Infection with West Nile Virus: Opsoclonus-myoclonus Syndrome

Victoria Birlutiu¹, Rares-Mircea Birlutiu¹, Cristina Rezi²

1 Introduction

West Nile Virus (WNV) is transmitted mainly to humans by mosquitoes (especially Culex species), which get the virus by feeding on infected birds. WNV induces asymptomatic or symptomatic infections, with symptoms ranging from febrile syndrome (fever, muscle pain, headaches and exanthema) to neurological disease, the latter affecting only about 1% of the cases.

2 Epidemiology

WNV is a zoonotic arbovirus, belonging to the genus Flavivirus in the Flaviviridae family. It was first identified in Uganda, in 1937, in the blood culture of a woman with a febrile episode. It drew the attention of experts again in the 90s, when a high number of cases were identified throughout the whole world. In Southeastern Europe (Campbell GL, 2001), a large outbreak of meningoencephalitis took place in Romania (in Bucharest), in 1996 — almost 400 cases were confirmed — and in Russia, in 1999, with approximately 200 cases (in Volgograd).

In 1999 sporadic outbreaks of neuroinvasive infections occurred in New York City, followed by other cases in other regions of the United States, Central America, the Caribbean, Canada (Dauphin G, 2004).

Isolated cases are reported annually in Russia, the Czech Republic, France during

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WNV has at least five different lineages (Mann BR, 2013). Lineage 1, spread worldwide, is subdivided into clades, 1a and 1b. Clade 1a was isolated in America, Africa, Asia, Europe and the Middle East, and was later divided into A and B sub-clades (Zehender G, 2011). Clade 1b, or the Kunjin virus (KUNV), is known to be endemic in Australia and only occasionally affects humans. Lineage 2 can be found in Sub-Saharan Africa, Madagascar, South Africa and in some countries in Europe such as (Sambri V, 2013) Russia, Hungary (Bakonyi T, 2006), Greece (Papa A, 2011), Italy (Bagnarelli P, 2011) (Magurano F, 2012). WNV lineage 2 from Europe has its origins in Africa and has become endemic in the last two decades (Ciccozzi M, 2013). Lineage 3 or Rabensburg virus, was isolated from *Culex pipiens* in the Czech Republic and South Moravia (Bakonyi T H. Z., 2005). Lineage 4 was isolated in the Caucasus region (Russia), from a Dermacentor tick and then from mosquitoes. WNV lineage 5 is considered to be clade 1c of lineage 1 and it was isolated initially in humans and mosquitoes in India. Some have discussed the existence of lineage 6 (Vazquez A, 2010), isolated from *Culex pipiens* in Spain, and also that of lineage 7, isolated from the Koutango virus in Senegal (King AMQ, 2011).

**Figure 1:** Worldwide distribution of WNV by lineage (after Ciota AT (2013)).
During 1999–2013, the Centers for Disease Control and Prevention (CDC) confirmed a number of 39,557 infections with WNV, 17,463 of which of the neuroinvasive kind (meningitis, encephalitis, acute flaccid paralysis), concluding that, in 2013, the WNV represented the most important cause of neuroinvasive infections produced by arboviruses. Recent studies suggest that WNV is currently the most important cause of viral encephalitis worldwide. (Chancey C, 2015)

In 2014, CDC reported a WNV incidence rate of over 1.00 to 100,000, i.e. 1,820 cases, 1,070 of which were neuro-infections (59% of the confirmed cases) (Centers for Disease Control and Prevention National Center for Emerging and Zoonotic Infectious Diseases, 2014). According to the European Centre for Disease Prevention and Control (ECDC), up to 20/11/2014, there were only 74 cases in Europe and 136 in the Mediterranean region (ECDC, 2014) (Figure 2).

The most frequent way of transmission of WNV is from birds, especially passerines (though over 300 species of birds have been identified as being at risk of WNV infection), via Aedes and Culex genus mosquitoes, to humans or to other 30 species of vertebrates: horses, cats, dogs, skunks, rabbits, squirrels or reptiles — alligators, crocodiles, amphibians.

Figure 2: ECDC report on WNV infection in Europe and the Mediterranean region. Distribution of West Nile fever cases by affected areas, European region and Mediterranean basin. Transmission season 2014; latest update 20 November 2014.

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tebrates: horses, cats, dogs, skunks, rabbits, squirrels or reptiles — alligators, crocodiles, amphibians.

Cases of vertical WNV transmission from mother to child during childbirth or breastfeeding have also been documented (Hayes EB, 2004). Transmission through blood transfusions was first confirmed in 2002 (Hayes EB, 2004) and in 2003 over 1000 collected samples which tested positive for WNV screening were eliminated from blood donation in North America. During the same period, 7 cases of blood transfusions with otherwise undetectable viral load were confirmed (Prevention, 2004).

