Case report

Herpes simplex encephalitis: A new type of “ICU-acquired infection”?

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ABSTRACT

Purpose: Although it is a well-known disease, the occurrence of Herpes simplex encephalitis (HSE) during a hospital stay may render the diagnosis particularly challenging. The objective of this report is to alert clinicians about the diagnostic pitfalls arising from hospital-developed HSE.

Materials and methods: Clinical observation of one patient.

Case report: An 87-year-old male was admitted to the Intensive Care Unit (ICU) because of respiratory failure due to an exacerbation of myasthenia gravis. After corticoids and azathioprine treatment, his clinical condition improved, allowing weaning from mechanical ventilation. One month after admission, while still hospitalized in the ICU, the patient developed fever and confusion. In the context of confounding factors, HSE was not suspected before a convulsive status epilepticus occurred, resulting in a significant delay in treatment. Diagnosis was confirmed by PCR-analysis in the cerebrospinal fluid. Serological status confirmed reactivation of prior herpes simplex infection. The patient died one week after the onset of confusion.

Conclusions: Hospital-“acquired” HSE must be suspected in case of new neurologic symptoms associated with fever, even in ICU-hospitalized patients. The diagnosis is made even more difficult by nonspecific symptoms due to previous diseases, leading to an even more severe prognosis in those vulnerable patients.

1. Introduction

Acute viral encephalitis can be caused by several types of virus, especially herpes viruses (Herpes Simplex virus 1, 2, 6, Varicella Zoster Virus, Cytomegalovirus, Epstein Barr virus etc.). Although it is a relatively rare disease, Herpes simplex Encephalitis (HSE) is the main cause of acute encephalitis [1, 2, 3]. Thanks to early diagnosis by Polymerase Chain Reaction (PCR) in the cerebrospinal fluid (CSF) and to acyclovir therapy, mortality dropped [1, 2, 3], even if neurological sequelae remain frequent. However, in immunocompromised patients atypical illness and poorer outcomes have been described [1]. Mechanisms exacerbating virulence of herpes simplex virus (HSV) in these patients are still unknown, but HSE is not yet considered as an opportunistic infection. We report the case of severe intensive care unit (ICU) “acquired” HSE after three weeks of corticosteroids and immunossuppressive therapy.

2. Case report

An 87-year-old male was admitted on August 15th to the neurological ward for an exacerbation of myasthenia gravis (swallowing disorder and dysphonia, Osseman myasthenia score at 61). His medical history included bulbar myasthenia gravis since 2015 (positive anti choline-acetyl receptor antibodies), atrial fibrillation, left middle cerebral artery infarctus of cardioembolic cause without sequelae five months prior (no visible on Figure 2), giant cell arteritis, and a prostatic adenocarcinoma considered as cured. Despite his medical history, he used to be self-sufficient at home, and he presented neither focal neurological deficits nor cognitive complaints. He had no fever. His usual treatment included pyridostigmine, apixaban, and prednisolone (10 mg/day). On August 19th, he was transferred to the ICU because of acute respiratory failure requiring endotracheal intubation with mechanical ventilation. CT scans of the chest showed parenchymal condensation of the two lung bases, with an effusion blade bilateral pleural, in favour of associated bilateral

