

Dear Candidate

The UEMS-EBN exam involves a case presentation which will be evaluated by a jury consisting of two examiners. You will be asked to present the case for 7 minutes, followed by 8 minutes of questioning (so 15 minutes in total and a time table that will be adhered to strictly). Please prepare a maximum of 7 slides, you can also bring a short video if applicable. The presentation can be performed on your own computer. The examiners will evaluate this presentation using the scoring form that is downloadable from the UEMS-EBN website. The examiners will take into account the quality of history taking and the presentation thereof, details of physical examination, whether investigations were performed in a logical sequence, whether the management was appropriate, and whether you showed clinical acumen. The final score can be corrected upwards, or downwards depending on the case difficulty. Finally, the originality of the case presentation will also be taken into account.

Please note: you are NOT required to write a case report; oral presentation will suffice.

This is an example of a case presentation:

#### OPSOCLONUS-MYOCLONUS SYNDROME: A CLINICOPATHOLOGICAL CONFRONTATION

Modified from: J. Baets, ..., P. Cras Acta Neurol Belg 106(3):142-6, 2006

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.

I will report a case of OMS of paraneoplastic origin associated with breast carcinoma.

Commonly detected serum antibodies against onconeural proteins (anti-Hu, anti-Yo, anti-Ri) were absent. In the patient I will also be presenting the neuropathological substrate of OMS was investigated.

#### CASE

The case that I would like to present 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 where 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.

# Case history

- 62-year-old female with a medical history of breast cancer 24 years ago and tumor resection in the right breast 19 years ago
- Three weeks prior to admittance complained of general malaise and vertigo
- Clinical condition deteriorated due to the appearance of diplopia and nystagmus
- Neurological examination at the time of admittance showed an alert and attentive woman
- Speech slurred due to cerebellar dysarthria
- Opsoclonus and limb ataxia with bilateral dysmetric finger-nose test (more pronounced at the left side)
- Further general physical examination showed no abnormalities (in particular, no axillar lymphadenopathies)

## Slide 1

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  $40/\text{mm}^3$  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.

# Case history

- Routine blood examination showed no abnormalities
- MRI of the brain was normal, except for a few small white matter lesions
- CSF revealed leukocytes of  $40/\text{mm}^3$  with 98% lymphocytes, protein content of 42.5 mg/dl, glucose content of 66 mg/dl and a gamma globulin fraction of 16.2% without oligoclonal banding
- anti-Hu, anti-Yo and anti-Ri antibodies in both serum and CSF absent
- standard set of serum tumor-markers (CEA, CA 15.3, CA 19.9, CA 125, NSE) negative
- EEG showed an abnormal pattern with important slowing in both hemispheres
- Repeated clinical examination, performed on day 18, revealed adenopathy in the right axillary region
- During hospitalisation, we witnessed the rapid deterioration of this patient's condition with myoclonus
- Different therapeutic strategies were successively tried without benefit: immunoglobulins, methylprednisolone and finally high doses of piracetam (12 g/day IV)
- Piracetam resulted in a transient (three days) amelioration
- Adequate general sedation (and discrete regression of symptomatology) was obtained by the administration of clotiapine and clonazepam

## Slide 2

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 x 1 daily IV) and clonazepam (1 mg 4 x 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.

# Clinical diagnosis

- Paraneoplastic opsoclonus-myoclonus syndrome
- Patient died approximately 10 weeks after the appearance of the first symptoms
- Autopsy demonstrated a poorly differentiated tumor in the right axilla, compatible with a metastasis from a primary breast carcinoma

