

# Autism Spectrum Disorder Secondary to Enterovirus Encephalitis

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Filipa Marques, MD<sup>1</sup>, Maria João Brito, MD<sup>1</sup>, Marta Conde, MD<sup>1</sup>,  
Mónica Pinto, MD<sup>2</sup>, and Ana Moreira, MD<sup>3</sup>

## Abstract

Millions of children are infected by enteroviruses each year, usually exhibiting only mild symptoms. Nevertheless, these viruses are also associated with severe and life-threatening infections, such as meningitis and encephalitis. We describe a 32-month-old patient with enteroviral encephalitis confirmed by polymerase chain reaction in cerebrospinal fluid, with unfavorable clinical course with marked developmental regression, autistic features, persistent stereotypes and aphasia. She experienced slow clinical improvement, with mild residual neurologic and developmental deficits at follow-up. Viral central nervous system infections in early childhood have been associated with autism spectrum disorders but the underlying mechanisms are still poorly understood. This case report is significant in presenting a case of developmental regression with autistic features and loss of language improving on follow-up. To our knowledge, this is the first published report of enterovirus encephalitis leading to an autism spectrum disorder.

## Keywords

enterovirus, encephalitis, children, autism spectrum disorder

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Enteroviruses are ubiquitous pathogenic agents, whose only hosts are human.<sup>1,2</sup> Most manifestations of nonpolio enterovirus illnesses are mild and include upper respiratory infections; hand, foot, and mouth disease; herpangina; pleurodynia; and fever with rash or myalgias and malaise.<sup>1-3</sup> Despite their protean clinical presentation and known neurotropism, a symptomatic infection of the central nervous system is not the rule.<sup>1-4</sup> Enteroviruses are responsible for 5% to 10% of encephalitis.<sup>3</sup> Fatal or long-term complications of central nervous system infections may occur rarely in patients with impaired humoral immunity and early childhood.<sup>4,5</sup> Furthermore, except for highly pathogenic viruses, such as enterovirus 71, that usually do not circulate in Europe, most cases of children with enterovirus encephalitis recover completely.<sup>6,7</sup>

The pathogenesis of enterovirus encephalitis is diverse and incompletely understood. Upon viral infection, the immune response leads to the production of various cytokines. The clinical presentation of enterovirus encephalitis seems to be caused by a hyperinflammatory syndrome resulting from hypercytokinemia and central nervous system inflammation of various inflammatory mediators.<sup>7-9</sup>

Long-term complications include neurologic sequelae, neurodevelopment delay, reduced cognitive functioning, and learning and behavioral problems.<sup>8,9</sup> Viral central nervous system infections during early life adversely affect brain development and have been suggested to play a role in the development of

autism spectrum disorders.<sup>5,9-11</sup> We report a patient with enterovirus encephalitis who after the acute episode has come to manifest developmental language regression with autistic features, irritability, and stereotypes, an association not previously described.

## Case Report

A previously healthy 32-month-old girl presented to the emergency department with fever (39°C) and vomiting. Parents reported bilateral limb movements and hypotonia with stool discharge. She had no rash, upper respiratory tract signs, or other symptoms. Her former global development, including language and communication, was adequate. The general physical examination was normal and meningeal signs were negative.

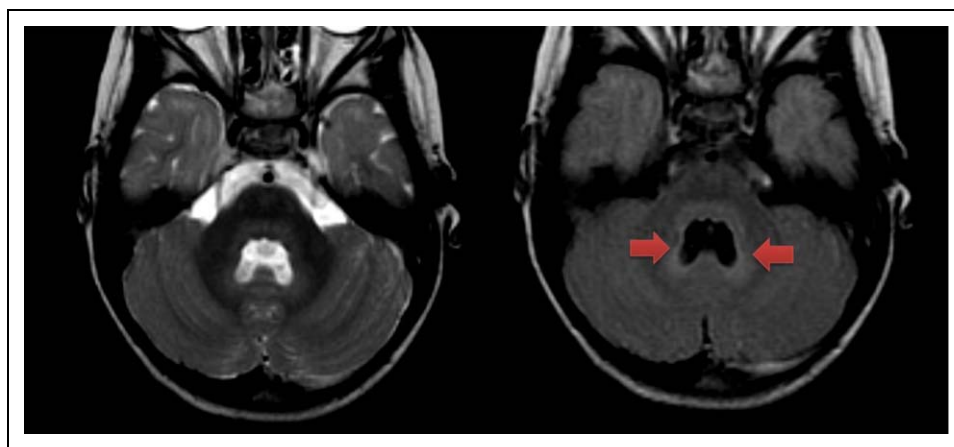
<sup>1</sup> Infectious Diseases Unit, Hospital Dona Estefânia, Centro Hospitalar Lisboa Central-EPE, Lisbon, Portugal

