Suspected covert lorazepam administration misdiagnosed as recurrent endozepine stupor

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We recently reported in Brain (Lugaresi et al., 1998) 20 cases of idiopathic recurrent stupor due to endozepine-4 accumulation in the blood. Samples obtained from nine of these patients were analysed by gas chromatography–mass spectrometry to rule out contaminating synthetic benzodiazepines (Rothstein et al., 1992). All these samples contained endozepine-4 concentrations high enough to account for the stuporous state of the patients. The other 11 cases of idiopathic recurring stupor were diagnosed on the basis of clinical criteria alone since they were identical to the patients with documented endozepine-4 accumulation. All presented the same clinical picture and EEG pattern (low amplitude, unreactive, background activity) during stupor and a reversal of the stuporous state after flumazenil administration (awakening and EEG normalization). Again, toxicological immunoenzymatic tests failed to detect even traces of synthetic benzodiazepines.

We subsequently investigated a cluster of nine patients presenting recurrent stuporous attacks with almost simultaneous onset which had occurred in a restricted rural area near Lucca in Tuscany. Except for the extraordinary clustering in time and space, these patients were in all respects similar to the sporadic idiopathic recurring stupor patients previously encountered by us. The stuporous episodes in fact lasted 1–2 days and were followed by confusion and amnesia; ictal EEG was characterized by the typical low voltage, 13–14 Hz background activity, and flumazenil administration led to transient awakening and EEG normalization. Routine toxicological immunoenzymatic assays had ruled out the presence of benzodiazepines.

However, in the meantime, a newer more specific toxicological assay, liquid chromatography–mass spectrometry, had become available to us. Because of the unusual epidemiology, we used this technique to re-analyse blood samples from the Tuscan patients. This time we detected in the blood of all of these patients the benzodiazepine lorazepam which had not been disclosed when we had used gas chromatography–mass spectrometry analysis. We could therefore deduce a fraudulent lorazepam intoxication in these patients, and exclude an endogenous benzodiazepine (endozepine) origin of the stupor.

Besides highlighting the difficulties inherent to the ascertainment of surreptitious benzodiazepine administration, we wish here to offer also the following conclusions:

(i) Toxicological immunoenzyme assays for benzodiazepines currently implemented by the hospital emergency services, though they may reveal diazepam and other benzodiazepines, may prove negative if the drug present in the blood is lorazepam.

(ii) Biological tests on the chromatographic fraction containing endozepine-4 do not rule out that the episodes of recurrent stupor are due to lorazepam intoxication since lorazepam migrates in the same chromatographic fraction as endozepine during high performance liquid chromatography.

(iii) The agent responsible for recurrent stuporous attacks can only be identified by means of liquid chromatography–mass spectrometry.

Finally, in the light of the above findings, the endozepine origin of the stuporous episodes in the patients we recently reported in Brain (Lugaresi et al., 1998), especially in those who did not undergo gas chromatography–mass spectrometry, should be considered as still unproven.

References


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The cerebellar cognitive affective syndrome

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We have read with great interest the article by Schmahmann et al (1997). Our objective was to delineate the neuropsychological profile in focal cerebellar lesions, to evaluate cerebral diaschisis and to correlate the findings. We studied 26 patients with focal and strictly unilateral vascular lesions (22 infarcts, 4 haematomas) and compared them with 16 controls matched for age, sex and educational levels. A neuropsychological battery of tests was employed that covered the main cognitive domains and included WAIS (Wechler Adult Intelligence Scale), Cancellation test, Modified Stroop test I and II, controlled oral word association test, Boston Naming Test, Numerical Calculations, Rey Complex Figure immediate copy and delayed, Logical Memory I and II, Verbal Paired Associates and Visual Reproductions I and II from the Wechsler Memory Scale, Trail-Making A and B, Purdue Pegboard and the Hamilton Depression Rating Scale. Lesions at any other level of the neuraxis were ruled out by MRI. Also, single photon emission computed tomography (SPECT) was performed in 19 patients and every control to evidence the presence of diaschisis and whether it could have some bearing on any neuropsychological derangement eventually found.

In contrast to Schmahmann and Sherman, who employed a battery of tests covering similar areas of cognition, we did not find any specific cognitive disturbances in our patients other than a mild naming deficit in patients with recent lesions (also present in 13 of Schmahmann’s and Sherman’s patients) and impairment of the Purdue Pegboard test (a test of motor function). There were no differences between side (left or right) or arterial territory of the lesions (postero-inferior cerebellar artery versus superior cerebellar artery). The age of the lesion (less or more than 6 months old) made no difference. We found diaschisis in 13 of 19 patients in whom SPECT was performed; it was contralateral to the cerebellar lesion (crossed diaschisis) in six patients and ipsilateral in seven. As mentioned earlier, diaschisis did not result in any specific cognitive deficit.

We concluded that cerebellar stroke results in motor control impairment and mild naming deficit, with preservation of declarative memory, language, visuospatial or executive abilities. In accordance with our results, other authors were unable to find a cognitive deficit in patients with cerebellar pathology as well (Daum et al., 1993; Glickstein, 1993).