## Slide 3

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*

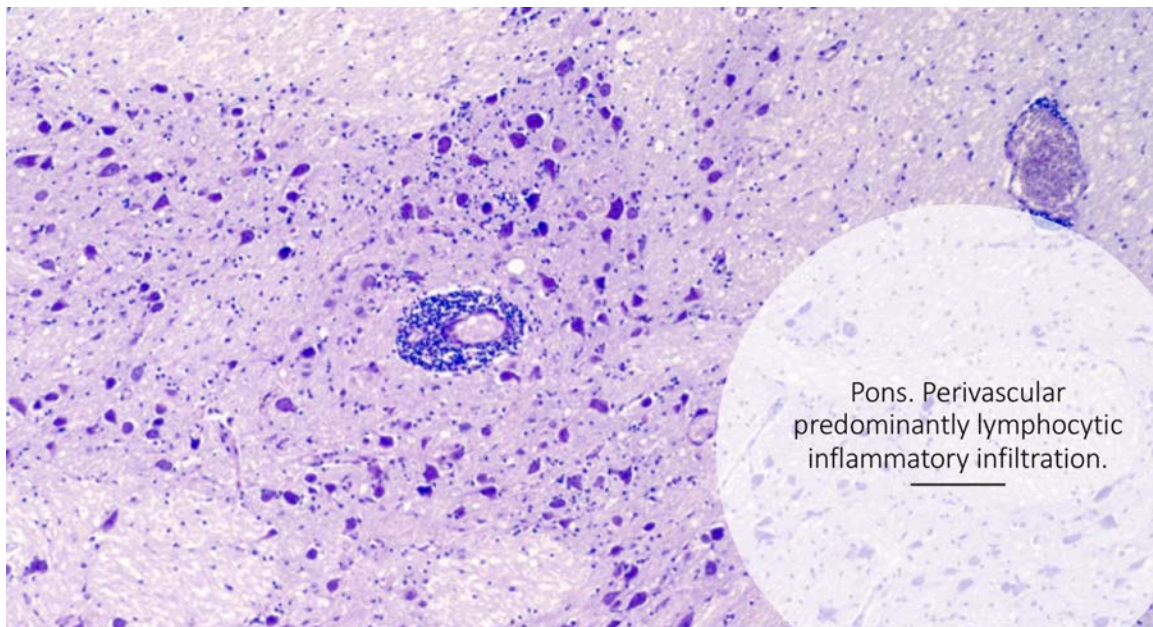
The brain was removed and fixed in 4% buffered formaldehyde. Macroscopic evaluation of the brain revealed no abnormalities. Seven 20µm paraffin sections were made and stained with haematoxylin eosin, cresylviolet and Bodian silver technique. Several neocortical areas including the frontal and temporal 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.

# Neuropathology

- Brain was removed and fixed in 4% buffered formaldehyde
- Macroscopic evaluation of the brain revealed no abnormalities
- Sections were made and stained with haematoxylin eosin, cresylviolet and Bodian silver technique, in addition GFAP immunostaining
- Extensive lymphocytic infiltrates both in perivascular areas, but also interspersed in the pontine tegmental tissue
- Cerebellum showed neuronal loss, both in Purkinje and granular cell layers

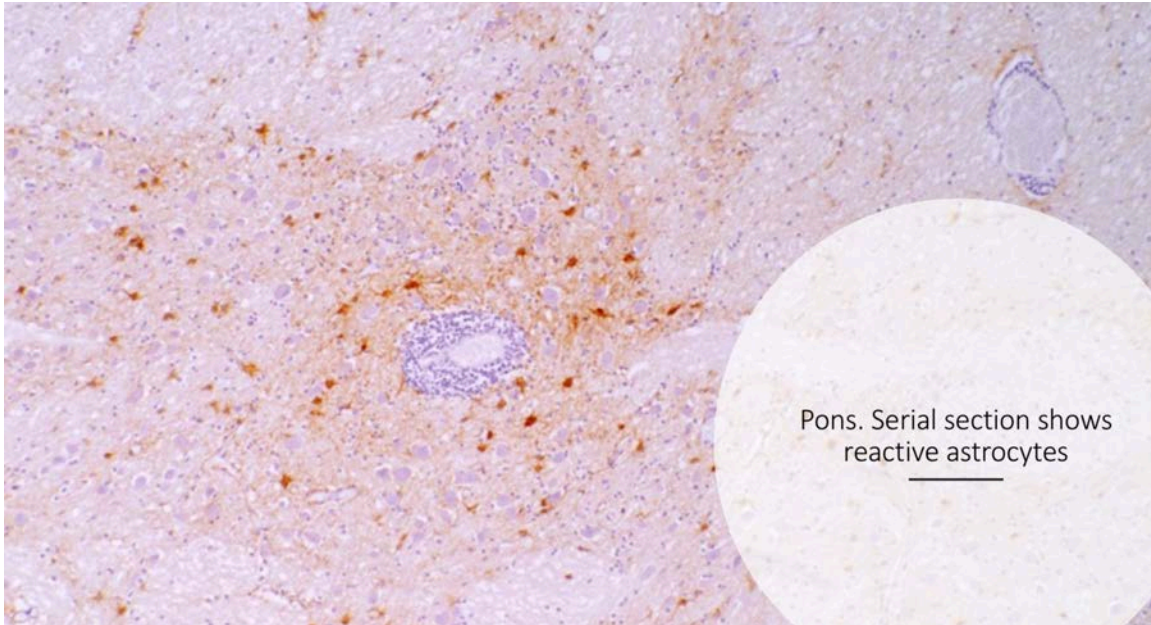
Slide 4

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.

