HHV6-related mild encephalopathy with reversible splenial lesion (MERS) presenting with urinary and fecal retention in an Italian adolescent

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SUMMARY

Mild encephalopathy with a reversible splenial lesion (MERS) is an uncommon clinical-radiological entity characterized by magnetic resonance imaging (MRI) findings of a reversible lesion in the splenium of the corpus callosum associated with a significant neurological manifestation of encephalopathy. The majority of reported cases involve the Asiatic population and are closely associated with infections. We report the case of an adolescent with an HHV6-related MERS presenting with hyponatremia and urinary and fecal retention. To our knowledge, urinary retention is not a constant aspect of the disease and has rarely been described, while fecal retention has never been reported before. Despite the self-limiting nature of the disease, it is mandatory to suspect it for a faster diagnosis and it might be useful to know its rare occurrences in order to better understand its etiopathogenetic mechanisms.

Keywords: HHV6, urinary retention, hyponatremia, acute febrile encephalopathy.

INTRODUCTION

MERS (Mild Encephalopathy with a Reversible Splenial lesion) is a clinical-radiological syndrome characterized by a transient mild encephalopathy associated to a reversible lesion in the splenium of the corpus callosum. First described in Japan in 2004, it’s not frequently reported in literature and it usually interests Asiatic population [1, 2]. It is characterized by a prodromal aspecific illness followed within one week by symptoms of encephalopathy which self-resolve completely without treatment [1]. The underlying pathogenesis of MERS is unknown: several mechanisms have been proposed but the infectious trigger seems to be the most likely one [2]. We report a case of an Italian adolescent with a HHV6-related MERS presenting with urinary and fecal retention.

CASE REPORT

A 14-year-old girl was admitted to the nearest hospital for aspecific malaise followed by fever and headache for two days and acute onset of confusional state. Her past medical history was silent, and she had not taken medications. Blood examinations were unremarkable and both bacterial cultures and viral isolations were negative. Also, the search for drugs on urine was negative.
The neuroimaging exams (head Computed Tomography -CT- and MRI) conducted 4 days after the onset of the symptoms showed no pathological findings. Analysis of cerebrospinal fluid (CSF) showed a normal cell count with an increase in protein content and the electroencephalography (EEG) described slow frontotemporal left waves. Therefore, in the suspicion of meningoencephalitis, a therapy with antibiotic, antiviral and steroid was started (ceftriaxone, acyclovir and methylprednisolone respectively, in unknown doses). After 5 days, because of the persistence of the symptoms, especially the alterations of consciousness, the girl was transferred to our hospital. At admission, the girl showed discreet clinical conditions, she was alert and oriented; no neurological focal deficits were observed, tropism tone and strength were adequate, tendon reflexes were normal and symmetrical in all four limbs. She had fasciculations of the tongue and she complained of headache, photophobia, phonophobia and pain at the eyeball’s movements. The day after, new clinical manifestations appeared: apnea, refusal of walking and sitting, urinary and fecal retention and psychomotor crisis characterized by tachycardia, tachypnea with sensation of breathlessness, fatigue and feelings of faintness. An indwelling catheter was placed because of urinary retention, a globe bladder and periodic enemas were prescribed, and vesicoureteral-pelvic rehabilitation was started. The steroid therapy was discontinued while ceftriaxone and acyclovir were confirmed at the doses of 2 g/day IV and 500 mg IV q8hr respectively. Blood tests showed a worsening hyponatremia up to a minimum of 123 mEq/L associated with high excretion of sodium in urine, while microbiological investigations highlighted a HHV6 infection; in particular, serology showed the presence of immunoglobulin M antibody (IgM) and the absence of immunoglobulin G antibody (IgG) and quantitative PCR DNA test on whole blood showed a number of 500 copies/mL, indicating the presence of specific DNA from HHV6 and thus supporting the diagnosis of infection with this virus. No other pathological results were obtained. The head TC and MRI scans performed at the other hospital were revalued and confirmed to be negative. However, because of the persistence of the relevant neurological symptoms, the girl underwent new brain TC, which was normal, and new EEG with the confirmation of already known frontotemporal waves anomalies. Alteration of somatosensory pathways in the right limb was highlighted to somatosensory evoked potential (SSEP) while other neurological electrophysiological studies as visual evoked potentials (VEP), auditory evoked potentials (BAERs) and electroretinogram (ERG) were normal. Water restriction and oral supply with sodium chloride and sodium bicarbonate were prescribed.

