Acta neurol. belg., 2006, **106**, 142-146

Case reports

Opsoclonus-myoclonus syndrome : a clinicopathological confrontation

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Abstract

Opsoclonus-myoclonus syndrome (OMS), a movement disorder characterised by chaotic eye movements and myoclonus, is a rare clinical entity. We present two cases of opsoclonus-myoclonus syndrome of paraneoplastic origin. In the first patient the syndrome was associated with a breast carcinoma and in the second patient with a non small cell lung carcinoma. However none of the commonly associated antibodies were found in these cases. From the neuropathological findings from the first patient we find arguments that support the current hypothesis on the pathophysiology of OMS namely a dysfunction in brainstem and cerebellum.

We conclude that in adults with OMS one has to be very suspicious of a possible neoplastic origin of the syndrome. The antibodies associated with some cases of OMS are thought to play a role in the pathophysiology of the syndrome although the exact immunologic mechanism remains unknown. Research into the neuropathological substrate of OMS yields a broad range of abnormalities in brain stem and cerebellum. However none of these findings seem to be pathognomonic. As for the possible therapy of OMS, several immunomodulating strategies can be used with varying success. At present there is no established standard therapy.

Key words : Paraneoplastic syndrome ; breast carcinoma ; NSCLC ; immunoglobulins ; plasmapheresis.

Introduction

Opsoclonus-myoclonus syndrome (OMS), also known as the “dancing eye dancing feet syndrome” (Voltz, 2002) is a rare clinical entity affecting children and adults. Opsoclonus – which is the only universal component of the syndrome – is the occurrence of involuntary, repetitive rapid conjugate ocular saccades that are irregular in amplitude and frequency and occur in all directions without an intersaccadic interval. Additionally, myoclonus occurs in a high percentage of OMS cases. Several other features can occur in the OMS such as ataxia, tremor, dysarthria (Caviness *et al*., 1995) and psychiatric symptoms (Turkel *et al.*, 2006).

In children the syndrome generally appears before the age of three as a parainfectious or paraneoplastic process, mostly in association with a neuroblastoma (Verma A., 2002 ; Dale *et al.*, 2003). Rarer causes such as celiac disease have also been described in children (Deconinck *et al.*, 2006). In adults the most frequent causes are idiopathic, para-infectious and paraneoplastic (Caviness *et al*., 1995 ; Vigliani *et al.*, 2001). Among this last group, different types of tumors involving a wide variety of organs have been reported, most commonly breast and lung cancers (Caviness *et al*.,1995 ; Bataller *et al.*, 2001).

We report two cases of OMS of paraneoplastic origin, the first case associated with breast carcinoma and the second with a non-small cell lung carcinoma (NSCLC). Commonly detected serum antibodies against onconeuronal proteins (anti-Hu, anti-Yo, anti-Ri) were absent in both cases. In the first patient the neuropathological substrate of OMS was investigated after a post-mortem. The second patient remained stable after curative treatment of her lung tumour.

Case reports

Case 1

The first case was a 62-year-old female. From her personal history, we note a left mastectomy for breast cancer with a curettage of the axillar lymph nodes 24 years ago and tumor resection in the right breast 19 years ago. Three weeks prior to admittance, the patient complained of general malaise and vertigo, symptoms for which no medical attention was sought at that moment. One week later the patient’s clinical condition deteriorated due to the appearance of diplopia and nystagmus. At this time, the patient was admitted to another hospital were the tentative diagnosis of vestibular neuritis was made. Magnetic resonance imaging of the brain showed no abnormalities in the posterior fossa, a few aspecific white matter lesions in both frontal lobes were detected. Upon further deterioration of

her condition, the patient was transferred to our hospital.

Neurological examination at the time of admittance showed an alert and attentive woman. Although the patient's speech was slurred due to a clear cerebellar dysarthria, verbal communication was possible. Opsoclonus and limb ataxia with bilateral dysmetric finger-nose test (more pronounced at the left side) were present. Further general physical examination showed no abnormalities (in particular, no axillar lymphadenopathies were present).