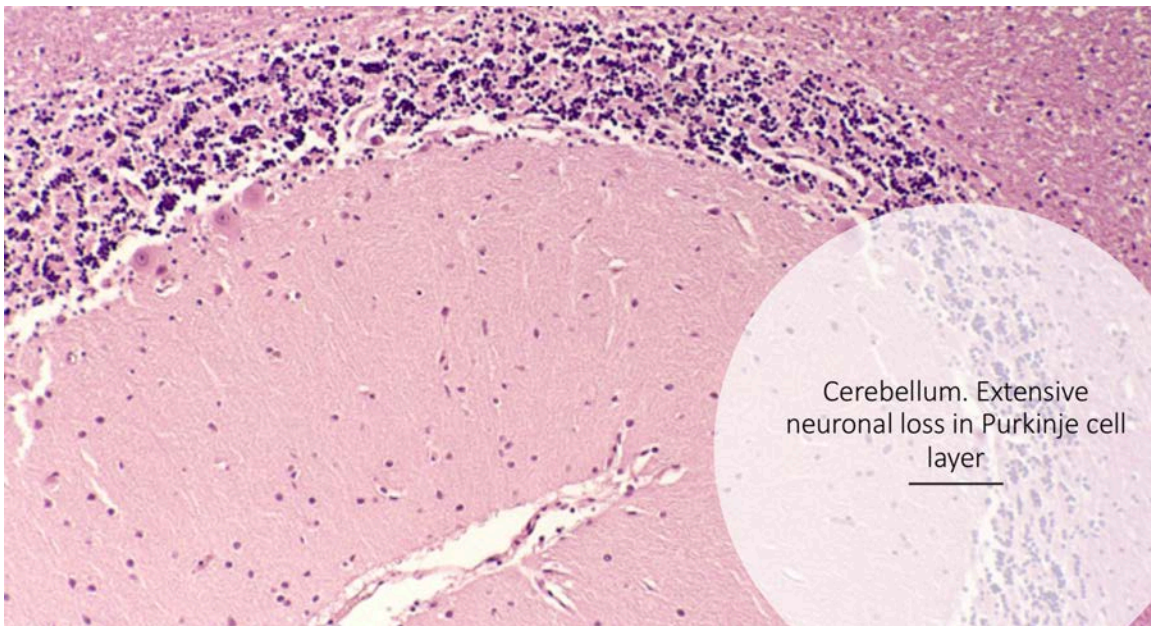


Slide 5





Slide 6



Slide 7

## DISCUSSION

I have described a patient with a clinical diagnosis of paraneoplastic OMS. In this patient the neoplastic origin of the syndrome could only be demonstrated post mortem by the analysis of metastatic lymph nodes of a primary breast carcinoma. In this patient 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 anti-Ta/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)

## Discussion

- Clinical diagnosis of paraneoplastic OMS
- Many cases of OMS are idiopathic or post-infectious
- Neoplastic origin in our patient could only be demonstrated post mortem by the analysis of metastatic lymph nodes of a primary breast carcinoma
- No known antibodies linked with this syndrome could be demonstrated, nor in serum, nor in CSF
- Brainstem dysfunction plays a key role in the pathogenesis of OMS in combination with an additional cerebellar dysfunction

### Slide 8

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 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.

## REFERENCES

BATALLER L., ROSENFELD M.R., GRAUS F., VILCHEZ J.J., CHEUNG N.K. *et al.* Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Ann. Neurol.*, 2003, **53**(3): 347-353.

BATALLER L., GRAUS F., SAIZ A., VILCHEZ J.J. Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain*, 2001, **124**(Pt 2): 437-443.

BLAES F., FUHLHUBER V., KORFEI M., TSCHERNATSCH M., BEHNISCH W. *et al.* Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. *Ann. Neurol.*, 2005, **58**(2): 313-317.

