Annals of Clinical Case Reports

Case Report
Published: 24 Jan, 2022

Post Infectious Measles Encephalitis: Challenges and Pitfalls

Ida Turrini[1], Ilaria Contaldo[1], Michela Quintiliani[1], Orazio Genovese[2], Marco Gessi[3], Roberta Onesimo[1], Eugenio Maria Mercuri[1], Piero Valentini[1], Silvia Maria Pulitanò[2], Domenica Immacolata Battaglia[1#] and Chiara Veredice[1#]*

[1]*Department of Woman and Child Health Sciences, University Hospital Agostino Gemelli, Italy*

[2]*Pediatric Intensive Care Unit, University Hospital Agostino Gemelli, Italy*

[3]*Department of Pathological Anatomy, University Hospital Agostino Gemelli, Italy*

[#]*These authors equally contributed to this work*

Abstract

Our brief report presents the case of a 15-year-old girl, affected by lymphocyte B depletion and hypogammaglobulinemia, died of subacute measles related encephalitis. The combination of clinical, neurophysiological and neuropathological features prompted toward a possible diagnosis of Measles Inclusion Body Encephalitis (MIBE). The presence of atypical clinical signs, such as super refectory status epilepticus, and histopathological features overlapping with subacute sclerosing panencephalitis hinder an already difficult diagnosis. Furthermore, in Literature, MIBE is associated with cellular immune defects, no cases are described in patients with humoral defects, since do not usually modify the course of measles infection. At the time when decrease in measles vaccine coverage are experienced in several countries, our findings suggest that even in the absence of a clear clinical history or lab results, measles infection must be suspected in every case of super refectory status epilepticus of unknown origin.

Introduction

Due to a decrease in measles vaccine coverage, several countries have been experiencing new outbreaks, with 7.5 million cases reported by the WHO in 2020 [1]. Measles-induced encephalitis, though uncommon, often results in severe disability or death [2], and include: Primary Measles Encephalitis, Acute Post-infectious Measles Encephalomyelitis, Measles Inclusion Body Encephalitis (MIBE) and Subacute Sclerosing Panencephalitis (SSPE) [3,4]. The last two forms occur after the acute phase: MIBE is mainly reported in immunosuppressed patient, generally six months after Measles Virus (MV) infection [5-10]; SSPE occurs after 1 to 10 years in previously healthy patients [11]. Even though the two forms may present some overlap, each form has distinct clinical and pathological features [2-4,11]. We report a case of a 15-year-old girl with clinical signs, onset and evolution suggestive of MIBE in whom the diagnostic process was complicated by the presence of associated atypical clinical signs and histopathological features.

Case Presentation

The patient was born in Romania and moved to Italy at the age of 6 years. There was no family or physiological history of note; she had completed the vaccination schedule, including two doses of measles vaccine at the age of one and eight years. At the age of 12, she had the diagnosis of asymptomatic thrombocytopenia, treated with corticosteroids, Immunoglobulin (Ig) and rituximab, completely recovered after about one year. In December 2017, presented to our attention for headache and rapid decrease of visual acuity suggestive of cortical blindness. A few months before the admission, she had shown acute diffuse macular rash without fever and, after that, persisting cough and asthenia, associated with lymphocyte B depletion and hypogammaglobulinemia (CD19 0.5%; IgA 9 mg/dL; IgM <10 mg/dL; IgG <30 mg/dL), requiring monthly infusions of Ig. No exposure to measles could be traced. At the admission physical examination revealed intraocular pressure increase and cranial CT was normal. On day 4, she presented with daily myoclonic seizures of left hemiface and anticonvulsant therapy with levetiracetam (2000 mg/die) and clonazepam (15 mg/die) was started. Brain MRI on day 7 showed subcortical and deep white matter changes in the occipital and right frontal lobes. A slight increase in protein (47 mg/dL) was found on a Lumbar Puncture (LP) performed on day 8. EEG showed intercritical slow-waves localized on

OPEN ACCESS

Correspondence:
Ida Turrini, Department of Woman and Child Health Sciences, University Hospital Agostino Gemelli, Italy, E-mail: ida.turrini@guest.policlinicogemelli.it

Received Date: *01 Dec 2021*
Accepted Date: *20 Jan 2022*
Published Date: *24 Jan 2022*

Citation:
Turrini I, Contaldo I, Quintiliani M, Genovese O, Gessi M, Onesimo R, et al. Post Infectious Measles Encephalitis: Challenges and Pitfalls. Ann Clin Case Rep. 2022; 7: 2092.