Routine blood examination showed a polyclonal increase of the gamma globulin fraction. Thyroid function was normal. Analysis of the cerebrospinal fluid (CSF) revealed leukocytes of 40/mm^3 with 98% lymphocytes), protein content of 42.5 mg%, glucose content of 66 mg% and a gamma globulin fraction of 16.2% without oligoclonal banding.

Analysis of antibodies commonly associated with OMS namely anti-Hu, anti-Yo and anti-Ri antibodies in both serum and CSF failed to demonstrate abnormalities. The same was true for a standard set of serum tumor-markers (CEA, CA 15.3, CA 19.9, CA 125, NSE). To exclude the possibility of a spongiform encephalopathy an analysis of the 14-3-3 protein in CSF was performed (Zerr *et al.*, 2000 ; Van Everbroeck *et al.*, 2003) which was negative as well. An EEG showed an abnormal pattern with important slowing in both hemispheres, however repetitive triphasic complexes (as found in Creutzfeldt-Jakob disease) could not be demonstrated.

A standard plain radiograph of the chest showed sequelae of the left axillary curettage and a calcified, ring shaped opacity in the upper right lobe (which was not seen on a control radiography). An initial gynaecological examination completed with an echography of the internal genitals failed to reveal any abnormality. Doppler examination of the carotid arteries was normal. No peripheral vestibular causes for the patient's symptoms and signs were found.

A repeated clinical examination, performed on day 18, revealed an axillar adenopathy in the right axillary region. A subsequent ultrasound showed 4 enlarged lymph nodes with signal characteristics suggestive for malignity. Computed tomography scan of the thorax confirmed this finding although no primary lesions (breast nor lung) were demonstrated.

During hospitalisation, we witnessed the rapid deterioration of this patient's condition with myoclonus.

Different therapeutic strategies were successively tried without benefit : immunoglobulins (0.4 g/kg/day IV during 5 days), methylprednisolone (500 mg/day IV) and finally high doses of piracetam (12 g/day IV). The first two therapeutic options gave no result at all. The administration of piracetam resulted in a transient (three days) amelioration of the patient's clinical condition. Finally, an adequate general sedation (and discrete regression of symptomatology) was obtained by the administration of clotiapine (40 mg 2 $\times$ 1 daily IV) and clonazepam (1 mg 4 $\times$ 1 daily PO).

On day 17 of the hospitalisation, total parenteral nutrition (TPN) was started (nasogastric tubes were removed due to the patient's generalized myoclonus). Blood examination at that time showed a discrete anemia and an elevation of the pancreatic enzymes (secondary to the TPN) and a transient leucopenia.

Based on the aforementioned findings, the most probable clinical diagnosis is a paraneoplastic opsoclonus-myoclonus syndrome. This syndrome has been described in association with breast-carcinoma. Although medical imaging techniques failed to demonstrate the primary tumor, an ultrasound of the right axillary region showed 4 lesions strongly suggestive for metastases. Given the rapid deterioration of the patient's clinical condition, the therapeutic unresponsiveness of the syndrome and the will of the patient's family, a biopsy of the aforementioned lesions was not performed.

The patient died approximately 10 weeks after the appearance of the first symptoms.

An autopsy demonstrated a poorly differentiated tumor in the right axilla, compatible with a metastasis from a primary breast carcinoma.