<sup>2</sup> Child Development Centre, Hospital Dona Estefânia, Centro Hospitalar Lisboa Central-EPE, Lisbon, Portugal

<sup>3</sup> Paediatric Neurology Unit, Hospital Dona Estefânia, Centro Hospitalar Lisboa Central-EPE, Lisbon, Portugal

## Corresponding Author:

Filipa Marques, MD, Infectious Diseases Unit, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central – EPE, Rua Jacinto Marto, 1169-045 Lisboa, Portugal.  
Email: filipa3marques@gmail.com



**Figure 1.** First brain magnetic resonance imaging (MRI) performed. Axial T2-weighted images demonstrate hyperintense signal on brain stem, posterior portion of the pons, medium cerebellar peduncle, and cerebellar medullar centers. This ring image around the fourth ventricle is typical of enterovirus encephalitis.

A few hours after admission, she showed somnolence and irritability when awake and hallucinations, and her balance was impaired when trying to walk. During the following days, she became lethargic, with choreic movements, orofacial dyskinesia, and eye movements. She also had loss of speech, eye contact, and sphincter control.

Head computed tomography on admission was normal. Toxic screen was negative. Cerebrospinal fluid analysis revealed 16 cells (50% polymorphonuclear); glucose 53 mg/dL; and proteins 31.7 mg/dL. Laboratory studies showed a white blood count of  $19.9 \times 10^3/\mu\text{L}$  (75.1% segmented neutrophils), C-reactive protein 10.6 mg/dL, aspartate aminotransferase 376 U/L, alanine aminotransferase 385 U/L, creatine kinase 700 U/L, creatine kinase-MB 203 U/L, fibrinogen 537 mg/dL, D-dimers 394 ug/L, prothrombin time 14.1 seconds, International Normalized Ratio 1.3, and activated partial thromboplastin time 31.6 seconds. Streptococcal antigen test was also negative. Serum and cerebrospinal fluid lactate and ammonia were normal.

She started acyclovir, ceftriaxone, and ciprofloxacin, which were subsequently suspended. She also had phenytoin plus phenobarbital, as the limb movements were suspected to have an epileptic origin, but these were also discontinued. Electroencephalogram exhibited diffuse background slowing, without epileptic activity.