ISSN: 2474-1655

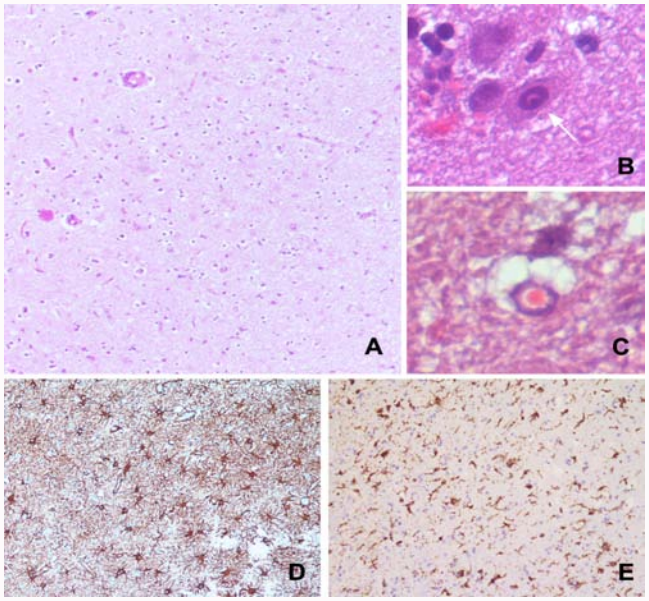

Figure 1: Neuropathological features of the brain biopsy. The brain tissue showed light oedematous changes (A). Scattered glial and neuronal cell presented with small intranuclear, sometimes eosinophilic inclusions, compatible with measles viral inclusions (B, C) (arrow in B). The tissue displayed reactive gliosis, microglia activation and presence of CD68+ macrophages (D, E, respectively). (A-C: H&E staining; D: Immunohistochemical stainings performed with monoclonal mouse anti human GFAP and anti human CD68/PGM1 antibodies, both from DAKO-Agilent, Cernuscosul Naviglio, Italy; immunohistochemistry performed on DAKO Omnis Auto stainer, DAKO-Agilent).

the right hemisphere and continuous rhythmic sharp-waves on the right regions, with contralateral diffusion, associated with focal motor seizures. Treatment with corticosteroids and mannitol was started. On day 12, the seizures evolved in Super Refectory Status Epilepticus (SRSE), resistant to bolus doses of midazolam at 0.2 mg/kg. Treatment with acyclovir and deep sedation with midazolam (12 gamma/Kg/min) and propofol (5 mg/Kg) were started. LP on day 14 confirmed protein increase (60 mg/dL). CSF culture test for neurotropic virus, fungus and bacteria were negative, as well as, Polymerase Chain Reaction (PCR) for neurotropic agents and serum antibodies. Metabolic and immunological screening, abdomen e thoracic CT was also normal. Clinical seizure persisted despite the association of several pharmacological and non-pharmacological therapies: Methylprednisolone (30 mg/kg/die), phenytoin (20 mg/Kg), ketamine (100 gamma/Kg/min), bolus doses of lacosamide (400 mg/die), hypothermia, plasmapheresis and Ig infusion. Continuous EEG monitoring showed delta brushes pattern predominant on the right side, followed after 10 days by periodic burst of diffuse sharp-waves. After one month, periodic lateralized epileptiform discharges or bilateral independent periodic lateralized epileptiform discharges appeared on EEG, associated to nystagmus. On day 21 a second brain MRI showed wide areas of altered intensity in the cortex, subcortical, and deep white matter of the occipital, parietal, temporal and frontal lobe with signs of cortical laminar necrosis. Mild parenchymal contrast enhancement was present. On day 27 brain biopsy was performed, revealing small fragments of brain tissue with edematous changes. Immunohistochemical analysis revealed microglia activation and presence of numerous intraparenchymal CD68+ macrophages and few perivascular CD3+/CD8+ lymphocytes. The tissue showed also reactive gliosis (Figure 1). Scattered glial and neuronal cell presented with intranuclear, sometimes eosinophilic inclusions, compatible with measles viral inclusions (Figure 1). Typical eosinophilic inclusions as found in MIBE were not detectable. Nor granulomatous or vasculitic changes, neither areas of necrosis were found. RT-PCR on brain tissue revealed wild type measles virus, genotype D8, and Parvovirus B19 RNA. After one month, SRSE progressively relapsed. The girl presented vegetative status with hypertension, tachycardia and some myoclonic seizures of the left hemiface, treated with doxazosine, transdermic clonidine, lacosamide (400 mg/die), and monthly IgG infusion (0.4 mg/kg). There was a constant increase of pancreatic enzymes up to 285 UI/L. Brain MRI on day 44, 80, 122, 178, 232, 264 showed progressive involvement of cortex and white matter bilaterally, of the cerebellar grey and white matter, and of the brainstem associated with ventricular enlargement (Figure 2). After ten months, the patient presented acute worsening with hypotension,