Transmission is also possible from handling dead birds or infected vertebrates (Centers for Disease Control and Prevention National Center for Emerging and Zoonotic Infectious Diseases, 2014), by skin contamination or through aerosols in laboratories.

3 Etiology

WNV belongs to the genus Flavivirus, in the Flaviviridae family, together with Japanese encephalitis virus (JEV), yellow fever virus, dengue virus, and tick-borne encephalitis virus which produce a unique subgenomic flavivirus RNA (sfRNA) derived from the 3’ untranslated region (UTR) (Roby JA, 2014), the product of incomplete degradation of the genomic RNA. The WNV virion has a diameter of 45–50 mm, with icosahedral symmetry and a structure similar to the one of Dengue fever virus. It has a lipid envelope with spike glycoprotein of surface M (membrane) and E (envelope), single-stranded genome, linear positive-sense RNA, containing between 11 000 and 12 000 nucleotides which encode seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) and three structural proteins: capsid protein C binds the viral RNA; pre-membrane protein (prM) blocks the viral fusion; and E protein. The viral genome is relieved by the noncoding variable regions – 3’ and 5’. The nucleocapsid is formed from 12 kDa block proteins, while the capsid derives from the cellular membrane of the host, altered under the action of viral glycoproteins. The E protein is involved in the viral attachment to the host cell receptor and it facilitates the fusion at the cellular membrane; it is the site of hemagglutination and viral neutralization. Protein E consists of three domains: domain III is involved in the interaction with the host cell; domain II consists of a conservative region with 13 hydrophobic amino-acids involved in fusion by forming a fusion loop and domain I binds the other two domains (Nybakken GE, 2006). The non-structural proteins are involved in the process of transcription, translation, replication (NS1 and NS4a) and assembling of WNV (NS2a). sfRNA inhibits the INF α/β activity, has a role in the viral infection pathogenicity and possibly many other functions which are not yet elucidated; the deficiency in sfRNA is correlated itself with the reduction of the cytopathogenic effect in mice. Protein E is a major antigenic protein. Other structures, such as prM, NS1, NS3 and NS5, also have antigenic properties. At the same time, NS2A, NS2B, NS4A, and NS4B proteins act as co-factors for viral replication complex assembly and localization (Youn S, 2013).

Once the mosquito bite is produced, the saliva may produce vasoconstriction, coagulation, platelet aggregation, the altering of the immune response of the host, favor-
ing a high viral load of the WNV and a severe form of the disease (Zeidner NS, 1999) (Schneider BS, 2007).

4 Pathogenesis

The virus is multiplying in the tegument, at the Langerhans cells level, in lymph nodes, the short time viral load being present before the central nervous system invasion. The asymptomatic infections are 300 times more frequent, compared with the symptomatic ones, due to the peripheral clearance of the virus, without neural invasion.

In the neural invasion, there are involved the Toll-like receptors 3, the CCR5 receptor and its ligand, CCL5, pushed by the WNV, with the local migration of the T CD4, CD8, NK1.1 lymphocytes and of the macrophages. The central nervous system invasion is produced from one cell to another, with the appearance of local inflammation, brain edema and encephalitis, especially by affecting the hippocampus, thalamus and temporal region, black substance and cerebellum. It is generally accepted that CNS invasion is the consequence of an inefficient systemic immune response, which allows a major viral replication whereby CNS is affected proportionally to the level and duration of the viremia (Stephanie ML, 2011). Several mechanisms of WNV entry into the CNS have been proposed, for which there is experimental evidence on mice: passive transport through the choroid plexus epithelial cells (Kramer-Hämmerle S, 2005), through the olfactory neurons or through the infected immune cells (Garcia-Tapia D, 2006). The CNS infection occurs most often in the cortex, cerebellum, basal ganglia and the brain stem, and rarely in the hippocampus or the olfactory bulb. WNV acts primarily at the neuronal level: at the level of microglia, astrocytes, endothelial cells, oligodendrocytes, and neuroblastoma cells but also at a spinal cord level, with the anterior gray column being affected most often.