As Schmahmann and Sherman mention, the cerebellum can contribute to the acquisition of motor skills as shown by functional neuroimaging, and to procedural learning (Molimari et al., 1997). In this regard, we have studied procedural learning in our cerebellar patients by a Serial Reaction Time Task, and have found that patients were unable to learn a motor sequence with the hand ipsilateral to the lesion (Gomez-Beldarrain et al., 1998). Based on our results, we suggest that the cerebellum plays an important role in the circuit of procedural memory.

In their paper, Schmahmann and Sherman state that ‘there are very few descriptions of clinically relevant cases that address the possibility of a cerebellar contribution to non-motor functions’. The accompanying editorial comments that ‘the size of the series and diffuse nature of the associated pathology do not allow clear answers to the question’ and raises the uncertainty about the relationship between pathology in circumscribed cerebellar regions and specific profiles of cognitive deficits, concluding that ‘the answer to this question will require further neuropsychological studies’. While we agree that well controlled studies with an adequate number of patients will shed more light on this interesting but controversial topic, we believe that our study answers, at least partially, some of the aforementioned questions.

References


Reply

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We thank Gomez-Beldarrain and Garcia-Monco for their comments and appreciate the opportunity to address their concerns. The evidence suggesting a role for the cerebellum in higher order functions is derived not only from studies of patients with degenerative diseases of the cerebellum, and from a consideration of the cerebrocerebellar circuits that link the cerebellum with associative and paralimbic cerebral areas. There is also a large body of functional neuroimaging data that demonstrates cerebellar activation by cognitive tasks; a wealth of physiological and behavioural data in experimental animals; and evolving theoretical notions that address the fundamental role of the cerebellum in motor, sensory, cognitive, and affective and autonomic behaviours (see Schmahmann, 1997). What had been missing until the description of the cerebellar cognitive affective syndrome was a convincing demonstration of clinically relevant behavioural changes in patients with lesions restricted to the cerebellum (Dolan, 1998).

At the clinical level we continue to be struck by the prominent aberrations of comportment and intellectual functioning in our patients on neurological examination, bedside mental state tests and neuropsychological evaluations as reported in Schmahmann and Sherman (1998). We have also been impressed by the observations of paramedical personnel and family members that patients are behaviourally impaired following acute cerebellar infarcts, particularly with large strokes that involve the territory of the posterior inferior cerebellar artery.

How can this be reconciled with the observations of Gomez-Beldarrain et al. (1997) who report that patients with focal cerebellar lesions perform normally on a range of neuropsychological tests, regardless of the site, size, or age of the lesions? The major focus of their study was to determine the presence or absence of reversed cerebellar diaschisis, and whether this could be correlated with neuropsychological findings. Unfortunately, the design and analysis of the data in their study raise questions about the validity of their conclusions. Patients were included if they had cerebellar infarction or cerebellar haemorrhage (three patients with haemorrhage in their Table 1, but four patients with haemorrhage mentioned in the text). The pathology and consequences on affected tissue and surrounding structures is dissimilar in these two disease entities. This potential confounding variable is not commented upon. The size of the infarcts, and the extent to which they involve parts or all of the affected vascular territory, is not presented in the paper. The patients in their study were older than our patients (mean age 62 versus mean age 48) and less educated (mean education 8 years versus 13.9 years). Both these variables significantly affect tests of cognitive function (Lezak, 1995).

The method of deficit measurement employed in the two studies was also quite different. In our study a deficit on an individual test was determined by the presence of a statistical difference between a patient’s performance on that test and that of a normative sample, using the normative data for each of the standardized tests administered based on age, educational level and gender. In the study of Gomez-Beldarrain et al. (1997), patients’ performance was compared to that of a control group, rather than a normative sample. Their two groups, however, were not matched in a ‘pair-wise’ fashion (each patient having a control subject matched for age and educational level). Rather, they were ‘matched’ as a group with mean education and age similar for the two groups, but without the standard deviation for these two variables reported.

The claim that the control group was ‘without cognitive impairment’ was based on the performance of control subjects on the Mini-Mental State Examination (MMSE), with scores falling at or above 23. The authors do not provide the range or the mean MMSE score for these controls. On this screening test scores below 24 are considered abnormal for dementia and for delirium. Cut-off scores higher than that used by

Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561–79.
Gomez-Beldarrain et al. (1977) are recommended for specific neurological conditions (e.g. 27 for multiple sclerosis; 25 for well-educated Alzheimer’s disease patients) (Lezak, 1995). Furthermore, Blecker et al. (1988) identify a cut-off score of 29 for 40–49-year-olds, 28 for 50–79-year-olds and 26 for 80–89-year-olds. Based on the information provided, therefore, it is doubtful that the control group of Gomez-Beldarrain et al. (1997) was indeed ‘without cognitive impairment’. Given the design of their study, this central flaw fundamentally affects the interpretation of the results of their patient group.