CAVINESS J.N., FORSYTH P.A., LAYTON D.D., MCPHEE T.J. The movement disorder of adult opsoclonus. *Mov. Disord.*, 1995, **10**(1): 22-27.

CHER L.M., HOCHBERG F.H., TERUYA J., NISCHKE M., VALENZUELA R.F. *et al.* Therapy for paraneoplastic neurologic syndromes in six patients with protein A column immunoadsorption. *Cancer*, 1995, **75**(7): 1678-1683.

DALE R.C. Childhood opsoclonus myoclonus. *Lancet Neurol.*, 2003, **2**(5): 270.

DECONINCK N., SCAILLON M., SEGERS V., GROSWASSER J.J., DAN B. Opsoclonus-myoclonus associated with celiac disease. *Pediatr. Neurol.*, 2006, **34**(4): 312-314.

DROPCHO E.J., KLINE L.B., RISER J. Antineuronal (anti-Ri) antibodies in a patient with steroid-responsive opsoclonus-myoclonus. *Neurology*, 1993, **34**(1): 207-211.

GATTI G., SIMSEK S., KURNE A., ZURRIDA S., NANINATO P. *et al.* Paraneoplastic neurological disorders in breast cancer. *Breast*, 2003, **12**(3): 203-207.

GLATZ K., MEINCK H.M., WILDEMANN B. Parainfectious opsoclonus-myoclonus syndrome: high dose intravenous immunoglobulins are effective. *J. Neurol. Neurosurg. Psychiatry*. 2003, **74**(2): 279-280.

HERSCH B., DALMAU J., DANGOND F., GULTEKIN S., GELLER E. *et al.* Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. *Neurology*, 1994, **44**(9): 1754-1755.



LUQUE A., FURNEAUX H.M., FERZIGER R., ROSENBLUM M.K., WRAY S. *et al.* Anti-Ri: an antibody with paraneoplastic opsoclonus and breast cancer. *Ann. Neurol.*, 1991, **29**(3): 241-51.

PRANZATELLI M.R. The immunopharmacology of the opsoclonus-myoclonus syndrome. *Clin. Neuropharmacol.*, 1996, **19**(1): 1-47.

PRANZATELLI M.R., CHUN K.Y., MOXNESS M., TATE E.D., ALLSION T.J. Cerebrospinal fluid ACTH and cortisol in opsoclonus-myoclonus: effect of therapy. *Pediatr. Neurol.*, 2005, **33**(2): 121-126.

SCARAVILLI F., AN S.F., GROVES M., THOM M. The neuropathology of paraneoplastic syndromes. *Brain Pathol.*, 1999, **9**(2): 251-260.

TURKEL S.B., BRUMM V.L., MITCHELL W.G., TAVARE C.J. Mood and behavioral dysfunction with opsoclonus-myoclonus ataxia. *J. Neuropsychiatry Clin. Neurosci.*, 2006, **18**(2): 239-241.

VAN EVERBROECK B., QUOLIN S., BOONS J., MARTIN J.J., CRAS P.; A prospective study of CSF markers in 250 patients with possible Creutzfeldt-Jakob disease. *J. Neurol. Neurosurg. Psychiatry*, 2003, **74**: 1210-1214.

VERMA A, BROZMAN B. Opsoclonus-myoclonus syndrome following Epstein-Barr virus infection. *Neurology*, 2002, **58**(7): 1131-1132.

VIGLIANI M.C., PALMUCCI L., POLO P., MUTANI R., SCHIFFER D. *et al.* Paraneoplastic opsoclonus-myoclonus associated with renal cell carcinoma and responsive to tumour ablation. *J. Neurol. Neurosurg. Psychiatry*, 2001, **70**: 814-815.

VOLTZ R. Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis and therapy. *Lancet Neurol.*, 2002, **1**(5): 294-305.

YIU V.W., KOVITHAVONGS T., MCGNIGLE L.F., FERREIRA P. Plasmapheresis as an effective treatment for opsoclonus-myoclonus syndrome. *Pediatr. Neurol.*, 2001, **24**(1): 72-74.

ZERR I., POCCHIARI M., COLLINS S., BRANDEL J.P., DE PEDRO CUESTA J. *et al.* Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology*, 2000, **55**: 811-815.