The emergence of severe cases in immunocompromised persons and in the elderly seems to be explained by the decrease of the immune response to new antigens, which follows as a result of fewer T cells being produced by the thymus and the ineffective response of neutralizing IgM antibodies. LyCD4+ support a viral clearance response of LyCD8+ in the CNS, the latter being responsible for controlling the infection and preventing viral persistence in the tissue. IgM and IgG antibodies are responsible for controlling the viremia (Diamond MS, 2003) and for preventing a fatal outcome. The role of the microglia, astrocytes and oligodendrocytes (involved in the production of myelin) in the WNV infection has also been studied. Present in a ratio to neurons of 1.4 (Hilgetag CC, 2009), astrocytes represent the neuronal metabolic support and are essential to brain homeostasis. They play a limited part in the synthesis of acute phase proteins and proinflammatory cytokines but a crucial one in controlling leukocyte influx in the CNS, maintaining the integrity of the Blood-Brain-Barrier (BBB) through the glia limitans network. Microglia represent the CNS macrophages and are activated during inflammatory diseases or neuronal injuries. Their plasticity allows them to modify their cellularity numerically, morphologically and as an expression of surface receptors, as well as to synthesize proinflammatory cytokines and growth factors. After
the viremia peaks, WNV enters into the CNS, where leukocyte recruitment takes place through the transmigration of peripheral leukocytes at the level of the BBB and at the vascular endothelium level. The leukocytes are then retained in the perivascular space. Leukocyte migration is influenced by not fully known mechanisms at the moment. The ability of TNF-α to increase vascular permeability is easy to see, as is the expression of the C-X-C motif chemokine 12 (CXCL12) (McCandless EE, 2006), and the effect of matrix metalloproteinases (MMP) produced by the astrocytes, which facilitate the leukocyte migration into the perivascular space and at the level of the glial limitans (Savarin C, 2010). The leukocyte migration in the brain parenchyma is the outcome of injuries that occur at the level of glia limitans components such as collagen degradation under the action of cysteine protease cathepsins K, S, and L, the conversion of plasminogen into plasmin and the fibronectin and laminin degradation (Reijerkerk A, 2008). During the CNS invasion of WNV, there is an increase in the expression of two CXC chemokine-type, CXCL1 and CXCL2 that contribute to the neutrophil recruitment in the brain. Neutrophils are the most important immune cells involved in the early local defense (Bai F, 2010). WNV induces neuronal apoptosis through the caspase-3 (Samuel MA, 2007) and caspase-9 pathways, activated by the presence of capsidic WNV proteins in the CNS, but also by the activation of calphin and cathepsin (Hail N Jr, 2006) (Kroemer G, 2005). High levels of WNV structural proteins (NS2A, 2B, 4A, 4B) and E glycoprotein may induce apoptosis via endoplasmic reticulum (ER) stress (Yu CY, 2006). Research in the pathogenesis of WNV neuroinvasive infection highlights the heightened viral action that follows the release by neurons of proinflammatory cytokines such as IL-1β, -6, -8 and TNF-α (Kumar M, 2010) (Swarup V, 2007). Differences in virulence among strains of WNV is explained by the ability of virulent strains – for e.g. WNV-NY99 1999 New York, to act as a potent antagonist of alpha/beta interferon (IFN-α / β), mediated by Janus kinase — signal transducer and activator of transcription (JAK-STAT) (Laurent-Rolle M, 2010) by inhibiting JAK phosphorylation, by the intervention of nonstructural proteins NS2A, NS2B, NS3, NS4A, and NS4B.

In contrast to NY99, Kunjin virus subtype (KUN) currently endemic in Australia, occasionally produces illness in humans, the nonstructural protein NS5 not acting as an interferon antagonist (Liu WJ, 2005). It has also been hypothesised that the insufficiency of down-regulated TLR3 macrophages, present in the elderly, is responsible for the presence of high levels of proinflammatory cytokines with vasculogenic property (Kong KF, 2008). Among the WNV nonstructural proteins, NS1 plays an antagonist role in antiviral defense by inhibiting complement activation (Avirutnan P, 2010), TLR3 signal transduction (Wilson JR, 208) and by activating STAT1/STAT2 (Peña J, 2014).

5 Clinical Aspects

80% of the cases of WNV infection are asymptomatic. In the forms of the disease without neurological disease, or West Nile fever (WNF), the onset can be sudden, after a variable incubation period of about 2–15 days, with influenza-like syndrome — high fever,
headache, muscle pain, joint pain, lymph nodes enlargements and digestive manifestations like nausea, vomiting, loss of appetite, profuse transpiration.

Approximately one third to one half of the cases present skin rash (see Figure 3 and Figure 4 from patients we have treated). The skin eruption is described as punctate exanthema, macula or papules, affecting mainly the extremities (Anderson RC, 2004), is of a transitory nature — the rash disappears in 24 hours — and is more frequently associated with WNV encephalitis or meningitis (Ferguson DD, 2005), probably in direct relation with the pro-inflammatory answer of the host. WNF appears mainly in younger people (Piperal C, 2003). Due to the digestive manifestations and fever there can appear different degrees of dehydration.