Gomez-Beldarrain et al. (1997) determined that the only scores that were significantly different between patients and controls was the Purdue Pegboard Test of motor function. Recent cerebellar stroke patients performed more poorly than controls on the Boston Naming Test, but the difference was not found to be statistically significant. We compared the performance of our patients with those of Gomez-Beldarrain et al. (1997) on those few tests for which scores were actually provided in their paper (see Table 1). These include the Trail-Making Test Part A, The Boston Naming Test, the Controlled Oral Word Association Test (F-A-S test) and the Vocabulary subtest of the WAIS-R (Weschler Adult Intelligence Scale—Revised). This comparison showed that the performance of our patients was similar to that of the patients in the study of Gomez-Beldarrain et al. (1997), and, indeed, in some instances was even better than their patients as well as their controls. The single exception was the F-A-S test on which our patients were worse. At the same time, however, for all these tests our patients performed below the mean when compared to normative data.

Gomez-Beldarrain et al. (1997) also performed a cross-sectional comparison of patients with recent and old infarcts and found no difference between these groups. Once again, both their methodology and findings were at odds with our own. In our study a longitudinal comparison of four patients tested acutely following cerebellar injury and again 1–9 months post-onset indicated that impairments improved over time, although executive functioning remained 1 SD below the mean.

Thus, the analysis of the limited data in patients with cerebellar strokes provided in the paper of Gomez-Beldarrain et al. (1997) indicates that their patients are indeed impaired on tests of cognitive functioning. Comparison of the results of their study and ours suggests that the differences do not lie in the results, but in important methodological differences that appear to have contributed to the erroneous conclusion that patients with large and acute cerebellar infarcts are cognitively normal. These include the design of their study, the inclusion of possibly impaired control subjects, the interpretation of the data, and the cross sectional rather than longitudinal approach used to compare patients with recent and old infarcts. These factors together could account for their failure to detect cognitive impairments in their patients.

The subsequent study of Gomez-Beldarrain et al. (1998) demonstrating that cerebellar patients have impaired procedural learning is an interesting addition to the literature on the cognitive impairments of cerebellar patients. This observation is consistent with the results of other studies of learning in cerebellar patients (Molinari et al., 1997a) and with the results of functional imaging experiments in normal subjects (e.g. Jenkins et al., 1994) and experimental observations in animals (see Molinari et al., 1997b). Interestingly, it is at odds with the results of Daum et al. (1993) that did not support the hypothesis of cerebellar involvement in procedural learning, and whom these authors cite as supporting their view that the cerebellum contributes exclusively to motor functions. Gomez-Beldarrain et al. also cite Glickstein (1993) who has made considerable contributions to the understanding, inter alia, of the neuronal circuitry of the cerebrocerebellar system, but who has not

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**Table 1** Neuropsychological test scores from Schmahmann and Sherman (1998) and Gomez-Beldarrain and Garcia-Monco et al. (1997)

<table>
<thead>
<tr>
<th>Test</th>
<th>Trail-Making A (seconds to complete task)</th>
<th>Boston Naming Test (number correct)</th>
<th>Controlled Oral Word Association Test (F-A-S) (number of words)</th>
<th>WAIS-R Vocabulary (scaled score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Beldarrain et al. Recent strokes</td>
<td>108.6</td>
<td>15.75 (for words 10–40)</td>
<td>34.56</td>
<td>9.43</td>
</tr>
<tr>
<td>Gomez-Beldarrain et al. Controls</td>
<td>77</td>
<td>18.62 (for words 10–40)</td>
<td>34.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Schmahmann and Sherman Recent infarcts (mean raw score)</td>
<td>64</td>
<td>50.6 (for words 1–60)</td>
<td>25.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Schmahmann and Sherman Recent infarcts (mean Z-score)</td>
<td>–1.2</td>
<td>–1.4</td>
<td>–2.7</td>
<td>–0.13</td>
</tr>
</tbody>
</table>

Gomez-Beldarrain et al. do not provide the unit of measurement in their Table 2. We make the assumption that these are mean raw scores in comparing our data.
directly studied clinical issues relating to cerebellar dysfunction.

The question of diaschisis remains a puzzle. It is not yet clear whether diaschisis represents a metabolic and clinically silent consequence of distant focal lesions, or whether it is causally related to the observed clinical phenomena. This is as true for reversed cerebellar diaschisis as it is for distant hypometabolism seen in cerebral lesions. Botez et al. (1991), for example, have suggested that diaschisis is causally related to the cognitive effects of cerebellar lesions, but this remains to be shown with certainty. The conclusions of Gomez-Beldarrain et al. are premature in dismissing a possible clinical and pathophysiological role of reversed cerebellar diaschisis, particularly given the fact that their patients, whom they claim to be normal, appear instead to display a range of cognitive impairments.

Further careful clinical evaluations of patients with the cerebellar cognitive affective syndrome characterized by executive, spatial, linguistic and affective disturbances may help to enhance the understanding of the role of the cerebellum in the organization of higher order function. In addition, well-designed studies in patients and in non-human primates with cerebellar lesions will be useful in defining the role of the cerebellum in cognitive processing, and in helping to establish whether there is a consistent relationship between reversed cerebellar diaschisis and the clinical manifestations that we have defined as non-motor hallmarks of cerebellar lesions, that is, the cerebellar cognitive affective syndrome.

References


Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561–79.

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