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inhalation pneumonia. Due to lack of clinical improvement after intra-
venous (IV) polyvalent immunoglobulin, he received a second-line
 treatment that consisted of azathioprine and methylprednisolone 0.75
 mg/kg/day. Tracheotomy was performed on September 8th, allowing
 meaning from mechanical ventilation on September 10th. Thus, acute
 respiratory failure lasted 22 days. On September 16th, although clinical
 state had improved (best Osserman myasthenia score 50 on the 12th), the
 patient became confused. On the 17th, apixaban was discontinued
 because of rectal bleeding. On the 18th, he developed fever (38.5 °C)
 and alveolar consolidation that motivated antibiotic therapy (piper-
 acillin–tazobactam). On the 20th, four days after the onset of confusion, he
developed a focal secondarily generalized tonic–clonic seizure starting on
 his right hemiface, evolving into a status epilepticus. The patient was
 treated with IV valproate 15 mg/kg as first-line treatment, and then with
 propofol and midazolam. The cerebral CT at 3 a.m. showed no significant
 changes, but the electroencephalogram (EEG), recorded at 6.30 a.m. revealed a right hemispheric status epilepticus, contralateral to his left
 posterior stroke sequelae (Figure 1A). Magnetic resonance imaging (MRI)
on September 20th at 9 p.m. showed bilateral insular, frontal and tem-
 poral hypersignal predominant on the left hemisphere (Figure 2) and
 motivated immediate treatment with acyclovir (15 mg/kg every 8 h). A
 second EEG at 10 p.m. was markedly aggravated with the emergence of
 high amplitude periodic complexes predominating on the left fronto-
temporal electrodes (Figure 1B). EEG was thus strongly in favor of HSV
 encephalitis. The lumbar puncture performed after a negative apixaban
 testing, showed 576 white blood cells/mm³ [3], 909 red blood
 cells/mm³, protein 144 mg/dl, glucose 2.63 mmol/l. The positive HSV-2
 PCR in the cerebrospinal fluid (CSF) confirmed the diagnosis of HSE on
 September 21st (HSV-1 and VZV PCR were negative). The blood soro-
 logical status was in favour of a viral reactivation: IgM negative and IgG
 positive for HSV1 and HSV2. Anti-NMDA receptor antibodies were also
 negative in serum, as well as anti-Yo, anti-Hu, anti-Ri, anti–amphiphysine, anti-Ma2, anti-CV2 (September 18th). Despite the treat-
 ment, the clinical state did not improve. A third EEG, performed on 21st,
 was compatible with a highly advanced state of HSE, displaying a typical
 bi-hemispheric monomorphic, ample, periodic and areactive sub-delta
 activity (Figure 1C). The patient died one week after the onset of
 confusion.

 The patient’s wife gave her consent for the publication of this case
 report and the two associated images (EEG and MRI).

 3. Discussion

 The present case study demonstrates the pitfalls of HSE-diagnosis in
 the context of the ICU. In our patient, HSE occurred one month after
 admission for acute respiratory failure related to myasthenia gravis. It is
 very unlikely that HSE was already present at admission, since the patient
 had no fever or confusion signs. Moreover, outcome was initially
 favourable without antiviral treatment. Due to the nonspecific nature of
 the early symptoms of HSE, which mimicked a bacterial ICU acquired-
 infection, diagnosis and antiviral treatment were delayed. This has
 certainly contributed to the fatal outcome, as did the patient’s general
 vulnerability after immunosuppressive treatment and one month of
 hospitalization in the ICU. Since our patient received IV polyvalent im-
 munoglobulins, one might speculate on a false positive HSV serology. In
 fact, both HSV 1 and 2 serologies were positive, but only HSV-2 was
 confirmed by PCR. HSV-2 encephalitis is less common than HSV-1, but
 can occur [2,3].

 An autoimmune encephalitis could have been suggested at the time of
 the secondary neurological worsening. However, the brutal clinical
 pattern, with general signs of sepsis (fever, mottling, chills) mainly evoke a
 septic complication. Moreover, although Anti-neuronal receptor anti-
 bodies have not been searched in CSF, they were negative in serum.
 Finally the MRI pictures and the evolution EEG towards bitemporal ne-
crosis in 24 h are quasi-pathognomonic of an HSE. The

 immunosuppressive treatment received by the patient for more than one
 month is yet another argument in favour of HSE.

 In the literature, there is a wide spectrum of medical conditions that
 could theoretically promote HSE: both systemic immunocompromised
 status (radiation, chemotherapy, corticosteroids, human immunodefi-
ciency virus, etc.) [1,2], and local brain injury (cranial trauma, brain
 surgery) have been suggested as possible risk factors for HSE, in single
 case reports, but higher level evidence is lacking. Especially, corticoste-
 roids have been recently described as a risk factor of HSE, either in
 monotherapy or in combination with chemotherapy. To our knowledge,
 except new-born cases, only three cases of “nosocomial HSE” have been
 reported [4,5]. Prognosis was poor in these patients, although there were
 not deeply immunosuppressed.

 As a matter of fact, pathophysiology of HSE remains elusive. It is
 generally accepted that it comes from the resurgence of the quiescent
 virus, and some authors claim that it would imply rather excessive
 inflammation than immunosuppression [1,6]. It is of note that those
 articles do not report the HSV serologies that would have allowed to
distinguish viral reactivation from actual nosocomial infection. In our
 case, the serological status was in favour of a recent viral reactivation.
 Moreover, since HSV-2 is most often sexually transmitted, it is very un-
 likely that the patient contracted it while in ICU. However, we called it
 “acquired-ICU HSE” because of the analogy with bacterial infections
 authentically acquired in ICU.