Other manifestations described in WNV infection include: hepatomegaly, splenomegaly (Goldblum N, 1954), occasionally myocarditis and pancreatitis.

The central nervous system involvement appears in less than 1% of the cases, mainly in men above 50, in patients infected with HIV, or patients immune-depressed by co-morbidities (diabetes mellitus, arterial hypertension) or by recent immunosuppressed therapy, as is the case, for example, in patients with organ transplants, for whom the incidence of neurological disease can be 40 times higher compared to the general population (Kumar D, 2004).

The CCR5 gene polymorphism, with defective alleles of the receptor for chemokine CCR5 (CCR5 Δ 52) is associated with a severe evolution of the WNV infection (Glass WG, 2006).

The neurological involvement is preceded by a febrile episode, lasting 1–7 days, sometimes the evolution being biphasic, associated with rash, eye pain, rarely lymph node enlargment.

The central nervous system involvement consists of encephalitis, meningitis, Guillain-Barre syndrome, optic neuritis, poliomyelitis-like paralysis. The mortality rate is estimated at 10–30% of the cases, being influenced by age (over 50), the presence of
co-morbidities or of immune-deficiency (Burton JM, 2004), or by the presence of a motor deficit. The neurological recovery is slow, about 6 months to one year, sometimes incomplete, with the persistence of fatigability, asthenia, headache, muscle pain (Sejvar JJ, 2003).

Encephalitis is the most frequent neurological manifestation of the WNV infection, with lesions which can be found in different cerebral areas: basal ganglions, thalamus, cerebellum, cerebral trunk. It involves fever, headache and consciousness disturbances. In 30–50% of the cases, there can appear muscular weakness, peripheral motor neuron syndrome, flaccid paralysis, hypo-reflexes (Carson PJ, 2006) (Flores Anticona EM, 2012).

In a study performed by Hart et al, from a number of 55 confirmed cases with encephalitis with WNV, 93% presented neurological deficit, 70% presented cognitive disturbances/the alteration of the consciousness status, 49% presented muscle weakness, 35% tremor, 25% coma, 16% the crania nerves involvement (Hart J Jr, 2014). Other manifestations which were present in WNV encephalitis were: myoclonus with the upper limbs and facial involvement, parkinsonism, hypo-mimia, postural instability, abnormal movements with changes in the consciousness status, by affecting medulla, substantia nigra, cerebellum, thalamus. The central nervous system lesions consist in chronic inflammatory per vascular process, neuronal loss, necrosis or neuro-phagy, microglia nodules (KA, 2009).

The evolution of the cases with central nervous system involvement is slow, with the persistence of functional deficit in half of the cases upon discharge, only a third of whom will recover in one-year’s time (Weiss D, 2001).

From our experience, the cases of WNV encephalitis in adults, presented fever or influenza-like syndrome, digestive manifestations in half of the cases, skin rash, localized especially in the lumbar or sacrum region in one third of the cases. The neurological manifestations were present in about half of the cases, and were dominated by dysmetria, tremor, nystagmus, problems with gait and balance. Other manifestations which were met were: motor deficit/hemiplegia, tonic-clonic seizures.

The laboratory exams revealed the presence in over 50% of the cases of neutrophilic leukocytosis, which appears also elsewhere in the literature (Nash D, 2001); high levels of C reactive protein and fibrinogen were also observed. The cerebrospinal fluid examination attests to the presence of low or moderate pleocytosis in about 50% of the cases, with the predominance of neutrophils (with a maximum of 56% from the cellularity), moderate protein levels in the cerebrospinal fluid, high levels of glucose in the cerebrospinal fluid in patients with normal glycemic levels (Birlutiu V, 2014) or normal values of glucose in the cerebrospinal fluid.

Until now there have been described five cases of WNV encephalitis, manifested as Opsoclonus Myoclonus Syndrome (OMS) (Khsola JS, 2005) (Shellenback L, 2012) (Aasim A, 2014) (Birlutiu V, 2014) (Cooper CJ, 2014), subject which will be discussed separately.

The WNV meningitis can be associated with encephalitis; symptoms include fever, headache, signs of meningeal irritation, photophobia, phonophobia. It cannot be clinically distinguished from other types of viral meningitis. The cerebrospinal fluid
alterations are: pleocytosis with less than 500 elements/mm³, usually dominated by lymphocytes, but with the possible predominance of polinuclears, like in WNV encephalitis.