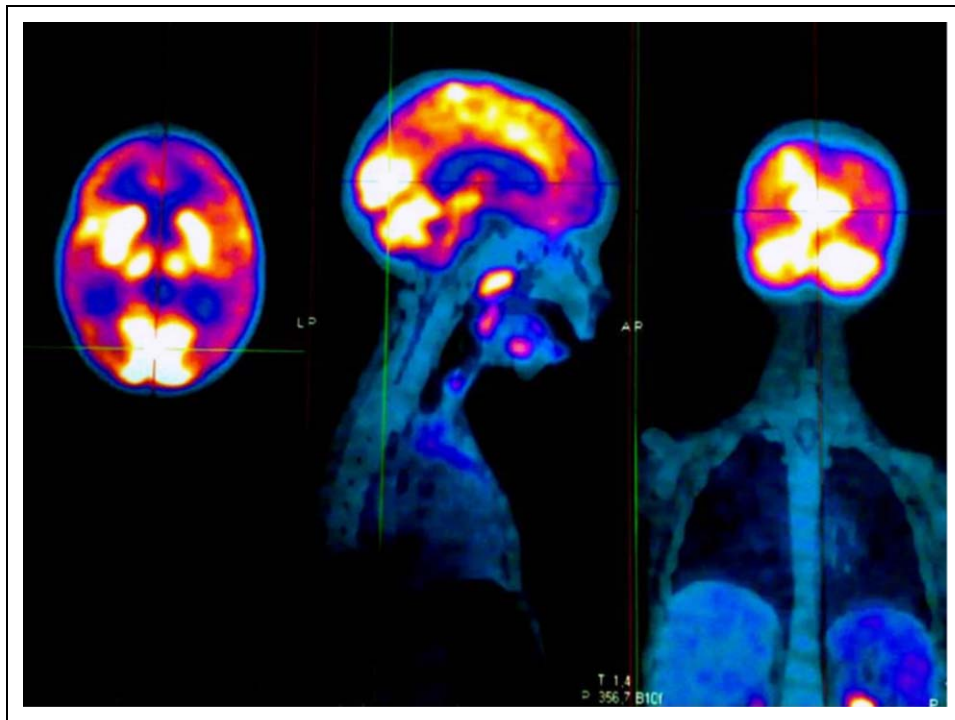
Cerebrospinal fluid bacterial (including *Listeria monocytogenes*) and viral cultures were negative. A polymerase chain reaction (PCR) assay for herpes virus (HSV1, HSV2, HHV3, HHV4, HHV5, HHV6, HHV7) was negative. PCR assay for other viral (human immunodeficiency virus [HIV], parvovirus, adenovirus, arbovirus) and bacterial (*Coxiella burnetii*, *Mycobacterium tuberculosis*, *Mycoplasma* sp, *Chlamydia* sp, *Borrelia burgdorferi*, *Bartonella* sp, *Rickettsias* sp) causes was negative. Cerebrospinal fluid electroimmunoassay revealed IgG oligoclonal bands. Evaluation for other infectious agents (bacterial, fungal, and viral sources, including serologies) and autoimmune etiologies, including anti-ganglioside, anti-NMDAR, and anti-VGKC antibodies were negative.

Brain magnetic resonance imaging (MRI) showed hyperintense signal on T2-weighted images in brain stem, posterior portion of the pons, medium cerebellar peduncle and cerebellar medullar centers (around the fourth ventricle; Figure 1), described as typical aspects of enterovirus encephalitis. Enterovirus PCR was positive (cerebrospinal fluid and stool). No enterovirus serotype was identified on cerebrospinal fluid and stool specimen cultures, despite enterovirus growth in culture medium.

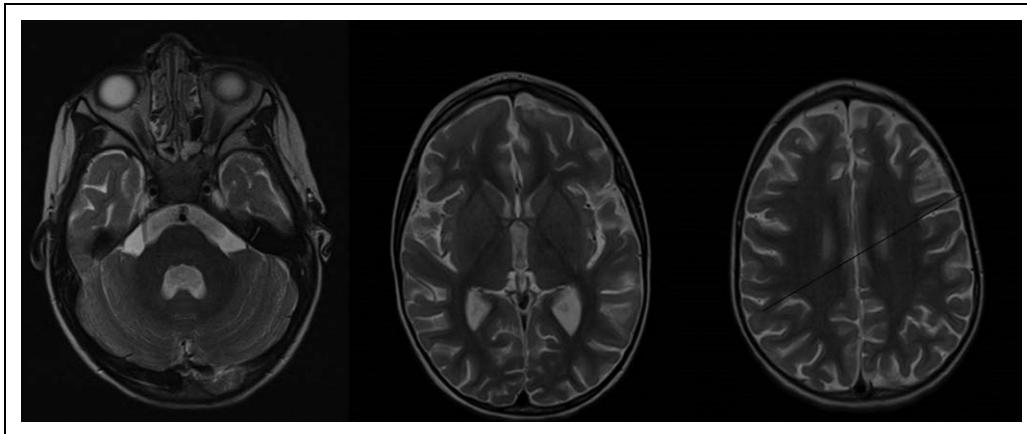
On hospital day 16, she became more alert and was able to walk with good balance; however, she did not react to her name, did not say any words, and had no eye contact and no sphincter control. She was hyperactive and had self-mutilation. Hand stereotypes and choreic movements persisted and she had body rocking repetitive movements. A second lumbar puncture was performed and revealed no cells. Enterovirus PCR in cerebrospinal fluid was negative. Cerebrospinal fluid electroimmunoassay was similar to the previous one. Single-photon emission computed tomography (SPECT) disclosed marked asymmetric heterogeneity on supratentorial areas with low uptake in both frontal and left parietal lobes and larger uptake in right parietal lobe. Temporal lobes uptake was symmetrical (Figure 2). Visual evoked potentials revealed right prechiasmatic perturbation. Another Brain MRI showed an enlargement of liquor spaces (more pronounced on the supratentorial areas), diffuse cerebral cortex atrophy, and a subtle T2 hyperintense signal on posterior pons, medium cerebellar peduncle, and cerebellar medullar centers (Figure 3).

