A case of cutaneous necrosis during interferon-β 1b (B-IFN) therapy in multiple sclerosis

Our patient, a thirty eight year old woman, had had relapsing-remitting multiple sclerosis since the age of 17. In September 1995 interferon-β 1b (B-IFN, Betafevon, Schering) was introduced. After a training session the patient injected 8 million IU on alternate days. Injection sites were the thighs and the abdomen. The patient was seen 2, 4, 8, and 12 weeks after the beginning of the therapy. Some erythematous patches were noted at the injection sites. Otherwise there were no side effects. Blood tests performed after four weeks were normal. From the third month of treatment the patient complained of multiple painful scars at the injection sites. We examined her and found multiple severe necrotic skin ulcers with surrounding erythema at the injection sites (figure, A). After a review of the literature we considered an interruption of the treatment. As the patient was eager to continue, an investigation on methods of self-administration disclosed that the patient kept vials of B-IFN and saline in a refrigerator (+5°C). The vials were taken from the refrigerator just before application. After mixing, the substance was injected. We decided to heat the saline to body temperature for five minutes before mixing and to bring the suspension to body temperature by keeping it in a breast pocket for 10 minutes. After modifying the mixing procedure, no new scars appeared in the next six months of treatment (figure, B). The few cases previously reported with severe necrotic cutaneous lesions during B-IFN therapy have stressed a possible immunological basis for this serious side effect. We postulate that a local reaction in the skin is improperly dissolved lyophilised substance has caused the necrotic ulcers.

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A pure amnestic syndrome after MDMA (“ecstasy”) ingestion

Because of the widespread use of 3,4-methylenedioxymethamphetamine (MDMA) as a recreational drug (“ecstasy”), incidences of MDMA intoxication are of high clinical relevance. Whereas acute and even chronic psychosis, hyperthermia with sometimes lethal outcome, and hepatic, cardiac, and neurological complications after ingestion of MDMA are well documented, persistent effects on memory function in humans have not been reported so far. This is especially remarkable, because of the known potential of MDMA to interfere with serotonin and dopamine brain metabolism and its established neurotoxicity in animals.

We present the data from a 26 year old woman who developed a pure amnestic syndrome after exposure to MDMA. Other than MDMA the patient had taken no other drugs during the months before onset of her symptoms. In the past she had had occasionally taken cocaine and heroin, but she had stopped heroin misuse one year and cocaine some months before onset. She did well at night school, worked part time in an office, and her organic and psychological state was inconspicuous according to her and her parents' reports. There was no indication of an unusual nutritive behaviour. Her own and her family's histories were unremarkable concerning seizures and psychiatric diseases. Three days after having taken half a tablet of ecstasy while taking part in a "rawl", she was brought to an emergency ward in a fearful state, which was interpreted as an MDMA induced psychotic episode. Her mother reported that the episode had started with loss of consciousness and—as far as she could remember—clonic movements of her arms and legs. Afterwards the patient was disoriented in time and place, and showed regressive infantile behaviour and fear. Routine blood examinations, in particular serum sodium, done immediately after admission, were normal. Blood and urine concentrations of drugs three days after onset were negative, as were the results of EEG, ECG, CT, and HMPAO-SPECT. Neuroleptic treatment with clozapine was started. The psychotic episode soon resolved and neuroleptic therapy could be tapered but the patient complained about ongoing memory problems,

Severe necrotising cutaneous lesions in a woman with multiple sclerosis undergoing treatment with interferon β-1b. (A) Multiple necrotic skin ulcers on the sites of injection, with surrounding erythema. (B) Two months after modifying the mixing procedure. The old lesions have healed and there are no new lesions.
The hippocampi, to that the clearly shown she has notional return to a material only after about utes) were yielded to semantic fluency: of words (the figure: 36/36), and “frontal” functions (phonetic fluency: 19 words beginning with “s” in two minutes, semantic fluency: 26 animals in two minutes) were all within the normal range. Memory function as assessed by a German version of the Warrington recognition memory test yielded results below the 5th percentile for words (37/50) and faces (36/50). Recall of the Rey figure (7/5/36) and the results of a list learning task (10/15 after five learning trials) were also highly impaired. The patient therefore had a rather pure non-material specific disorder of episodic memory. After nine months formal testing showed only a slight improvement in her memory performance. She is still not able to return to night school or her part time job, but she has learned to make extensive use of a diary and a timetable. She had occupational therapy in an outpatient clinic for several months.

Brain MRI (figure) performed three weeks after onset showed bilateral hyperintense lesions in the globus pallidus. Additional involvement of basal temporal structures was suspected, but could not be shown clearly because of movement artefacts. In a second MRI examination about two months later these hyperintense lesions in the globus pallidus had partly disappeared and the basal temporal structures were normal.