The poliomyelitis-like syndrome is caused by lesions of the anterior horn of spinal cord and it involves muscular weakness or asymmetric flaccid paralysis, monoparesis or quadriplegia, without sensorial or sensitivity alterations; the paralysis can appear in the absence of fever, sometimes affecting respiratory muscles and leading to acute respiratory insufficiency.

The Guillain-Barre syndrome presents with symmetric progressive ascending paralysis, with the involvement of the proximal and distal muscularity, paresthesia, loss of sensibility; the cerebrospinal fluid examination shows no pleocytosis, but an increased level of proteins, i.e. albuminocytological dissociation.

The evolution of the neurological manifestations does not correlate with the initial clinical appearance; cases with motor deficit, or coma may have a complete resolution in time, while cases with ataxia may present persistent abnormal movements, headache and tiredness. From the experience of the WNV breakout in New York, 37% of the patients with WNV encephalitis were considered cured in about one year after the acute episode (Klee AL, 2004).

The ocular manifestations, like chorioretinitis or vitritis can be associated both with WNF and with neurological manifestations, in the latter case with lesions of the optical nerve. On rare occasions there can occur hemorrhages in the retina or progressive eyesight loss (Adelman NA, 2003) (Bakeri SJ, 2004). Manifestations like myositis due to WNV, with rhabdomyolysis were observed in the absence of the WNV isolation from the muscle (Jeha LE, 2003).

In children, one can encounter neural infections with WNV such as meningitis, rarely encephalitis, rhombencephalitis, poliomyelitis-like paralysis, hepatitis; the prognosis is influenced by the immune-compromised status of the children.

6 Diagnosis

The laboratory diagnosis of WNV infection is performed routinely by serologic testing, using the ELISA method. The presence of specific IgM antibodies in serum and cerebrospinal fluid, respectively, in the cases with neurological involvement, confirm the diagnosis. Neurological impairment in WNV infection can be confirmed by a four-fold increase in the IgG titer in samples collected between the acute and convalescent period or by detecting the viral genome using reverse transcription-polymerase chain reaction with a sensitivity in the range of 10–40 genome copies/mL. The cerebrospinal fluid changes include lymphocytic pleocytosis, or characteristically neutrophilia (Tyler KL, 2006), increase in proteins and a normal level of glycorrhachia.

Some laboratories use indirect immunofluorescence technique in order to detect the specific antibodies, with a sensitivity of 95%. It should be noted that IgM can persist in the serum for up to 16 months in some cases (Rochrig JT, 2003), which brings about some problems of acuity of the etiological diagnosis.
Other tests, not routinely performed are hemagglutination-inhibition, the dosing of neutralized antibodies. Real time PCR is used in WVN screening in order to exclude positive samples from donation. One can identify WNV in cell cultures in case of a fatal outcome using sampled tissues, but this method is confined to reference laboratories. In the same situation, one can perform histopathology examination with immunohistochemistry and nucleic acid amplification. Through a multiplex enzyme-linked immunosorbent assay-based protein array (ELISA-array), an indirect ELISA, one can identify specific antibodies against WNV, Japanese B, tick-borne encephalitis, dengue and yellow fever viruses (Wang D, 2015).

7 Treatment. Prophylaxis.

The cases of WNV without neurological involvement need support with iv fluids and electrolites, fever and headache control. In the cases with neural infections, in the absence of a specific antiviral treatment, the patient is hospitalized and should avoid physical efforts, which may exacerbate the motor deficit. The cases with acute respiratory insufficiency benefit from mechanical ventilation.

In the WNV neural infection the administration of immunoglobulin seems to be beneficial (Shimoni Z, 2011), as well as the administration of monoclonal antibodies targeting WNV envelope protein (Oliphant T, 2005) (Morrey, Day, Julander, Blatt, Sme, & Sidwell, 2004); the administration of interferon alpha did not show any efficiency (Morrey JD, 2007). The antiviral therapy that uses inhibitors of NS3 proteases of the WNV flaviviruses is far from being usable now (Poulsen A, 2014) but remains a therapeutic possibility for the future.

There is no human vaccine on the market for now. In the US, horses are vaccinated with a formalin-inactivated vaccine or canarypox-vectored WNV vaccines. Some live attenuated vaccines (Hall RA, 2007) and combinations with Dengue virus vaccines are currently under evaluation for their degree of protection (Pletnev AG, 2004).