On day 19, because of this unfavorable outcome, she received 2 doses of intravenous immunoglobulin (1 g/kg) and a 5-day course of methylprednisone (30 mg/kg), with slight clinical improvement. Humoral and cellular immunologic studies were also normal.

At discharge, on day 31, she maintained developmental regression with autistic features, self-mutilation, and persistent stereotypes. However, she had improved language, had some nonfunctional words, responded to name, had some eye contact, and explored objects in a more functional way. A formal



**Figure 2.** Single-photon emission computed tomography. Images demonstrate marked asymmetric heterogeneity on supratentorial areas with low uptake in both frontal and left parietal lobes and larger uptake in right parietal lobe. Temporal lobe uptake was symmetrical.

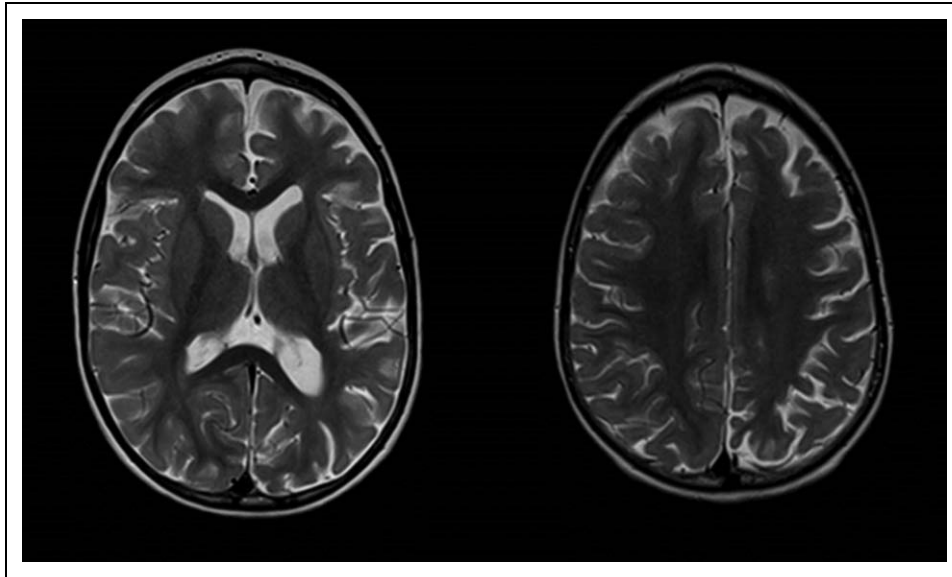


**Figure 3.** Second brain magnetic resonance imaging (MRI) performed. Images demonstrate diffuse cerebral cortex atrophy and a subtle T2 hyperintense signal on posterior pons, medium cerebellar peduncle, and cerebellar medullar centers.

development evaluation (Griffiths Mental Development Scale) showed a general development quotient of 30, corresponding to a 10-month mental age. She was started on an early intervention program, including speech and language therapy and occupational therapy. Three months after discharge, she had improved language skills, more words, and was more responsive to interaction but did not initiate social interaction with others. Her eye contact had improved but was still avoidant. She showed some functional play and use of objects but still had some stereotyped movements and repetitive behaviors. She regained sphincter control. Nine months after discharge, she

had made major improvements in all areas and had a general development quotient of 53, corresponding to a mental age of 21 months. She still had some problems in social interaction and reciprocal speech and showed some need for sameness and repetitive behaviors but much less self-mutilation, and better eye contact was present. This met criteria for an autistic spectrum disorder but showed much improvement with intervention.

A brain MRI performed at that time revealed asymmetric atrophy of cerebral cortex with left predominance, hyperintense signal on fluid-attenuated inversion recovery-weighted images in the left posterosuperior temporal area, and parietal lobe



**Figure 4.** Third brain magnetic resonance imaging (MRI) performed. Images demonstrate asymmetric atrophy of cerebral cortex with left predominance, hyperintense signal on fluid-attenuated inversion recovery–weighted images in the left posterosuperior temporal area, and parietal lobe transition and a subtle hyperintense signal on T2-weighted images in supratentorial areas.

transition and a subtle hyperintense signal on T2-weighted images in supratentorial areas (Figure 4).

