

CASE REPORT

## Olivopontocerebellar atrophy: paraneoplastic syndrome of brain tumour?

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We describe a patient who, three years after the onset of an olivopontocerebellar atrophy, developed a right cerebral tumour. The cerebellar symptomatology also included, as in other cerebellar patients previously described, a peripheral dysgraphia. Because this deficit of writing is generally reported in patients with right cerebral lesion, the authors hypothesized that functional alterations of supratentorial structures preceding the tumour by years may be able to damage the neural substrates connecting cerebral and cerebellar structures and to produce cerebellar atrophy.

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### Introduction

Cerebellar paraneoplastic syndrome (see Bolla and Palmer, 1997, for a review) is a relatively rare complication, of possible autoimmune aetiology (Posner, 1993), that develops in patients affected by a wide variety of tumours, especially small-cell lung carcinoma, Hodgkin lymphoma or carcinoma of the breast or ovary. Pathological changes outside the cerebellum (spinal cord, basal ganglia, brainstem, cerebral hemispheres) are indeed quite frequent in cases reported as paraneoplastic cerebellar degeneration (Posner, 1993; Dropcho, 1994; Mason *et al.*, 1997). However, only sporadically do these changes represent the typical aspect of multiple system atrophy. In particular, only two cases have been reported of olivopontocerebellar atrophy (Ishida *et al.*, 1990; Quinn *et al.*, 1992) associated with neoplasm; in these two cases the paraneoplastic nature of the syndrome is under discussion and the possibility of an incidental association with cancer is not excluded (Quinn *et al.*, 1992).

Silveri *et al.* (1997) reported a patient with a severe cerebellar atrophy of unknown origin who presented peripheral dysgraphia, a symptom previously described in subjects with right supratentorial lesions and more recently also in patients with primary cerebellar pathology (Haggard *et al.*, 1994; Silveri *et al.*, 1999). This finding was interpreted in terms of disconnection between the motor programs of writing elaborated in the supratentorial right structures (corticopontocerebellar pathway) and the proprioceptive afferent from muscles and the skeleton (spinocerebellar pathway)

conveying information on the actual movements of the hand during writing.

Three years after onset of the cerebellar symptoms, a right temporoparietal glioblastoma was diagnosed. A reconsideration of the radiological data allowed exclusion, with assurance, of the presence of a tumour at the time of the clinical investigation of the cerebellar dysgraphia and in the following years. The presence of multisystemic (olivopontocerebellar) atrophy was confirmed, consistently with the hypothesis that cerebellar dysgraphia might be related to pathology of the neocerebellar circuit.

The possibility that the pontocerebellar atrophy could have been the first expression of a tumour, and thus considered a 'paraneoplastic' manifestation, has been taken into consideration, together with the hypothesis on its possible pathogenic mechanisms.

### Case report

The patient, a 67-year-old man, without significant familial history of neurologic disease or alcohol abuse, was admitted to the Neurological Department in April 1995 (Silveri *et al.*, 1997). The patient had complained of the onset of dysarthria and disorders of balance and gait since 1993. He had already been admitted to another hospital in 1994 for this symptomatology. At that time the neurological examination revealed truncal ataxia and moderate dysarthria; a brain computerized tomography (CT) scan showed moderate corticosubcortical atrophy and cerebellar atrophy.