The general prophylaxis refers to the routine control of birds and the use of pesticides for maintaining the mosquito population at a low level in risk-prone areas. Veterinaries and public health authorities need to be informed regarding the appearance of deaths or diseases in birds or horses, the control of chemical products or the biological control of the transmission and need to drain pools of standing water. Personal protection measures against WNV include using insect repellent containing DEET, picaridin, oil of lemon eucalyptus, and IR3535 and wearing protective clothing to prevent mosquito bites, application of permethrin on clothes or avoiding direct contact with sick animals. In high-risk areas for WNV, the prevention of transmission through blood donation or organ transplants should be performed by real time PCR laboratory method.

8 Opsoclonus Myoclonus Syndrome

Opsoclonus myoclonus syndrome (OMS) also named Opsoclonus-Myoclonus Ataxia,
Dancing Eyes — Dancing Feet Syndrome, Dancing Eyes Syndrome, Kinsbourne syndrome, Myoclonic Encephalopathy of Infants, was described in the literature as a multi-etiological neurological disorder, responsible for approximate 60 diseases per year, worldwide.

In children, OMS is frequently a paraneoplastic syndrome, immune mediated, associated with neuroblastoma, with thoracic, abdominal, pelvic or cervical localizations, in over 50% of the cases, or with ganglioneuroblastoma, the manifestations starting early, between 1.5 and 2 years. There were extremely rare cases described which appeared before the age of 6 months; the gender repartition was equal. There has been a description of an exceptional association with a retroperitoneal tumor, prenatally diagnosed (Jamroz E, 2011). The evolution can be monophasic or chronic, with relapses, followed by motor, behavioural or cognitive disorders.

In adults, OMS appears as a paraneoplastic manifestation associated with breast, pulmonary, renal and pancreatic or gallbladder cancer. There are cases described in association with autoimmune diseases, in the presence of mainly type 2 antineural nuclear antibodies: Hashimoto disease, post streptococcal infections and the celiac disorder. Other cases of OMS have been reported during hydro-electrolytic imbalance, cerebral anoxia and cerebral hemorrhages.

More and more information appear related to the involvement of the viral infections in OMS unset: viral infections with Coxsackie virus (B2, B3), Epstein-Barr, herpes simplex virus (Klaas, et al., 2012) Saint Luis viral encephalitis, C virus hepatitis, rubella, mumps virus, cytomegalovirus, human immunodeficiency virus (HIV).

OMS was also described in infections with Mycoplasma pneumoniae, Rickettsia or Borrelia burgdoferi. There are also cases of OMS in which there wasn’t any etiology identified.

8.1 Clinical Aspect

OMS in manifested by opsoclonus - rapid, multivectorial, conjugated movements of the eyes, which persist during sleep, without involving the alteration of the visual field, and by myoclonus — short involuntary movements of the body, limbs, and sometimes, but not mandatory associated with ataxia or other cerebellums signs, sleep disorders or dysphasia, strabismus, vomiting. In children, there can be irritability, excitability or lethargy. The signs and symptoms of OMS are extremely varied as frequency, the concomitant presence of all manifestations not being absolutely necessary: opsoclonus-myoclonus-ataxia.

8.2 OMS Physiopathology

Even though the etiology of OMS is not completely elucidated, the answer to the immune-suppressor treatment and the presence of auto-antibodies, both in children, and in adults, suggest an autoimmune mechanism, by the presence of anti-neural, Purkinje cerebellar antibodies, the intense activity of the B cells at the cerebrospinal fluid, suggesting a cross-over reaction between the antigens which are present in the tumor lesion
(neuroblastoma) and the central nervous system. The immune answer explains the persistence of the lesions for a long time and implicitly of the neurological sequels.

The histological exam of the neuroblastoma, excised from the patients with OMS, reveals the presence of an interstitial and perivascular inflammatory infiltrate, which is rich in B and T lymphocytes. The B lymphocytes activation is secondary to the T lymphocytes answer to the presence of tumor antigen, with the antibodies production. Although the tumor is located remotely, the central nervous system involvement is due to the cerebellum lesions, sometimes cerebellum atrophy, demyelination or loss of Purkinje cells.

The OMS diagnosis cannot be sustained by the presence of a certain biomarker (Gorman, 2010); it is admitted that the appearance of the syndrome is due to an autoimmune mechanism, through the action of the T lymphocytes and of the autoantibodies which are synthesized by the B lymphocytes on the cerebral structures, similar as characteristics to the tumor cells, more frequently at the level of the cerebral trunk, cerebellum and limbic system.

It was suggested, that the relative B cell expansion in CSF should be the marker of the OMS.; in these patients, the presence of an important percentage of CD19+ B cells can be observed in the cerebrospinal fluid, not in the serum, in comparison with the healthy population (Pranzatelli MR T. A., 2004). Compared to the patients with non-inflammatory neurological diseases, in the patients with OMS, previously to the immune-modulator treatment, high values of B-cell activation factor (BAFF) can be observed, which decrease dramatically in the serum after the treatment initiation (Pranzatelli MR T. E., 2008).