In the last formal development evaluation, 17 months after discharge (5 years old/61 months old), she continued to show major improvement in interaction and language skills, with only residual repetitive behaviors and on the Griffiths Mental Development Scale showed a general development quotient of 81.65, corresponding to a 4-year mental age (50 months old).

## Discussion

This is the first published case of enterovirus encephalitis leading to developmental regression with autism spectrum disorder and correlating these 2 distinct entities. Enterovirus encephalitis usually has a benign course. Unusual complication can occur in children with risk factors for chronic sequelae. In patients with altered immunity, enterovirus infections are known to lead to a chronic enterovirus encephalitis syndrome, which can be fatal.<sup>3,5</sup> In addition, early childhood infection with enteroviruses can result in significant morbidity and mortality,<sup>1,12</sup> and central nervous system infections within the first 2 years of life may lead to permanent neurologic deficits.<sup>5</sup> In this patient, chronic enterovirus encephalitis syndrome, primary immunodeficiency, immune-mediated encephalitis, as well as metabolic and genetic disorders were excluded. At follow-up, only a mild developmental deficit persisted.

The laboratory and imaging studies did not predict a poor outcome. This patient had very discrete pleocytosis and normal cerebrospinal fluid protein values with a positive enterovirus PCR (stool and cerebrospinal fluid). The degree of clinical or biochemical severity of encephalitis does not necessarily correlate with the central nervous system abnormalities.<sup>13,14</sup> Patients with encephalitis usually reveal pleocytosis with mononuclear

cell predominance and an elevated protein level, but values can be normal in approximately 3% to 5% with severe viral encephalitis, including enterovirus encephalitis.<sup>12-14</sup>

Diagnosis of enteroviral infection by viral culture is limited by a sensitivity of 65% to 75%, their serotypic diversity, prolonged time for incubation, and high level of technical expertise required.<sup>15,16</sup> In contrast, PCR test for enterovirus in cerebrospinal fluid has a sensitivity of 86% to 100% and a specificity of 94% to 97% versus viral culture.<sup>14-16</sup> These diagnostic difficulties are illustrated in our case in which the PCR test for enterovirus in cerebrospinal fluid and stools were positive; however, serotype enterovirus could not be isolated in cell culture. Thus, it may well have been a serotype that usually does not circulate in Europe and therefore could not be identified in available kits.

A study of the MRI findings in a Taiwanese outbreak of enterovirus encephalitis<sup>12</sup> demonstrated a pattern of major central nervous system lesions in the brain stem, midbrain, medulla oblongata, pons, and the dentate nuclei of the cerebellum, with some cases involving the spinal cord and thalamus. These imaging characteristics showing a hypodense ring around the fourth ventricle were felt to be diagnostic of enteroviral encephalitis.<sup>17</sup> The first MRI of the patient we describe was consistent with these imaging studies and guided us to the etiologic diagnosis. The second MRI showed a more diffuse involvement of supratentorial structures with cortical atrophy and a third MRI, 9 months after discharge, showed frontal cortical atrophy predominant on the left side as well as hyperintense images on left superior temporal and parietal lobe. The progression and distribution of lesions on MRI scans in our patient seemed to correlate well with clinical severity in the acute phase of the disease.

At follow-up, patients with mild symptoms had no neurologic sequelae, and the lesions within brain stem became small or

vanished in most cases. In the majority of patients with severe disease, neurologic sequelae could be found and the involvement of the ventral horns of the spinal cord and supratentorial areas are typical. In children with persistent signs of brain stem dysfunction, areas of brain stem and spinal cord are usually atrophic.<sup>17,18</sup> These findings, present in our patient MRI, are normally described in severe enterovirus encephalitis, like enterovirus 71 encephalitis, although the clinical presentation and course of our patient does not suggest this etiology.

Brain SPECT has been reported to be a useful tool for the diagnosis and follow-up of patients with viral encephalitis. Generally, focal hypoperfusion on brain SPECT may reflect either a decreased metabolic demand in the condition of neuronal loss or cerebral ischemia caused by vascular changes in the large cerebral arteries and cerebral microvessels. Focal hypoperfusions after the acute phase are associated with poorer neurologic outcomes.<sup>19</sup> In our patient, hypoperfusion images in both frontal lobes and left parietal lobe in the acute phase were in agreement with the second and third MRI images.