Neuropathology

The brain was removed and fixed in 4% buffered formaldehyde. Macroscopic evaluation of the brain revealed no abnormalities. Seven mm paraffin sections were made and stained with haematoxylin eosin, cresylviolet and Bodian silver technique. Several neocortical areas including the frontal and temporal cortex and the area striata showed no meningeal abnormalities, intact grey and white matter, but some small perivascular lymphocytic infiltrates were found. In several instances, the structure of the vessel wall was disturbed and thickened by the lymphocytic infiltrate, although no necrosis was observed. The cingulate gyrus, lateral geniculate body, caudate nucleus, putamen, pallidum and the rostral part of the thalamus were normal. The brain stem was examined at several levels : in the mesencephalon, the oculomotor nucleus revealed no abnormalities, nor did the substantia nigra. The locus coeruleus and other pontine structures showed no neuronal loss, but in several places, extensive lymphocytic infiltrates were found, both in the perivascular areas, but also interspersed in the pontine tegmental tissue. The cerebellum showed neuronal loss, both in the Purkinje cell layer and the granular cell layer. In some places, the number of Purkinje cells was severely depleted. Extensive gliosis was demonstrated by

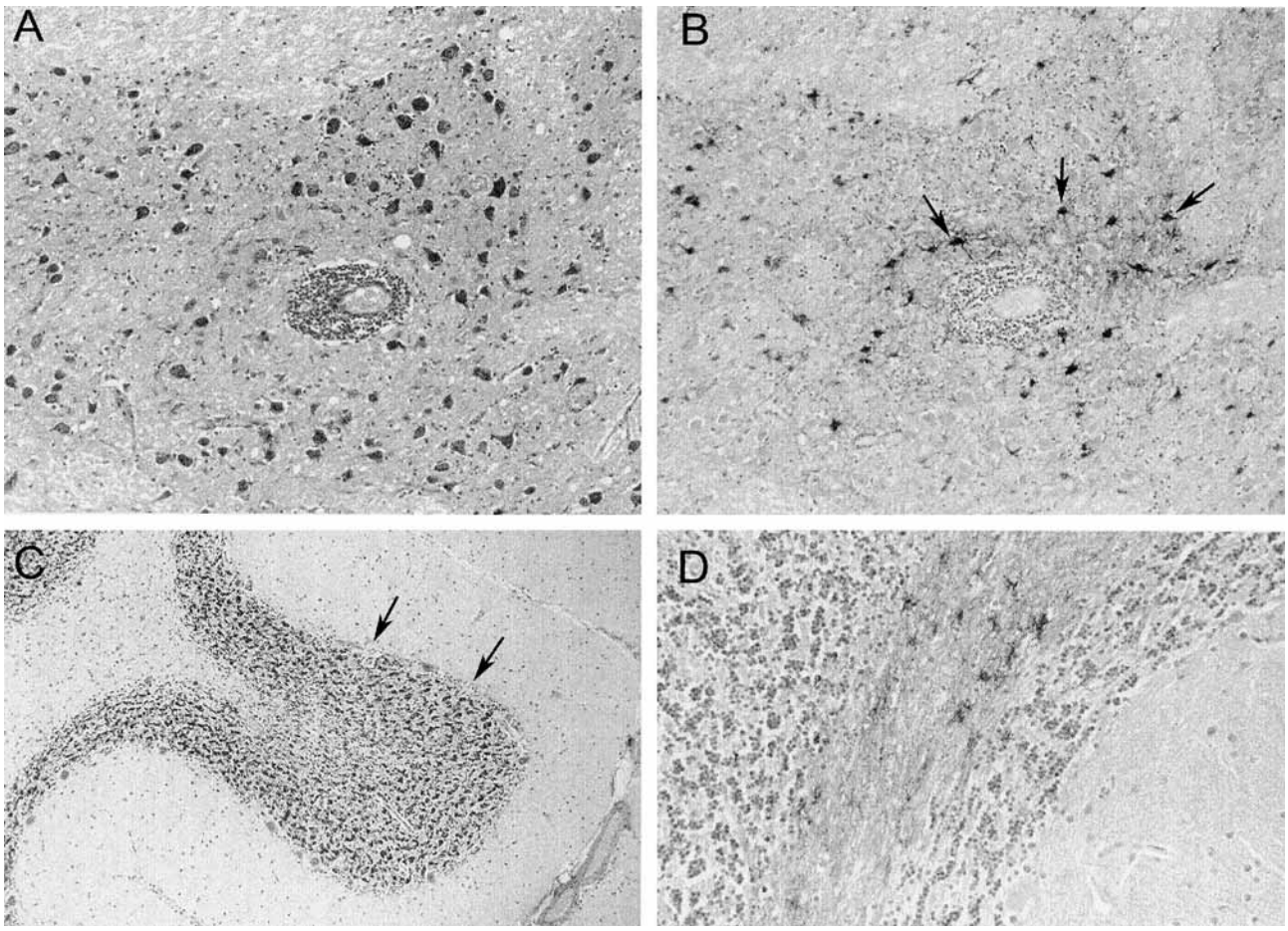

FIG. 1. — A : Pons. Perivascular predominantly lymphocytic inflammatory infiltration (Cresyl violet stain, 103×). B : Pons. Serial section shows reactive astrocytes (arrows) (GFAP, immuno-staining for glial fibrillary acidic protein, 103×). C : Cerebellum. Extensive neuronoal loss in Purkinje cell layer (arrow) (Cresyl violet stain, 46×). D : Cerebellum. Reactive gliosis in the white matter (GFAP stain, 143×).

glial fibrillary acidic protein (GFAP, monoclonal antibody, Dako) immunostaining. The dentate nucleus, and the inferior olivary nucleus in the medulla oblongata remained undamaged.

Throughout the pons, there was both GFAP-immunoreactive gliosis and HLA-DR (TAL1B5) immunostaining of numerous microglial cells. Also, microglial proliferation was observed in the cerebellar white matter and granular cell layer. Immunofluorescence using autologous serum and anti-human IgG revealed no specific binding to cerebellar, pontine or mesencephalic structures.

CASE 2