In OMS, we most frequently identify antineuronal nuclear antibody type 2, anti-Hu antibodies, anti-Ri antibodies (gynecologic cancers) or more rarely, anti-Yo, and anti-Ma-2 antibodies, IgG and IgM antibodies to neurofilament and peripheral nerve, anti-N-methyl-D-aspartate receptor encephalitis (Kurian M, 2010) with elevated IgG index, and positive oligoclonal banding.

The diagnosis is completed with the neurological evaluation of the case, by using cerebral MRI, EEG and the cerebrospinal fluid exam, by lumbar puncture in order to identify the white abnormal cells using the immunophenotyping technique. The B and T cells recruitment in the cerebrospinal fluid is associated with neurological manifestations and with relapses and the progression of the disease (Pranzatelli MR T. A., 2004).

The tumor identification needs both blood tests (the B cells population is most of the times over the normal ranges), urine tests, and imagistic exams, like body CT, PET and nuclear MIBG scans.

We illustrated a case from our casuistic from a patient with West Nile infection, in which the magnetic resonance scan of the brain showed: demyelination lesions and lacuna images in the left cerebellum, para-median in the right punt, and in the white substance per and supra ventricular bilateral. There were also described two lacuna zones per and supra-ventricular in the right, with the diameter of 4–5mm, with peripheral gliosis and restriction of peripheral diffusion (Figures 5, 6, 7 and 8).

In the cases associated with bacterial or viral infections, the confirmation is based on detecting the presence of specific antibodies type IgM in serum and concomitantly in
Figure 5: Magnetic resonance of the brain, T1-weighted image.

Figure 6: Magnetic resonance of the brain, T2-weighted image.
Figure 7: Magnetic resonance of the brain, T2-weighted image.

Figure 8: Magnetic resonance of the brain, T2-weighted image.
the LRC or detecting the infectious agent through RT PCR. In practice, we use the OMS scale as to evaluate the severity of the disease and the therapeutic response.

The confirmation in the cases which are associated with viral or bacterial infections, is based on the detection of specific IgM antibodies in the serum, and concomitant in the cerebrospinal fluid or on the detection of the infectious agent by using RT PCR.

In the clinical practice, there is used the OMS scale, for evaluating the disease’s severity and also the therapeutic answer:

<table>
<thead>
<tr>
<th>Scale Items</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking, side-to-side imbalance</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Walking, front-to-back imbalance</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Walking, wide base</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Instability while standing (feet apart)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty achieving standing position</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Truncal instability while sitting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Targeting difficulty</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty grasping with one hand</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty with pincer grasp</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal eye movements while tracking (fixation)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal eye movements while resting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Speech abnormality (dysarthria)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1:** OMS scale.

The higher severity score of the neurological involvement in OMS is 36 points, the severe forms of disease being frequently correlated with intrathecal increasing of neopterine, as a marker of cellular immunity activation, especially by activating the T cells in this disease; there are also cases with important neurological manifestations which do not involve an increased level of the neopterine, possibly due to the immunomodulator therapy initiated before the dosing of this marker (Pranzatelli MR H. K., 2004).

### 8.3 Treatment

The conventional treatment is ACTH (adrenocorticotropic hormone), which is considered the gold standard, administrated intramuscularly, on a 20 week period. The side effects of the therapy should be monitored properly: the Cushing syndrome, the cardiovascular effects, the risk for diabetes mellitus, gastric ulcer, osteoporosis, psychical effects, medullar suppression, reversible at the therapy disruption, skin atrophy. The answer at the ACTH treatment is favorable in 80–90% of the cases, the treatment disruption being associated with the risk of relapse.
The glucocorticoids: prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone may be used in the OMS treatment instead of ACTH, with similar potential side effects. Prednisone or methylprednisolone is administered in high doses — 500mg-2g/day, on a 3–5 days period, as an alternative of treatment in OMS.

The intravenous human immune-globulins (IVIG) are administrated in doses of 1–2g/kg/day 3–5 days/week, on a 6 week period. They associate a favorable answer in 40–60% from the cases, with less secondary effects in comparison with corticotherapy or ACTH, in 1–15% of the cases there can be fever, headache and flu-like symptoms. It is recommended to administer IVIG in children in whom neurological deterioration occur in the OMS evolution.

The patients who do not respond to the treatment, are candidates for the treatment with cyclophosphamide with dexamethasone, azathioprine or cyclosporine.