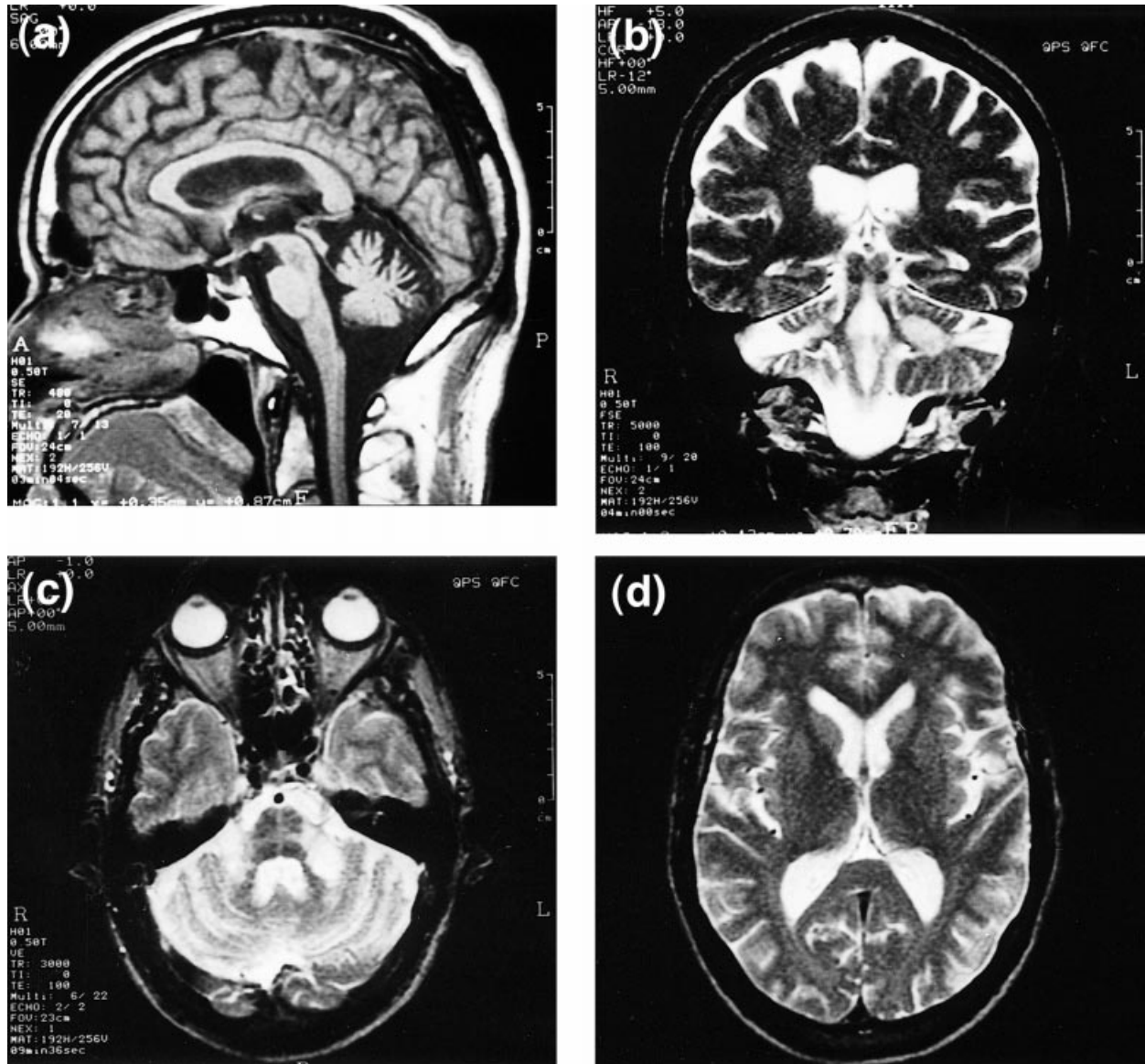
Upon admission at our hospital (April 1995) the physical examination revealed postural tremor of the legs, wide-base ataxia of gait and stance, bilateral action tremor and dysmetria. A moderate scanning dysarthria and occasional nystagmus to the right was also present. A moderate peripheral dysgraphia was