The second case was a 51 year old female. From her personal medical history we note hypertension, severe tobacco-use and depression. One week prior to admittance to our ward, the patient developed progressive complaints of vertigo associated with blurred vision. In addition the patient complained of important instability while standing and walking.

At the time of admittance we saw an attentive woman, with normal speech. Upon examination we noted chaotic movement of both eyes in all directions and an ataxic gait pattern. Apart from the gait instability, coordination was normal as were tendon reflexes, sensitivity and muscle strength. Further general physical examination revealed no other abnormalities.

Routine blood examination at that time showed discrete oligoclonal bands in the gamma globulin fraction. Examination of cerebrospinal fluid revealed glucose content of 54 mg%, 6 leucocytes/mm^3, protein content of 114.8 mg% with gamma fraction of 18.6%. Anti-Hu and anti-Ri antibodies were negative and an additional set of tumor markers including NSE and CEA were negative. Except for a strongly positive anti-nuclear antibody (ANA) (1/25.000) no other abnormalities were found on further immunologic screening.

Magnetic resonance imaging of the brain showed an atypical white matter lesion in the right fronto-parietal region. A standard radiography of the thorax was normal. Additionally a mammography and breast-ultrasound were performed which revealed no suspicious lesions. A CT thorax was performed which showed a possibly malignant lesion in the right lower lobe, several smaller

nodules in the right lung and enlarged lymph nodes in the mediastinum. Additional staging showed no distant metastases. Sampling of the enlarged lymph nodes in the mediastinum revealed a poorly differentiated non-small cell lung carcinoma (NSCLC).

After induction chemotherapy the patient underwent surgery with curative intention. A lobectomy of the right lower lung lobe was performed.

Prior to the operation different therapeutic strategies were successively tried without success : methylprednisolone (160 mg/day IV), clonazepam (1 mg 4 × 1 daily PO), carbamazepine (200 mg 3 × 1 daily), immunoglobulins (0.4 g/kg/day IV during 5 days).

The intensity of symptoms of the OMS diminished discretely during the first four weeks following the operation. After this period the opsoclonus and the ataxia worsened again upon which the patient was hospitalized for plasmapheresis which did not result in any improvement. Six months later the patient died due to progression of the primary tumor.