After a multidisciplinary evaluation, a new brain MRI was carried out 12 days after onset of symptoms with evidence of lesions in the corpus callosum at the splenius level, not present in the previous images and having characteristics compatible with MERS [Figure 1]. The steroid therapy with methylprednisolone was started again at the dose

Figure 1 - Diffusion weighted images (DWI) and ADC maps show a single area of restricted diffusion within the splenium of corpus callosum corresponding to a slightly hyperintense lesion in axial T2-FLAIR weighted images (arrows).
of 25 mg q12hr IV and few days later the antibiotic and antiviral therapies were discontinued, respectively 10 and 12 days after their first administration. A progressive resolution of the clinical condition and the normalization of laboratory and instrumental examinations were observed within one month of the onset of the symptoms. The catheterization, continuous at the beginning, was subsequently carried out intermittently and finally suspended at the full bladder control. The brain MRI performed after 18 days from the previous one (30 days from the onset of the symptoms) described a resolution of the lesions of the corpus callosum [Figure 2]. After 17 days, steroid therapy was administered orally and progressively reduced until suspension after 40 days. The girl had neither neurological nor urinary and intestinal sequelae resulting from the disease.

**DISCUSSION**

The evaluation of clinical manifestations of MERS is necessary to suspect the disease but it is not sufficient. The onset of MERS is characterized by prodromal nonspecific symptoms as fever, cough, vomiting or diarrhea followed after few days and within one week by an acute phase with neurological manifestations of significant clinical entity as headache, altered consciousness, drowsiness, seizures, ataxia, vertigo, delirium and behavioral change [3]. The symptoms subside completely within a month without any sequelae [1, 2]. A brain MRI conducted during the acute episode is mandatory for diagnosis, revealing usually lesions in the splenium of the corpus callosum (MERS type 1 lesions), as in our patient, even if sometimes the lesions extend to other areas of the corpus callosum and to adjacent parenchymal white matter (MERS type 2 lesions) [1]. The symmetrical lesions show the typically high-signal-intensity on T2-weighted images (T2WI), fluid-attenuated inversion recovery images (FLAIR) and diffusion-weighted images (DWI), with corresponding diffusion restriction and no contrast enhancement [1, 4, 5].

In our case, after considering other possible and more frequent diagnosis such as viral encephalitis, metabolic diseases and psychiatric disorders, only MRI allowed us to have the right diagnosis. Regarding the evidence of the specific lesions on MRI, literature data report positive findings within 7 days from symptoms onset, or even within 2 days [2, 3, 6]. In our case, the neurological investigation carried out at the other hospital 4 days after the onset of the symptoms reported negative findings so our data is not consistent with that reported by Yildiz et al. [6]; the subsequent MRI was performed only 8 days after the previous one. Consequently, we are not able to date accurately the appearance of the brain lesions and to confirm that our findings are consistent with those reported in other literature works [2, 3].

The localization of the disease in the brain justifies the clinical manifestations as disorder of motor control, spatial orientation, vision, hearing, and language-related behaviors: the corpus callosum...
is a fiber bundle that projects into prefrontal, premotor, primary motor, primary sensory, parietal, temporal, and occipital cortical areas and its disconnection may explain the neurologic symptoms of MERS. However, it seems not to be responsible for the impairment of the bladder, reported only in few cases, for which further investigations are needed [2, 3, 7-10]. To the best of our knowledge, before now the fecal retention has never been described in MERS in the pediatric age, and it was reported only once in adults [11]. In our patient, this symptom resolved as well as the urinary retention and all the other neurologic manifestations of the disease, so we can assert that it was related to the MERS and that all the described manifestations are linked with each other. We suppose that the underlying mechanism of these clinical manifestations may be the same described in the shock phase of acute disseminate encephalomyelitis (ADEM) in which urinary and bowel dysfunctions are often observed or that, on the contrary, MERS could represent a mild variant of ADEM [12]. However further investigations are needed to understand the reason of urinary and bowel dysfunctions. Certainly, these rare manifestations have a very low diagnostic value and can not be considered sufficient to suspect the diagnosis of MERS which is currently supported from a clinical point of view only by neuro-psychological findings.