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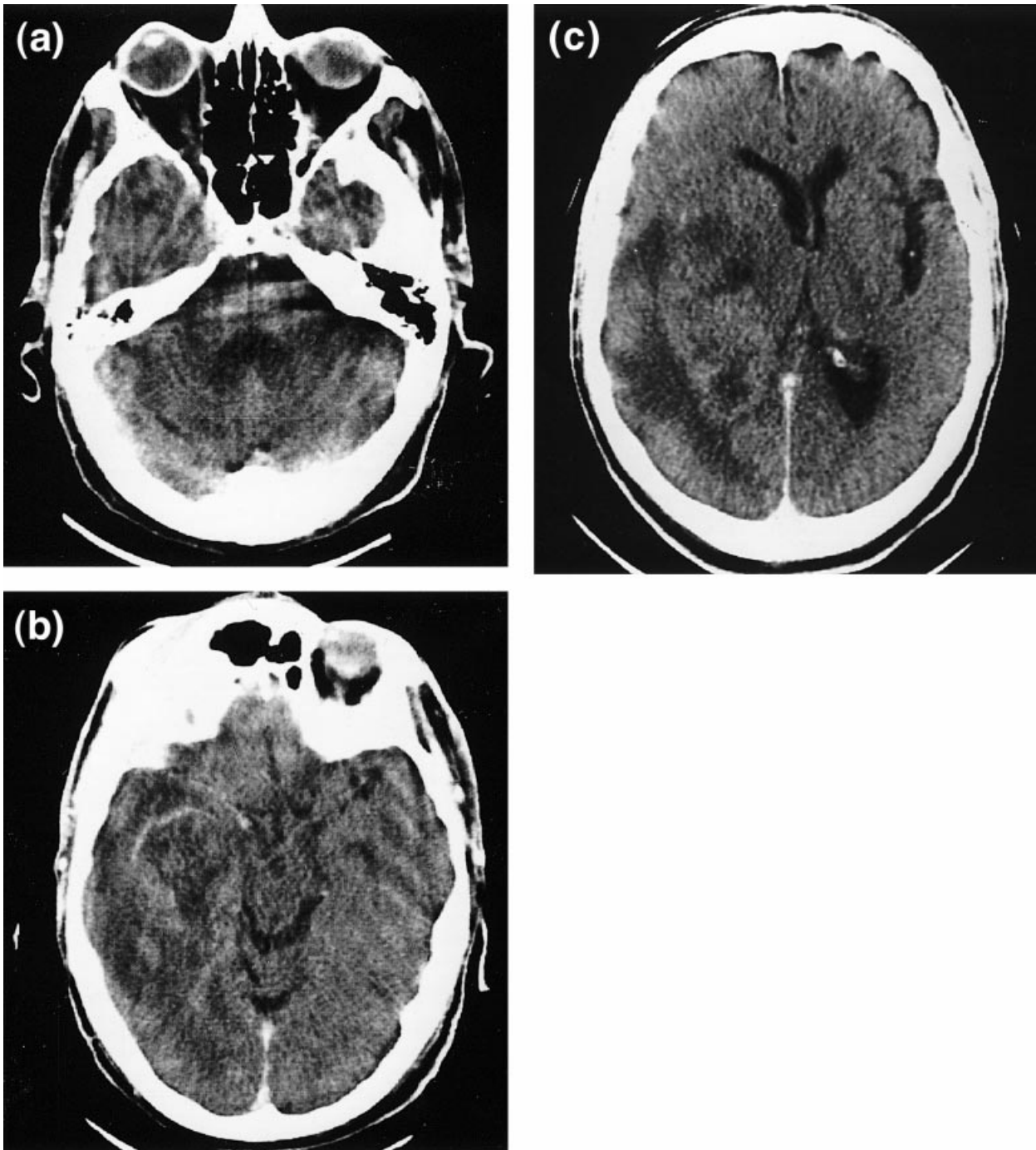
also described but no other sign of cognitive deficit. Qualitative analyses of serum and cerebrospinal fluid (CSF) were negative for anti-Purkinje cell antibodies; the albumin fraction of the CSF was increased and oligoclonal bands were demonstrated indicating a reduced blood–CSF barrier. Serological tests of blood and CSF were negative for neurotropic viruses. In order to exclude a paraneoplastic genesis of the cerebellar symptomatology the patient underwent a detailed diagnostic screening to search for a primary tumour.

The search was negative except for the detection of a small prostatic adenoma. The brain magnetic resonance imaging (MRI) scan (April 1995) (see Figure 1) did not show any significant focal supratentorial alteration but revealed diffuse corticosubcortical atrophy with striking cerebellar atrophy.

Over the next 17 months the patient was admitted to our hospital five times and was also often checked as an outpatient. At each admission both blood and CSF serology and search for primary neoplasm was negative.



**Figure 1** Brain MRI obtained on April 1995. (a) Sagittal T1-weighted image; (b) coronal T2-weighted image; (c and d) axial T2-weighted images. There are obvious signal alterations in both of the middle cerebellar peduncles, more extended in the left side (b and c). More subtle signal intensity modifications are seen in the transverse pontine fibres (c). CSF spaces in the posterior fossa are clearly enlarged. The IV ventricle as well as the vermian and hemispheric cerebellar cisterns appear dilated. The vermis is atrophic, and there is only a minimal reduction in the size of the pons. No modification is visible in the right temporo-parietal white matter (d).



