Ann Ist Super Sanità 2017 | Vol. 53, No. 2: 167-169
DOI: 10.4415/ANN_17_02_15

A case of fulminant subacute sclerosing panencephalitis presenting with acute myoclonic-astatic epilepsy

Fabio Magurano[1], Gian Luca Marella[2], Antonella Marchi[1], Antonietta Filia[3], Luigi Tonino Marsella[2], Saverio Potenza[2], Roberto Massa[4], Paola Bucci[1], Melissa Baggieri[1] and Loredana Nicoletti[1]

[1]*Laboratorio Nazionale di Riferimento per il Morbillo e la Rosolia, Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento di Sanità Pubblica, Sezione Medicina Legale, Università degli Studi di Roma "Tor Vergata", Rome, Italy*
[3]*Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
[4]*Dipartimento di Neuroscienze, UOC Neurologia, Università degli Studi di Roma "Tor Vergata", Rome, Italy*

Abstract
The neurologic sequelae post-measles are less common than other complications measles-related and can lead to severe disability or death: primary measles encephalitis (PME), acute post-infectious measles encephalomyelitis (APME), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE). SSPE syndrome can affect people years from the acute measles virus infection, as result of the persistence of defective viral particles in brain cells. Clinical onset typically manifests with progressive intellectual deterioration, behavioral changes, and myoclonic jerks. The course of SSPE in the majority of affected children is that of a progressive worsening with fatal outcome within two years. This report described an Italian case of fulminant SSPE syndrome that led to death within few months from the initial onset.

Key words
- SSPE
- measles
- vaccination
- death
- virus

INTRODUCTION

Measles virus (MV) can affect the CNS inducing encephalitis in at least 4 different paradigms that can cause serious and permanent brain dysfunction or death [1]: primary measles encephalitis (PME), acute postinfectious measles encephalomyelitis (APME), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE).

Most patients with SSPE have a history of primary measles infection at an early age: children who contract measles before the age of 2 years are at great risk for subsequent development of SSPE [2]. Even, children who contract measles before the age of 1 year carry a risk of 16 times greater than infected after the age of 5 years [3]. This suggests that the pathogenesis of SSPE involves an immature immune system [4]. Although the usual age of onset between 5 and 15 years, with males affected more than females [5], cases have been reported as young as 22 months [6] and 4 months [7], and as old as 30 years [8].

SSPE disease results difficult to be diagnosed in its earliest stage since initial symptoms manifest by decrease in school performance, irritability, and emotional lability. Weeks to months later, decline in intellectual functioning becomes more obvious, and motor dysfunction develops with myoclonic jerks tending to be generalized with prominent axial musculature involvement [9]. Individuals may develop seizures, and ocular involvement occurs in at least 50% of SSPE cases [10]. Loss of swallowing, and bladder/bowel dysfunction become obvious along the course of illness. Latest, the patient becomes stuporous, with decorticated rigidity ultimately progressing to vegetative state and death. In the majority of patients, the interval between the onset of symptoms and death is between 1 and 2 years [11, 12]. Diagnosis of SSPE measles-related is based on the characteristic symptomatology, specific electroencephalographic changes, and elevated titers of measles antibodies in serum and cerebrospinal fluid (CSF). A definitive confirm of the diagnosis can be obtained by the detection of measles virus antigen by brain biopsy using reverse-transcriptase polymerase chain reaction for measles virus RNA [13].

We describe a fulminant SSPE case whose initial clinical and neuroradiological picture was suggestive of myoclonic-astatic epilepsy (MAE).

Address for correspondence: Fabio Magurano, Laboratorio Nazionale di Riferimento per il Morbillo e la Rosolia, Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: fabio.magurano@iss.it.

CASE REPORT

A 5-year-old, previously healthy, girl with 7 weeks history of poor balance and frequent episodes of muscle weakness was admitted to an emergency department with a first diagnosis of myoclonic-astatic epilepsy (MAE) suggested by a electroencephalogram (EEG) showing several epileptiform abnormalities such as widespread paroxysmal spikes short in duration during sleep, and episodes of atonies of the axial muscles associated to a widespread slow paroxysmal. After a period of hospitalization lasted almost four months she died.

By the first physical examinations the child was interested by episodes of sudden falls during walking without loss of consciousness, head drop attacks of short duration (1-2 episodes/day) and sporadic loss of trunk control, prior to the appearance of episodes of seizure. The patient had been under a not effective therapy of sodium valproate and ethosuximide for controlling myoclonus, presenting a marked increase of episodes of seizure (50 episodes/day).