Azathioprine (Imuran®) is the most easily administered immune-suppressor in slowly progressive doses, with a prompt supervision of the leucocytes and platelets number, and of the liver tests. The therapeutic effects become evident at 6–12 months from the beginning of the treatment with azathioprine, the maximum benefits being observed in 2 years. The side effects presented in all cases are related to the medullar suppression; 10% of the cases present flu-like symptoms, being known the risk of malignity in time.

Chemotherapy, by administrating cyclophosphamide (Cytoxan®), methotrexate, cyclosporin or cellecept (therapy which is limited as general experience) in children with neuroblastoma, does not influence the neurological manifestations already appeared, but it is beneficial by its anti-tumor effect.

In the moderate or severe forms of idiopathic or paraneoplastic OMS, two or three etiological are recommeded with different actions on the immune system: ACTH, IVIG and azathioprine or the association of cyclophosphamide (3–6 cycles), steroids and IVIG. The studies demonstrate the efficiency of associations based on ACTH, in comparison with those based on steroids (Tate ED, 2012). In viral encephalitis or in meningitis, the use of corticotherapy is rational.


Other immune-modulating therapies in the OMS treatment are being evaluated for example Ofatumumab, a fully humanized anti-CD20 antibody, Alemtuzumab (with action on the T CD 52 cells), Daclizumab (inhibits the activation or proloferation of the T CD25 cells) and the inhibitor of mTOR Sirolimus, with promising results.

The treatment of the cases of OMS as manifestations of autoimmune N-methyl-D-aspartate receptor encephalitis by plasmapheresis, seems to be the best option (Smith JH, 2011), (Nunez-Enamorado N, 2012).

In the cases in which OMS in the consequence of the anti-epileptic medication, the change of this medication is imperative. The symptomatic treatment with Trazodone is efficient in the amelioration of irritability, sleep disorders, or with Clonazepam, which
has the ability to link to the cerebral benzodiazepine receptors that facilitate inhibitory GABAergic transmission, valproic acid and 5-hydroxytryptophan.

According to the etiology, the OMS **prognosis** is variable, but it is admitted that the long term evolution is associated with neurological sequels in 80% of the cases — frequently manifested through speech disorders, learning problems, behavior problems, which can be controlled by a immune-modulating therapy (Brunklaus A, 2011).

### 8.4 Therapeutic Apheresis

Apheresis is a method used in different severe diseases, with an autoimmune mechanism, in which the patient's stabilization is needed; one can perform plasmapheresis, leukocytapheresis or lymphocytapheresis, in a limited number of 5–6 episodes, with a clinical improvement which is evident in the next 2 months. The disadvantages are related to the risk of hypotension and the impossibility of using it in small children. Immunoabsorption, a type of apheresis, uses an immunoabsorbant column for antibodies, using for example, as antigen, the staphylococcal A protein; this method is also limited, as clinical experience, in children.

### 8.5 Prognosis

The OMS prognosis depends on the clinical severity at the moment of therapeutic initialization, on the period from the diagnosis to the therapeutic answer, and also on the presence of relapses.

The easy forms of diseases remit completely. In the mild or severe forms of the disease, although the myoclonus has the tendency of diminish in time, the incongruity persists. The surgical ablation of the tumor in children (of the neuroblastoma, most frequently), is not associated with the remission of the neurological manifestations. The problems related to the behavior and learning disorders, the attention deficit and even the obsessive-compulsive disorders need specific medication in association with the immunomodulatory one.

A favorable evolution is associated with the viral infections, in the meningoencephalitis produced by the enteroviruses or EBV or in the idiopathic forms of OMS. In the severe forms of OMS, with the persistence of neurological manifestations and of the diminished intellect, the dependence of these children on adults is definitive.

### 8.6 Relapses

The reappearance or augmentation of the symptoms is known as being associated with some special affective situations, with febrile episodes, during surgical interventions, after anesthesia, immune-prophylactic therapy, or with the attempt of immune therapy suppression. The cases which present a relapse will repeat these episodes several times, at short intervals, exceptionally after long periods of slack time (several years). The relapses therapy is similar to the first episode, with one or more therapeutic agents.
8.7 Treatment of Failures

The lack of therapeutic answer to immune-therapy in children, requires completing the investigations in order to identify the tumor or viral cause; a combined therapy with two or more therapeutic agents, plasmapheresis, etc. is also necessary.

8.8 Treatment of Complications

The complications are most of the time associated with immune-suppression, produced by chemotherapy or immune-therapy. It is necessary to carefully monitor the medullar suppression and the risk of severe infections which can appear in the immune-suppressed patient.

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