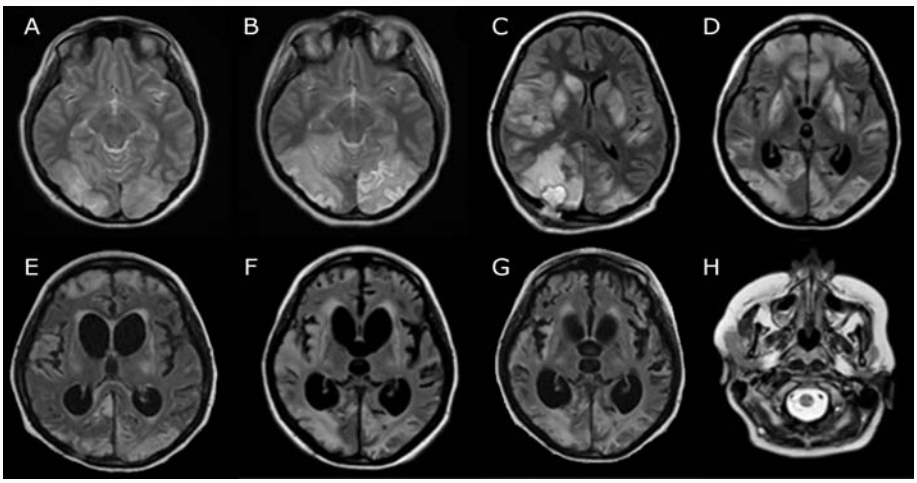

Figure 2: Serial brain MRI findings showing the progressive changes: A) T2-weighted image on day 7 showed increased intensity in the subcortical and deep white matter in both occipital lobes and in the right cortical frontal lobe, with mild mass effect; B) T2-weighted image on day 21 highlighted progressive involvement of cortical-subcortical occipital, parietal and temporal lobes; C) T2-weighted image on day 44 showed swelling of basal ganglia and further progressive extension of areas of high signal in parietal and frontal lobes, mark of right parietal minicraniotomy for brain biopsy; D) T2-weighted image on day 80 showed new high signal of temporal and frontal lobes associated with initial atrophic evolution, E,F) FLAIR -weighted image on day 122 and on day 178 showed progression of cortical-subcortical atrophy with enlargement of the lateral ventricles; G) FLAIR-weighted image on day 232 high signal in left frontal and temporal lobes, H) T2-weighted image on day 264 showed new altered signal in the occipital lobe, right hemisphere cerebellar and focal lesion in bulb and pons.

bradycardia, associated to ST segment elevation, significant increase of troponin and left ventricular regional wall motion abnormalities. She died after 24 h. Post mortem investigation was not permitted.

Discussion

We report a case in which the presumed diagnosis of MIBE was complicated by several atypical findings. The presentation with headache and cortical blindness was typical of MIBE, with no behavioral or cognitive difficulties, more often observed in SSPE [11]. Motor deficits (hemiparesis, hemiplegia, ataxia), dysarthria and dysphagia, often reported in MIBE, were not present [11]. Focal motors seizures and early EEG findings, with intercritical slow-waves and continuous ipsilateral rhythmic sharp-waves, were also consistent with MIBE [4]. In contrast the rapid worsening of focal motor seizures, refractory to AEDs, and the onset of SRSE were not typical of MIBE. Severe seizures occur more often in patients with SSEP, but we did not observe the Radermecker's complexes, recurring at regular intervals of 5 sec to 10 sec and having clear relationship with myoclonic jerks, often reported in SSEP [12]. Brain MRI, showing widespread changes, affecting the grey, subcortical and deep white matter, with posterior-anterior progression, subsequent atrophy and involvement of brain stem, was also consistent with the multifocal areas of increased T2 signal intensity in the cortex, subcortical, and deep white matter, followed by progressive atrophy reported in MIBE [11]. Widespread lesions with posterior-anterior progression are also reported in SRSE but with a different pattern, as the early changes are characterized by early demyelination, particularly in the temporal and parietal lobes [4]. CSF analysis revealed only increased protein, also previously reported in MIBE patients [11]. Brain biopsy showed the presence of macrophage infiltrates, perivascular lymphocytes, edema, microglia activation and gliosis and, in scattered neurons, of intranuclear inclusions, sometimes eosinophilic, compatible with MV inclusions. The typical eosinophilic inclusions, often found in MIBE, were not detectable. The neuropathological findings were overall not completely typical of MIBE and in some way overlapping with SSPE, which is however also associated with a more evident inflammatory infiltration and demyelination, that was not found in our patient [13]. The mismatch between clinical and histopathological features has already been described in another case [10]. The absence of antibodies against MV in our case was consistent with the immunocompromised status typical of MIBE [11]. However, cellular immune defects were not present in our patient, who had hypogammaglobulinemia, which should not modify the course of measles infection [14]. A high Incidence of Immune Thrombocytopenia (ITP), also found in our patient, has in contrast been previously reported in 315 SSPE cases, assuming a non-casual relationship between the two pathologies. The possible mechanisms considered were immune dysregulation, alteration of the immune response due to ITP pharmacological treatments or antigenic stimulation from persistent MV [15]. The atypical features did not allow to fully ascribe our case to the well characterized forms but the combination of clinical, neurophysiological and neuropathological features prompted toward a possible diagnosis of atypical MIBE. The diagnostic process was also complicated by other elements that contributed not only to hinder a specific diagnosis of MIBE but also to suspect a subacute measles related encephalitis. Our case had no clear exposure to MV, had complete vaccination schedule, reduced exanthema, undetectable serum antibodies, negative CSF culture. It was only the brain biopsy, detecting the presence of MV RNA by RT-PCR that allowed to confirm our hypothesis of a subacute measles related encephalitis [16].

