DIDMOAD (Wolfram) syndrome

SIR: The DIDMOAD (Wolfram) syndrome (*Diabetes insipidus, diabetes mellitus*, optical atrophy and deafness) is a rare, autosomal, recessively inherited disabling disorder of yet unknown aetiology. Additional neurological symptoms, for example ataxia, dysarthria, nystagmus, dysdiadochokinesia, dysphagia, anosmia, and electroencephalogram (EEG) changes may also be present (*Lancet*, 1986). Furthermore, psychiatric alterations, such as episodes of severe depression, psychosis, organic brain syndrome, and impulsive verbal and physical aggression, have been documented in about 25% of these patients; also heterozygote carriers of the gene seem to be predisposed to significant psychiatric illness (Swift *et al*, 1991).

Case report. We report the case of a 27-year-old female patient with DIDMOAD syndrome, who was in a somnolent state (with normal metabolic and electrolyte profile) and recovered after discontinuation of anticholinergic medication she had received for urge incontinence. Physical examination showed hyposmia, non-reactive pupils in response to light, pale optic discs, diminished gag and uvular reflexes, and diminished tongue motility. In the course of her illness she had developed organic personality syndrome according to DSM-III-R (American Psychiatric Association, 1987) with impaired impulse control, affective incontinence, deficient judgement and reduced initiative.

Her computerised axial tomographic (CAT) scan revealed enlarged third and fourth ventricles, slight atrophy of the cerebellum, a small pons and mesencephalon, and fibrous dysplasia of several skull bones. In the EEG a slowed basic rhythm persisted; in the auditory-evoked potentials of the brainstem, there were normal interpeak latencies but diminished V amplitudes. Organ-specific IgG-class autoantibodies against epitopes of central nervous system tissue and against several gangliosides (GM 1, GD 1a, and GT 1b) (Klein *et al*, 1991) were detected in plasma; unfortunately, lumbar puncture for the respective antibody tests was refused by the patient. Cytogenetic studies revealed a normal female karyotype (46, XX). Amino acid analysis showed unremarkable normal results; there was no evidence for diminished concentrations of thiamine in serum, erythrocytes, and of intra-erythrocyte thiamine pyrophosphate levels, which have been proposed to cause neuronal degeneration (A. Speitling, personal communication).

While in other patients no signs of abnormality could be found, this is not so for a 32-year-old woman (Kehl & Keller, 1982); the second report confirming necropsy findings of pontocerebellar atrophy in DIDMOAD syndrome by CAT scan. The possible role of an auto-immune process in the pathogenesis of DIDMOAD syndrome and its connections to the still poorly characterised psychiatric symptoms of this disorder is proposed by our case and warrants further research.

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Cognitive impairment and clozapine

SIR: We wish to report the association of a deterioration in memory for verbal and visual material with high doses of clozapine in a patient with schizophrenia.

Case report. The patient was referred to the rehabilitation services following an 18-month in-patient admission. She had spent her early years in Ghana but was educated in the UK and had a good academic record, achieving eight 'O' levels and one 'A' level. Her family report that she had been unwell for approximately 16 months before presenting to the psychiatric services, during which time she had returned to Ghana and had an unplanned pregnancy.

During the 18-month admission she developed a systematised delusion that her baby was a chicken, reported hearing the voices of angels talking to her, and believed that her mind was being controlled by an outside force. Clozapine up to a maximum dose of 500 mg daily was used to relieve her psychotic symptoms, and maintained on discharge.

On transfer to rehabilitation services the patient had no psychotic symptoms but reported a three-month history of deterioration in her memory. Specifically, she was now unable to find her way to the nursery with her small child, regularly forgot appointment times, and had difficulty finding offices she had visited several times previously. Mental state examination and neurological examination revealed no abnormality. A computerised tomographic scan was reported as normal, and electroencephalography showed

generalised background slowing with paroxysmal sharp wave and spike activity, findings consistent with clozapine treatment. Investigations to exclude an organic cause of cognitive impairment were negative.