Discussion

We have described two patients with a clinical diagnosis of paraneoplastic OMS. In the first patient however the neoplastic origin of the syndrome could only be demonstrated post mortem by the analysis of metastastatic lymph nodes of a primary breast carcinoma. In the second patient the neoplastic origin, a NSCLC, was found and treated with chemotherapy and surgery. In both patients no known antibodies linked with this syndrome could be demonstrated, nor in serum, nor in CSF.

About the presence of antibodies in serum or CSF in OMS, current opinion is undecided. As a rule, in children no auto-antibodies are found, but exceptions have been reported. In some but not in all cases of OMS in adults antibodies are found of which the anti-Hu (Hersch *et al.*, 1994) and anti-Ri antibodies (Luque *et al.*, 1991) have been reported most frequently. Especially anti-Ri antibodies seem to be associated with breast cancer (Gatti *et al.*, 2003). Recently other antibodies such as anti-Ma and antiTa/Ma2 have been reported (Voltz, 2002). Although the immunopathogenesis of OM has been suspected for many years, at present no consensus exists about the possible etiological role of these antibodies (Pranzatelli *et al.*, 1996 ; Bataller *et al.*, 2003 ; Blaes *et al.*, 2005)

This case indicates that one has to be very suspicious of malignancy in any case of OMS whether commonly associated auto-antibodies are found or not. However in some cases the syndrome can precede the discovery of the associated malignancy months or even years as the tumour can be too small to be detected (Gatti *et al.*, 2003).

The current hypothesis suggests that a brainstem dysfunction plays a key role in the pathogenesis of OMS in combination with an additional cerebellar dysfunction (Caviness *et al.*, 1995). A disruption of the tonic inhibitory control on the saccadic “burst” neurons by the omnipause neurons in the pontine reticular formation is thought to be a possible explanation for the phenomenon of opsoclonus. However neuropathological examination usually fails to demonstrate damage to these neurons (Gatti *et al.*, 2003). In the literature, a broad range of abnormalities on neuropathological examination have been described (Scaravilli *et al.*, 1999). Some patients showed no neuropathological abnormalities at all. In others the olivary nucleus was affected. But also inflammatory infiltrates in the periaqueductal gray matter and variable loss of Purkinje cells have been reported (Gatti *et al.*, 2003).

Neuropathological examination of our case no. 1 revealed distinctive abnormalities in the brainstem and cerebellum (lymphocytic infiltration in neocortex, pons and cerebellum and loss of Purkinje cells and cerebellar granular layer cells). These findings confirm the proposed pathophysiological mechanism for OMS.

Some authors stress the possible reversible character of this syndrome, once the primary tumor has been resected. Tumor therapy seems to stabilize the disease and there have even been reports of spectacular improvement after removal of a primary renal cell carcinoma (Bataller *et al.*, 2001 ; Vigliani *et al.*, 2001). The initial improvement in the clinical condition of the patient in our case no.2 seems to confirm these findings. However a primary tumor is often not found since many cases of OMS are idiopathic or post-infectious.

Additionally, several types of immunomodulating therapies have been used : IV immunoglobulins, plasmapheresis, steroids, ACTH and other immunosuppressants (Dropcho *et al.*, 1993 ; Cher *et al.*, 1995 ; Yiu *et al.*, 2001 ; Glatz *et al.*, 2003 ; Pranzatelli *et al.*, 2005). Currently however no information is available on the efficacy of these different strategies due to the absence of larger scale controlled studies.

Acknowledgements

The authors wish to express their gratitude toward Prof. Dr. Van Den Bogaert (Departement of Radiotherapy, Oncology, University Hospital Leuven). Furthermore we want to thank Evelyn De Leenheir, Ulla Lübke and Inge Bats for the preparation of the excellent figures of the neuropathology and K. Segers M.D. for performing the autopsy in case no.1.

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