The EEG after admission documented the presence of widespread paroxysmal polyphasic slow waves during sleep ranging from 3 to 4 s in duration associated to axial atonies and massive myoclonus, with no improvement under administration of Frisium 7.5 mg during EEG recording. Following the first investigations, a presumptive diagnosis of "status epilepticus" was established and benzodiazepine (Midazolam) 2 g/kg/min was added to the current therapy.

Sudden the child felt in a sleepy and drowsy state with persistence of critical episodes characterized by myoclonus segmental distal of upper limbs and face, and atonies of head and trunk. Because of the increasing of episodes of myoclonus, the therapy was supported with rufinamide (100 mg x 2/day).

To investigate the causes of neurological symptoms, a cerebrospinal fluid (CSF) sample was collected. Molecular tests for Cytomegalovirus, EBV, Herpes Simplex and Enterovirus were negative; albumin was 129 mg/dL (normal: 140-200 mg/dL) and immunoglobulin G (IgG) was 150 mg/L (normal: 20-40 mg/L), no oligoclonal bands were identified and protein electrophoresis showed an increase of monoclonal components of the immunoglobulins IgG Lambda and Kappa. The patient underwent a therapy with immunoglobulins (0.4 g/kg/die) but without any neurological improvement.

Despite several changes and adjustments in the therapy, after a month of hospitalization a particularly marked deterioration of overall clinical condition occurred together with a progressive reduction in the level of consciousness and response to external stimuli to a level of Glasgow Coma Scale of 3-4, which reached level 1 the following month. Repeat lumbar puncture was performed and high level of anti-measles IgG, not tested in the first CSF sample, was measured in the second CSF. Then, also high level of neutralizing antibodies (titer 1:2560) to measles virus were also detected in serum, even if the patient had no a documented history of measles.

Brain magnetic resonance imaging (MRI) examination of the skull and spinal in T2-weighetd and FLAIR images performed after the admission showed tenuous hyperintensity of the white matter bilaterally with non-specific meaning, probably referring to areas of terminal myelination. It revealed a small amount of spilling in the right mastoid and the thickening of soft-tissue of the nasopharynx. An additional MRI was performed twenty days after the first.

The radiological pattern was indicative of a suffering and bilateral diffuse parenchymal abnormalities and the hippocampal alterations. These alterations caused neuronal hyperactivation phenomena which were expression of epileptic status.

On the basis of clinic, instrumental and laboratory data a diagnosis of SSPE post-measles was established and an antiviral therapy included isoprinosine (100 mg/kg/day) and lamivudine (10 mg/kg/day) and subcutaneous interferon alpha-2a (10 mU/m2/three times a week) was added to the symptomatic supportive care but soon suspended because the onset of thrombocytopenia.

The evolving EEG pattern revealed widespread slow activity and appearing of polyphasic slow-waves followed by brain electrical activity depression with a pseudo periodic trend, associated to blinking and spams.

Neurological and systemic state worsened with frequent vomiting, fever and electrolyte disorders and the patient showed a progressively worsening, until the patient presented hypotension, a severe metabolic acidosis, hypothermia (34 °C), anuria and bradycardia that led to the death.

A postmortem examination was performed. Brain biopsy of white and gray matter preserved in formalin were specifically threated and total RNA was extracted. Specific PCR assay was performed to detect measles genome but no RNA was detected.

DISCUSSION

Measles is a highly contagious infectious disease whose complications account for nearly half of the 1.6 million deaths caused by vaccine-preventable diseases every year worldwide [14]. The incidence of SSPE has been calculated to be between 4 and 11 cases per 100 000 cases of measles but reported rates of SSPE tend to be much lower [15, 16].

Cases of SSPE similar to that described above have been reported: such cases are likely to be associated with the delay in diagnosis, resulting in unnecessary diagnostic and therapeutic interventions [17].

In the case described above symptoms were of rapid progression. In the early stage of the disease the patient manifested progressive balance deterioration, axial atonies and massive myoclonus. The EEG pattern was characterized by epileptiform abnormalities such as generalized slow paroxysmal activity with polyphasic spike-wave complexes during sleep. Myoclonous and atonies were further recorded in association to slow wave polyphasic complexes.

