Shyattz et al have produced a similar syndrome with intracerebral 6-OHDA injections in neonatal rats.11 We await further research in this area.

Although dopamine agonists such as bromocriptine may be effective in treating akathisia, they are contraindicated in schizophrenic patients, as they exacerbate psychotic symptoms. Anticholinergic agents have traditionally been used in this population, although there is no theoretical support for this in the above model. Furthermore, recent studies indicate that anticholinergics are no more effective than placebo in the treatment of akathisia.12

Benzodiazepines have been used for akathisia for many years, with limited success. Their mechanism of action in akathisia is not clear, although they may provide only non-specific anxiolytic and muscle relaxant effects. In this case, the response to diazepam was helpful but less than definitive.

Finally, beta-adrenergic blockers such as propranolol have recently been shown to be quite effective in the treatment of akathisia.13 Although the mechanism of action of these agents is not clear, one study indicates that rats do not become restless with prefrontal 6-OHDA lesions if pretreated with desipramine,14 without such pretreatment, both dopamine and norepinephrine depletion occur. This may suggest a relative balance between prefrontal dopaminergic
and noradrenergic function in the pathogenesis of akathisia. Considering the enormous public health problem of non-compliance with neuroleptic medication and its relationship to akathisia, further research in the direction of a rational pharmacology for this problem is clearly needed.

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References

Accepted 17 February 1989

Cartilage embolism of spinal cord

Sir: Acute spinal cord infarction due to cartilage emboli is rare, with an onset of dramatic suddenness which affects previously healthy individuals. Only 20 cases had been reported up to 1981, and the pathogenesis remains unclear.

We report the first case from India. A 21 year old healthy male suddenly developed pain which started at the nape of the neck and spread to the left upper limb. Within two hours all four limbs had become weak. Retention of urine, diminished sensation below the level of the neck and difficulty in breathing had developed when he was brought to the hospital. There was no preceding history of injury or any other illness. On examination the pulse rate was 108/minute and respiratory rate 30/minute. Respiration was diaphragmatic; he could count up to only six in one breath, chest expansion was less than 1 cm, the trachea was deviated to the right, chest percussion was resonant bilaterally and breath sounds absent over the right hemithorax. He was fully conscious and well oriented but had difficulty in speech due to respiratory distress. All higher functions and cranial nerves were normal. He was quadriplegic with grade zero power in all limbs. The deep tendon reflexes were absent. Abdominal and plantar responses could not be elicited. All cutaneous sensation was absent below C4 level. Position and vibration senses were normal at admission, but were absent later.

Laboratory investigations showed normal haemoglobin, total leucocyte count was 16,000 mm3 with 70% neutrophils, 29% lymphocytes and 1% monocytes but no biochemical abnormalities, and blood culture was sterile. Arterial blood gases showed hypoxaemia with respiratory alkalosis. Chest radiograph showed cardiomegaly and the cervical spine were normal. The patient was managed with endotracheal intubation, ambu-bag assisted ventilation and antibiotics. He developed pneumothorax on the right side for which a intercostal drainage was established. His condition progressively deteriorated and he died two days after admission.

Necropsy showed a collapsed right lung, pulmonary oedema, broncho-pneumonia and changes in the spinal cord. The heart, major blood vessels, other extracranial organs and the brain were normal. There was no exudate, haemorrhage or any other abnormality of the surface of the cord. The cut surfaces of serial slices showed focal softening and occasional petechiae in segments C2 to D6. Microscopically, these segments exhibited features of recent infarction affecting the anterior horns, lateral columns and the anterior columns (fig 1). The extent varied in different segments but remained confined to the perfusion areas of anterior spinal artery. The necrotic areas showed loss of details of tissue constituents and cavitation. Mild perivascular leucocytic and macrophage response were present. More peripheral parts showed spongiosis and numerous axonal retraction balls. The major blood vessels outside the parenchyma were normal but several intraparenchymal medium and small arteries were occluded by cartilaginous material (fig 2). These were strongly positive with alcian blue at pH 2.5 and not associated with thrombus. This type of vascular occlusion was observed at several levels of the affected portions of the spinal cord. The veins were not involved. No abnormality was observed in sections of the cord beyond mid-dorsal segments.

The patient's clinical features are consistent with the infarct shown at necropsy which was the result of occlusion of branches of anterior spinal artery by cartilaginous emboli. They are also similar to those in previous cases1 in some of these involvement of veins has also been noted.2 A prominent feature of all cases has been the dramatic sudden onset. The other features of note include the absence of history of significant trauma, involvement of the cervical and upper dorsal segments of the cord and fatal outcome. The diagnosis has seldom been made during life,1 which may be due to the rarity of such cases and the rather obscure.

Fig 1 Section of cervical segment of spinal cord showing multiple foci of myelomalacia. Haematoxylin and eosin (HE), × 6.5.

Fig 2 Section of spinal cord showing cartilage embolus in a medium size artery. (HE), × 120.