 HSE diagnosis in immunocompromised patients is made difficult by
 the atypical symptoms and low leucocytes count in the CSF [1]. Fur-
 thermore, assessment of ICU-developed HSE is difficult because of
 nonspecific symptoms like confusion and moderate fever that could
 emanate from a multitude of other pathologies, e.g. hypotenatremia, sed-
 atives, pneumonia or other nosocomial infections, etc. Individual cir-
cumstances may add up to hinder rapid diagnosis. In our case, the CSF
 examination was delayed because of long acting anticoagulant. EEG and
 MRI helped crucially in therapeutic decision making, but their specificity
 was all the more pronounced as HSE had already been evolving for four
days. In fact, access to early cerebral MRI is mandatory to shorten the
 diagnostic delay [2,4].

 Very little is known about hospital-developed HSE, but according to
 the sparse existing literature, the diagnosis of HSE is probably under-
estimated [6], and the outcome appears to be dramatic. Delayed diag-
nosis and treatment on one hand, and patient vulnerability on the other
 contribute to the poor prognosis.

 4. Conclusion

 Physicians should be aware of the possibility of HSE during hospi-
talization, probably by virus reactivation due to immunosuppression or
 local inflammation. The diagnosis of HSE is probably underestimated,
 and must be evoked in the presence of fever associated with any new
 onset neurological symptom (confusion, alteration of consciousness,
 meningeal signs, seizures...). In this situation, neurological in-
 vestigations are urgent. Early MRI and EEG are sensitive and specific, and
 are even more useful when the lumbar puncture has to be delayed. A
 systemic antiviral treatment must be initiated before definitive virologic
 confirmation.

 HSE: Herpes simplex encephalitis, ICU: Intensive Care Unit, CSF: ce-
 rebrosplid fluid, EEG: electroencephalogram, MRI: Magnetic resonance
 imaging, PCR: Polymerase Chain Reaction, IV: Intravenous, CT: Computed Tomography.

 Declarations

 Author contribution statement

 All authors listed have significantly contributed to the investigation, development and writing of this article.
Figure 1. EEG recordings of epileptic and periodic discharges. 1A. September 20th at 6.30 a.m.: Status epilepticus: Continuous rhythmic spike-wave activity prevailing on the right hemisphere with left hemispheric propagation and a minor attenuation by propofol. 1B. September 20th at 10 p.m.: Within 16h, substantial changes were visible on EEG, which now showed unreactive right paroxysmal fronto-central spikes waves of short periodicity and left fronto-temporal monomorphic periodic delta activity in favor of HSE. Midazolam had no effect on the periodic pattern. 1C. September 21st: Slow monomorphic bi-hemispheric periodic subdelta complexes, unreactive to external stimuli, indicating very advanced stages of HSE.
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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] I.L. Tan, J.C. McArthur, A. Venkatesan, A. Nath, Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised, Neurology 79 (2012) 2125–2132.
[2] P. Jaquet, E. de Montmollin, C. Dupuis, C. Sazio, M. Conrad, V. Susset, et al., Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a multicenter cohort study, Intensive Care Med. 45 (2019) 1103–1111.
[3] D. Dhull, V. Sharma, Y. Sharma, S. Kaushik, Applicability of molecular assays for detection and typing of herpes simplex viruses in encephalitis cases, Virusdisease 30 (2019) 504–510.
[4] P. Doshi, M.J. Donovan Post, G. Saigal, A. Podda, R. Quencer, Nosocomial Herpes Encephalitis: rare but treatable with early MR diagnosis, NeuroRadiol. J. 26 (2013) 168–174.
[5] H. Algahtani, B. Shirah, M. Hmoud, A. Subahi, Nosocomial herpes simplex encephalitis: a challenging diagnosis, J Infect Publ. Health 10 (2017) 343–347.
[6] Y. Jouan, L. Grammatico-Guillon, A. Guillou, Nosocomial herpes simplex encephalitis: does it really exist? J Infect Publ. Health 11 (2018) 142.

Figure 2. MRI (September 20th at 9 p.m.). High signal intensity lesions in Diffusion (A,B,C) and in T2 fluid-attenuated inversion recovery (FLAIR) (D) sequences in the bilateral temporal, frontal lobes and cingular gyri.