**Figure 2** Contrast-enhanced CT obtained on June 1996. In the posterior fossa (a) atrophic changes are similar to the previously shown MRI picture. There is a large malignant right temporo-parietal glioma (b and c). The tumour exhibits irregular contrast enhancement, involves the ventricular trigone and results in extended peritumoral oedema. The tumour appears largely necrotic and deeply infiltrating the brain parenchyma up to the right ventricular trigone.

The physical examination revealed progressive worsening of the cerebellar symptomatology, in particular of the trunkal ataxia.

In June 1995 tendon reflexes were increased at the

lower limbs and, shortly after, also in the upper limbs. A very mild pyramidal syndrome was detected in the right side, with arm weakness, Babinski sign and reduced abdominal reflexes. The patient also started

complaining of dysphagia. Electromyography was negative. Autonomic cardiovascular control was borderline. Nocturnal vocalizations were reported. Repeated MRI did not show any modification compared with the previous one. It is worth noting that extrapyramidal signs were never detected at any time during the disease. Clinical conditions remained relatively stable over time until June 1996 when the patient complained of a sudden worsening of the ataxia with severe gait difficulty, vertigo, insomnia, agitation and visual hallucinations. Memory disorders were also reported. The CT scan performed at the readmission (June 1996) revealed a right temporoparietal tumour. The tumour was not considered susceptible to surgical treatment or chemotherapy. In spite of X-ray therapy the patient's clinical conditions evolved very rapidly and he died in August 1996.

### Imaging

The first brain MRI obtained in April 1995 (see Figure 1) did not show any significant alteration in the cerebral hemispheres, but revealed a pattern that was considered indicative of olivopontocerebellar atrophy. The control MRI on June 1995 did not demonstrate any modification.

Brain CT scan performed in June 1996 (see Figure 2) disclosed a large heterogeneous tumour in the posterior deep right temporal lobe resembling the typical radiological picture of glioblastoma multiforme. No change was observed in the posterior fossa findings.

### Discussion

The patient's clinical symptomatology and the neuroradiological findings were consistent with multisystemic atrophy and in particular with olivopontocerebellar atrophy. Cerebellar atrophy was more marked in the left cerebellar hemisphere. The familial history was not significant and the conclusion was in favour of a sporadic form. When the case was initially described (Silveri *et al.*, 1997), in order to explain the dysgraphic deficit the hypothesis was formulated of a corticocerebellar involvement, that is, of a pontocerebellar damage. At the time of the examination the patient did not have detectable signs of a cerebral tumour. On the other hand, other cases have been described of cerebellar dysgraphia (Haggard *et al.*, 1994; Silveri *et al.*, 1999) due to cerebellar vascular lesions, thus confirming that the deficit may be generated by a primary pathology of the cerebellum. However, why did the tumour develop precisely in the cerebral hemisphere which, when damaged, may produce peripheral dysgraphia? Many functional studies on

blood flow and oxygen or glucose utilization demonstrate that cerebral hemispheric lesions, including tumours, may produce contralateral cerebellar hypoperfusion (crossed cerebellar diaschisis: Baron *et al.*, 1980; Fulham *et al.*, 1992) according to the seminal hypothesis by VonMonakow (1910). Contralateral diaschisis has been mainly demonstrated in frontal tumours but it can also be observed in parietal or temporal tumours (Otte *et al.*, 1998). We advance the hypothesis that functional alterations of the supratentorial structures preceding onset of the tumour by years may be able, by as yet unknown mechanisms, to damage the neural substrates connecting cerebral and cerebellar structures (corticopontocerebellar fibres) and to produce cerebellar atrophy. In this view, olivopontocerebellar atrophy could be considered a paraneoplastic syndrome, to the extent that it represents damage remote from the primary lesion.

This explanation is obviously only a hypothesis and the possibility of an incidental association between olivopontocerebellar atrophy and cerebral tumour cannot be excluded. However, the onset of the tumour in the expected cerebral hemisphere for peripheral dysgraphia, the described prevalence of the atrophy in the left cerebellar hemisphere, consistent with a crossed cerebellar diaschisis, and the temporal relation between onset of the cerebellar symptomatology and of the cerebral tumour, also suggest a non-incidental association. Further studies on the functional basis of crossed cerebellar diaschisis might be able to shed light on this hypothesis.

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