The pathogenesis of MERS is still not fully understood. A probable role is due to intra-myelinic edema, interstitial edema in tightly packed fibers, or inflammatory infiltrate resulting in the transiently reduced diffusion seen on MRI. Such edema may develop either as a result of electrolyte/water imbalance, especially hypotonic hyponatremia, or axonal damage and oxidative stress due to myelin neurotoxins released by pathogens [1, 3, 13-16].

In particular, the hyponatremia, defined as a lower serum sodium level of less than 136 mmol/L, is a constant finding in almost all patients with MERS. It has been postulated to be a possible cause of intramyelinic edema of splenial area even if the underlying pathogenetic mechanism is not fully understood and further studies are necessary to define it [16]. Regarding infections, both viral and bacterial ones have been reported in literature associated with MERS even if the first are most common [1, 6, 17]. However, most MERS patients have been reported to have non-CNS infection. Starting from these considerations, there are different reported explanations for transient cerebral edema such as myelinic-specific neurotoxins release causing inflammatory infiltrate, the effects of viral antigens or receptors on the antibodies, induced by antigens, that might share affinities for specific receptors on splenial axons, inducing inflammatory response [1, 6, 17]. This immune-mediated CNS damage has been also postulated after description of noninfectious conditions, such as Kawasaki disease and systemic lupus erythematosus (SLE), associated to MERS. However, antiepileptic medications, metabolic factors and high-altitude edema are described related to the disease as well [18-21].

In our case both hyponatremia and viral infection were present, and we suppose, on the basis of literature, that both of them could have played a role in the pathogenetic mechanism underlying the disease. Contrary to the well-known association with hyponatremia, the association of MERS with HHV6 infection has been rarely described compared to other viral infections. However, we don’t think HHV6 may have played a different role in determining the assonal transient damage than the ones previously described regarding other viruses. So, we believe the role of HHV6 in our case could be the same of all other viral pathogens reported in MERS patients in literature and we are not able to determine which of the two factors (hyponatremia and HHV6) may have contributed most to the splenial damage.

Finally, the prevalence of the disease among Chinese and Japanese and Australian populations suggests a strong genetic predisposition in these populations [2]. Such a genetic vulnerability hypothesis has been supported after the description of sisters with MERS [22].

The differential diagnosis of MERS includes infections, ischemia, multiple sclerosis, lymphoma, acute disseminate encephalomyelitis, and posterior reversible encephalopathy. The meningitis retention syndrome (MRS) has to be considered when acute urinary retention is present, but it shows no anomalies in MRI scans [12]. Moreover, any patient with encephalopathy and acute urinary retention could have an acute disseminated encephalomyelitis (ADEM): in this condition white matter lesions, asymmetrical lesions with T2 hyperintensity without diffusion restriction...
and possible enhance with gadolinium, are evident on MRI [23]. Finally, it has to be considered that the acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is more common than MERS, based on a study conducted in Japan upon the acute encephalitis [24]. Methylprednisolone pulse therapy and IVIG are recommended for patients with infectious encephalopathy regardless of pathogen but there are no guidelines about the treatment of MERS. A review of literature reports patients with MERS with full recovery irrespective of the therapies, suggesting that there is no supporting evidence of treatments with steroids or IVIG for MERS so far [25, 26].

**CONCLUSION**

We report of a patient with encephalitis and reversible splenial lesions associated to HHV6. The patient’s symptoms recovered quickly and the splenial lesion completely disappeared, as the other cases reported in literature. To our knowledge, this is one of the very few cases of HHV6-related MERS described worldwide and the first one in an European country [27]. The girl had hyponatremia, already well described in several cases, but also urinary retention, that is not a common feature, and fecal one, never described before in the pediatric age.

The neurological manifestations of the disease in our patient, due to the transient splenial lesions, can be associated both to hyponatremia and HHV6 infection according to the pathogenetic mechanisms described before and already reported in the other cases of literature. A separate consideration is necessary for the urinary and the fecal dysfunctions that are purely descriptive findings; they are not explained by the splenial lesions and have no diagnostic value in diagnosis of MERS. However, considering their simultaneous regression to the neurological manifestations of the disease we assume they are related to MERS. However, further descriptions are mandatory to confirm this hypothesis and to better understand the etiopathogenetic mechanisms.

**Conflict of interest**

None

**REFERENCES**

[15] Guarner J., Hochman J., Kurbatova E., Mullins R. Study of outcomes associated with hyponatremia and