The symmetric lesions in the globus pal-
lidus resemble the findings of Squier and colleagues’ in their neuropathological study, who pointed out that the pallidum is rich in serotonin releasing neurons. They suspected that a local release of serotonin might have led to prolonged vasospasm and necrosis. The hippocampus, essential for episodic memory function, are also rich in serotonin releasing neurons and are known to be targets of MDMA in experimental animals. Therefore we propose that in the present case MDMA ingestion led to alterations in the globus pallidum (seen in MRI but clinically silent) and in the hippocampi (causing persistent memory problems “horizontally”). In post-mortem studies of patients who died after MDMA ingestion, other mechanisms of damage were suspected.2 In the present case there was no pathological evidence that a water intoxication could be ruled out by normal serum sodium concentration. The sudden onset with a suspected generalised seizure could point to cerebral anoxia due to asphyxia as another possible reason for the patient’s memory disorder, but the fit was observed and no apnoea or even cyanosis was reported.

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**Rotated drawing: a mini mental state examination performance with strong lateralising significance**

Neuropsychological evidence clearly has a strong bearing on our understanding of the process of object recognition. Of particular relevance are the recent reports of a few patients who have drawn dramatically misorientated, although otherwise quite accurately repro-
duced, drawings when attempting to copy a line drawing. The copies are almost invariably rotated relative to the model by 90° or in one case by either 90° or 180°. It has been difficult to draw conclusions about the localising significance of this unusual neuropsychological sign. However, it is notable that, with the exception of one report of two instances of transient global amnesia,4 all of the cases have involved right sided-4 or bilateral pathology. These data suggest that the sign has some localising significance. However, previous investigations have involved only single case data.

The records of a consecutive series of 63 patients were reviewed. All had been admitted for the purpose of rehabilitation, and all had had a cerebrovascular accident with subsequent hemiparesis. Forty one of the patients were male and 22 were female. All had been fitted for the mini mental state examination (MMSE), which includes a geometric figure to be copied. The figure is oblong, and the standard administration position involves the placement of the figure with the principal axis of the figure aligned “horizontally”. In the present study the figure was presented on a sheet of paper, placed in the patient’s midline, with the main axis of the page aligned “horizontally” on the desk. A separate blank sheet of paper was positioned closer to the patient (also in the patient’s midline, and with the main axis of the page aligned “horizontally”) on which the patient attempted their copy.

Seven of the 63 patients grossly rotated their copies of the MMSE figure relative to the desk. As mentioned above, the rotation of the principal axis, these misorientations were invariably by 90°, so that the principal axis was “vertically” oriented. The major component parts of the drawings were positioned in an appropriate relation to these positions, although there were occasional omissions of minor components. Some patients also rotated drawings on other tests.5 The seven patients who rotated items on copy were not significantly different from those who did not rotate in terms of sex (six male, one female v 35 male, 21 female), age (63-1 v 62-4 years, SD 12.9), or years of education (6.57 v 6.24 years, SD 1.07). However, all of the patients who rotated the figures on copying had right sided lesions. Interestingly, all seven of these patients also showed some evidence of left sided visuospatial dysfunction.

The data from the present study show some strikingly consistent features, which are similar to those reported previously. Firstly, all of the patients in the study who rotated their drawings of the MMSE did so by 90°, so that the principal axis of elongation of the figure was vertically positioned. With one exception,6 previous studies of rotated drawing have suggested that the rotation of the Rey complex figure (the principal axis of which is horizontal) to an orientation in which the principal axis was vertical.7,8 We have recently been able to investigate this phenomenon in more detail using two of the patients reported in the present study.5 When the orientation of the principal axis was systematically presented in all of the cardinal orientations, drawings were repeatedly rotated to a horizontal orientation, and were invariably rotated to a vertical orientation. Thus it is not surprising that the copying task from the MMSE, where the original drawing is hori-

zontally oriented, is a sensitive indicator of such rotations.

Secondly, in the present study all of the patients who rotated the MMSE on copy had lesions in the territory of the right middle cerebral artery. This finding of a strong rightward lateralisation of lesion is also consistent with the literature, which has involved right sided 9,10 or bilateral lesions9 in all patients who were suitable for the pur-
poses of localisation.4 However, the lesion location within the right hemisphere has var-
ed greatly, often exclusively involving the frontal lobes,17 by contrast with this study. These data suggest that rotated drawing might well have lateralising relevance as a clinical sign—although its localising relevance within one hemisphere is less clear.

One of the most interesting clinical phenomena is the co-occurrence of rotated drawing and left visuospatial neglect. None of the previous case reports of rotated drawing have involved cases of left neglect; nor have the actual reproductions of patient performance depicted in these papers shown the classic signs of left neglect.9,10 However, it is possible that the co-occurrence of rotated drawing and neglect in the present
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