Conclusion

Our findings suggest that even in the absence of clear clinical history or lab results, measles infection must be suspected in the diagnostic flow of every case of SRSE of unknown origin, especially at the time when decrease in measles vaccine coverage are experienced in several countries. In Italy the measles vaccine coverage did not reach the target of 95%, coverage needed to get herd immunity, leading to a further increase in the pool of susceptible adolescents and children. Ongoing efforts to raise confidence in vaccines should be intensified.

References

1. World Health Organisation.
2. Buchanan R, Bonthius DJ. Measles virus and associated central nervous system sequelae. Semin Pediatr Neurol. 2012;19:107-14
3. Fisher DL, Defres S, Solomon T. Measles-induced encephalitis. Q J Med. 2014;108:177-82.
4. Patterson MC. Neurological Complications of measles (Rubeola). Curr Neurol Neurosci Rep. 2020;20(2):2.
5. Chakraborty AP, Ray A, Mukherjee D, Gupta S, Pandit A, Dubey S. Subacute measles encephalitis in a case of late presenting congenital HIV with epilepsia partialis continua as the first manifestation: A case report. J Family Med Prim Care. 2021;10(9):3502-4.
6. Freeman AF, Jacobsohn DA, Shulman ST, Bellini WJ, Jaggi P, de Leon G, et al. A new complication of stem cell transplantation: Measles inclusion body encephalitis. Pediatrics. 2004;114;e657.
7. Baldolli A, Dargèrea S, Cardineau E, Vabretc A, Dinac J, de La Blanchardièreet A, et al. Measles Inclusion-Body Encephalitis (MIBE) in a immunocompromised patient. J Clin Virol. 2016;81:43-6.
8. Bitnun A, Shannon P, Durward A, Rota PA, Bellini WJ, Graham C, et al. Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. Clin Infect Dis. 1999;29(4):855-61.
9. Chadwick DW, Martin S, Buxton PH, Tomlinson AH. Measles virus and subacute neurological disease: An unusual presentation of measles inclusion body encephalitis. J Neurol Neurosurg Psychiatry. 1982;45(8):680-4.
10. Mustafa MM, Weitman SD, Winick NJ, Bellini WJ, Timmons CF, Jane D. Siegel. Subacute measles encephalitis in the young immunocompromised host: Report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. Clin Infect Dis. 1993;16(5):654-60.
11. Anlar B. Subacute sclerosing panencephalitis and chronic viral encephalitis. In: Dulac O, Lassonde M, Sarnat HB, editor. Handbook of clinical neurology. Pediatric Neurology Part II Elsevier. 2013;112(3rd Series):1183-9.
12. Jović NJ. Epilepsy in children with subacute sclerosing panencephalitis. Srp Arh Celok Lek. 2013;141(7-8):434-40.
13. Hatanpaa KJ, Kim HK. Neuropathology of viral infections. In: Tselis AC, Booss J, editor. Handbook of clinical Neurology. Neurovirology. Elselvier. 2014;112(3rd series):193-214.
14. Permar SR, Klumpp SA, Mansfield KG, Carville AAL, Gorgone DA, Lifton MA, et al. Limited contribution of humoral immunity to the clearance of measles viremia in rhesus monkeys. J Infect Dis. 2004;190(5):998-1005.
15. Oncel I, Saltik S, Anlar B. Subacute sclerosing panencephalitis and immune thrombocytopenia: More than a coincidence? Med Hypotheses. 2018;111:70-2.
16. Vaccinazioni pediatriche e dell'adolescente, le coperture vaccinali nel 2018.