Neuropsychological assessment confirmed deficits in memory and spatial memory with a Rey Osterreith figure recall of 9.7% (impaired), a Benton Visual Retention Test score of 6 correct and 7 errors (both moderately impaired), and a Rivermead Behavioural Memory Test score of 8 (poor). There was also a significant deterioration in full-scale and non-verbal IQ (80 and 68 respectively; Wechsler Adult Intelligence Scale–Revised) from the estimated premorbid level of 105–110 as indicated by the National Adult Reading Test. The clozapine dose was decreased to 450 mg and the patient subjectively reported an improvement in her memory.

Repeat EEG showed moderate improvement with mild diffuse background abnormality. Repeat neuropsychological testing showed an improvement in non-verbal IQ with a change of 68–76 on performance IQ. Follow-up neuropsychological assessment at one year, with clozapine dosage now reduced to 400 mg, showed improvement on cognitive testing to have been maintained together with improvement in verbal and non-verbal IQ to 96. Overall memory performance is now in the normal range with a Rey Osterreith figure recall of 58.5%, a Benton Visual Retention Test score of 7 correct, 3 errors, and a Rivermead Behavioural Memory Test score increased to 10.

Neuropsychological deficits in schizophrenia are well recognised. Goldberg *et al* (1990) concluded that neuropsychological dysfunction is a consistent feature of schizophrenia related primarily to the clinical disease process. Goldberg *et al*'s study (*BJP*, January 1993, **162,** 43–48) confirmed that although clozapine is associated with an improvement in both positive and negative symptoms in a group of schizophrenic patients, a wide range of cognitive functions remain impaired. However, clozapine did have an adverse effect on a measure of visual memory. A number of investigators have observed a relationship between impaired memory and the anticholinergic properties of medications in schizophrenia. Clozapine is the most potent anticholinergic of the available neuroleptics and may impair cognition as a result of this activity. Saletu *et al* (1987) have confirmed this in normal subjects. Drowsiness and EEG abnormalities confirmed to be associated with clozapine use may also be implicated in deficits on cognitive testing.

Cognitive deficits in our patient could be seen as part of the schizophrenic disease process or, alternatively, as a result of the high doses of clozapine used. This is supported by the patient's subjective report and the evidence of improved reversible EEG changes and neuropsychological performance following decreased dose. This case highlights the importance of adequate neuropsychological testing before treatment with clozapine and the importance of using the minimum effective dose.

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Lithium dosage and inositol levels

SIR: Lithium reduces brain inositol levels by inhibition of inositol monophosphatase (Hallacher & Sherman, 1980). While serum inositol, originating in the diet, provides inositol to peripheral tissues, some peripheral tissues have been shown to have reduced inositol after lithium treatment (Sherman *et al*, 1986). Recently, Bersudsky *et al* (1992) reported that inositol (3 g daily) greatly ameliorated lithium-induced polyuria-polydipsia. In two patients, an improvement of lithium-induced skin lesions was also noted. We hereby report a case where severe lithium-induced psoriasis was almost eliminated by inositol treatment.

Case report. A 57-year-old, retired, high-school teacher with bipolar manic–depressive illness had a 36-year history of bipolar mood disorder. Severe psoriasis, exacerbated by lithium, limited lithium levels to 0.6 mM, at doses of 900 mg/day, and lithium was often stopped for long periods. Six months ago the patient was started again on lithium (900 mg/day), since he was in a manic state, which resulted in a severe exacerbation of psoriasis. Following Bersudsky *et al* (1992), we added 1.0 g inositol, three times a day for one week, resulting in a mild improvement of the psoriasis. The dose was then raised to 6 g daily, after consideration of the possible risk of reversal of the clinical benefit of lithium. Since the patient could not tolerate lithium because of the psoriasis, the possible benefit of inositol in our view outweighed the risks of reversal of its therapeutic effect. After 48–72 hours on inositol (6 g daily), the patient's psoriasis was dramatically improved with regression of diffuse scaling, papules and plaques and absence of new lesions. He had never before had an improvement of psoriasis on lithium. After one week inositol was stopped and lesions returned within 48–72 hours. Return of inositol after seven days led to a rapid regression of psoriasis. It was then possible to raise the lithium dose to 1200 mg, reaching levels of 0.9–1.0 mM and complete clinical psychiatric remission. Further withdrawals of inositol have led to exacerbations of psoriasis but not as severe as in the past.