During few weeks the general picture worsened, leading the child to death after 4 months. The patient had no history of measles-like illness, actually it remain unknown how much time has elapsed from the infection to the onset of neurologic disease. Moreover, no vaccination anti-measles had be administered to the child in infancy or early childhood. Although, serological profile

shows a previous measles infection in absence of vaccination, and the high measles IgG titer is suggesting of reinfection or reactivation of the virus. Moreover, MRI scans show data compatible with a SSPE disease. The characteristic symptomatology, the specific MRI patterns, and elevated titers of measles antibodies in the CSF and the serum samples were strong for the conclusive diagnosis of SSPE syndrome.

The clinical case described highlights the importance of measles vaccination: despite the development of an effective vaccination, measles continues to take the lives of hundreds of thousands of children worldwide each year.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 3 October 2016.
Accepted on 21 March 2017.

REFERENCES

1. Klein de Licona H, Bonthius DJ. Measles. In: Biller J (Ed). *Interface of neurology and internal medicine*. Philadelphia, PA: Lippincott, Williams &Wilkins; 2007. p 877-83.
2. Bonthius DJ, Stanek N, Grose C. Subacute sclerosing panencephalitis, a measles complication, in an internationally adopted child. *Emerging Infect Dis* 2000:6:377-81. DOI: 10.3201/eid0604.000409
3. Garg RK. Subacute sclerosing panencephalitis. *J Neurol* 2008;255(12):1861-71. DOI: 10.1007/s00415-008-0032-6
4. Gershon AA. Chickenpox, measles and mumps. In: Remington JS, Klein JO (Eds). *Infectious diseases of the fetus and newborn infant*. Philadelphia, PA: WB Saunders; 1995. p. 565-618.
5. Modlin JF, Halsey NA, Eddins DL, Conrad JL, Jabbour JT, Chien L, Robinson H. Epidemiology of subacute sclerosing panencephalitis. *J Pediatr* 1979;94:231-6.
6. Barram TZ, Gonzalez-Gomez I, Xie ZD, *et al*. Subacute sclerosing panencephalitis in an infant: diagnostic role of viral genome analysis. *Ann Neurol* 1994;36:103-8.
7. Zwiauer K, Forstenpointner E, Popow-Kraupp T, Hauser E, Jellinger KA. Rapid progressive subacute sclerosing panencephalitis after perinatally acquired measles virus infection. *Lancet* 1995;345:1124.
8. Cape CA, Martinez AJ, Robertson JT, Hamilton R, Jabbour JT. Adult onset of subacute sclerosing panencephalitis. *Arch Neurol* 1973;28:124-7.
9. Bonthius DJ, Stanek N, Grose C. Subacute sclerosing panencephalitis, a measles complication, in an internationally adopted child. *Emerging Infect Dis* 2000:6:377-81. DOI:10.3201/eid0604.000409
10. Babu RB, Biswas J. Bilateral macular retinitis as the presenting feature of subacute sclerosing pan encephalitis. *J Neuroophthalmol* 2007;27:288-91. DOI: 10.1097/WNO.0b013e31815b98e6
11. Dyken PR. Subacute sclerosing panencephalitis: current status. *Neurol Clin* 1985;3:179-96.
12. Gascon GG. Subacute sclerosing panencephalitis. *Semin Pediatr Neurol* 1996;3:260-9.
13. Mustafa MM, Weitman SD, Winick NJ, Bellini, WJ, Timmons CF, Siegel JD. Subacute measles encephalitis in the young immunocompromised host. Report of two cases measles virus and associated central nervous system 113 diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. *Clin Infect Dis* 1993;16:654-60.
14. Katz SL. A vaccine-preventable infectious disease kills half a million children annually. *J Infect Dis* 2005;192:1679-80. DOI: https://doi.org/10.1086/497172
15. Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. *Int J Epidemiol* 2007;36:1334-48. DOI: 10.1093/ije/dym207
16. Bellini WJ, Rota JS, Lowe LE, Katz RS, Dyken PR, Zaki SR, Shieh WJ, Rota PA. Subacute sclerosing panencephalitis. More cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* 2005;192:1686-93. DOI: 10.1086/497169
17. Goraya J, Marks H, Khurana D, Legido A, Melvin J. Subacute sclerosing panencephalitis (SSPE) oresenting as acute disseminated encephalomyelitis in a child. *J Child Neurol* 2009;24(7):899-903. DOI: 10.1177/0883073808330184