Autism spectrum disorders are common neurodevelopment disorders characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted, stereotyped interests and behaviors.<sup>10,20</sup> Autism is most likely the result of multiple etiologies with genetic and environmental contributions.<sup>21</sup> One proposed etiology for autism is prenatal or early infantile viral infections.<sup>21</sup> Autism spectrum disorders may be caused by autoimmunity to the brain possibly triggered by a viral infection. This hypothesis is supported by a positive correlation among brain autoantibodies, viral serology findings, and elevated proinflammatory cytokine levels.<sup>11</sup> Through receptor-mediated events, cytokines substantially affect immune and cerebrospinal fluid cells. For instance, cytokines such as interleukin (IL)-1, IL-2, and IL-6 have been shown to alter neuronal release of dopamine, acetylcholine, serotonin, and norepinephrine in the hippocampus and other brain regions.<sup>21</sup>

An acute infection could lead to transient levels of cytokines without viral persistence, or infection could instigate an autoimmune process resulting in chronically elevated cytokine production. A persistent viral infection could also lead to chronically elevated cytokine levels. Abnormal brain cytokine levels have been associated with altered central nervous system development.<sup>21</sup>

Frontal and temporal lobes also play a role in the genesis of autism.<sup>22,23</sup> Language and executive functions as well as the ability of reading other people's mental status, the so-called theory of mind, seem to need structural and functional integrity in these areas. Genetic and environmental factors, such as infections, can cause impairment in this neuronal network.<sup>22</sup>

A Swedish cohort study revealed that serious viral central nervous system infections during childhood appear to be associated with the later development of schizophrenia and nonaffective psychoses, such as autism spectrum disorders.<sup>5</sup> Concerning specific infectious agents, they found that the risk for nonaffective psychoses was related to central nervous system infections by the mumps virus (risk ratio = 2.7, 95%

confidence interval = 1.2-6.1) or cytomegalovirus (risk ratio = 16.6, 95% confidence interval = 4.3-65.1). Some authors showed close relationship between autism and herpes encephalitis.<sup>20-22,24</sup> Libbey, Gillberg and Ghaziuddin described previous normal children who showed autistic features after the disease, some of whom never recovered,<sup>21,23,24,25</sup> although to our knowledge there are no previous studies linking autism spectrum disorder to enterovirus encephalitis.

Enterovirus encephalitis in early childhood has been associated with behavioral and psychotic disorders. The Swedish cohort study identified 3319 enterovirus encephalitis (50.7%) and only 3 of them developed a psychotic illness (schizophrenia). Enterovirus encephalitis was not associated with the later development of nonaffective psychotic illness in this study (risk ratio = 1.0, 95% confidence interval = 0.4-2.1).<sup>6</sup> Some serotypes, such as enterovirus 71, are associated to severe disease and outcome and an increased prevalence of hyperactivity/impulsivity and attention deficit/hyperactivity.<sup>6</sup>

Another proposed etiology for autism is inborn errors of metabolism: this can account for less than 5% of individuals. Several metabolic disorders have been associated with autistic symptoms. These include phenylketonuria, histidinemia, creatine deficiency syndromes, adenylosuccinate lyase deficiency, 5'-nucleotidase superactivity, and metabolic purine disorders. Mitochondrial disorders can also present with features of autism.<sup>26</sup>

The undetected phenylketonuria is nowadays rare in industrialized countries practicing newborn screening. Clinical manifestations appear early in life and untreated children progress to severe mental retardation.<sup>26,27</sup> Autistic traits associated with behavioral disorders may be the initial symptoms in classical homocystinuria. In general, the clinical picture is enhanced by a suite mental retardation of varying severity and/or dislocation of the lens and/or musculoskeletal abnormalities. Some diseases of urea cycle can begin by excess recurrent unexplained behavior problems with autism signs. As a rule, these symptoms do not remain isolated and are associated with hepatodigestive and/or neurologic symptoms caused by hyperammonemia. Sanfilippo disease or mucopolysaccharidosis III is a nontreatable lysosomal storage disease. So far, the first manifestations may be limited to autism with behavioral disorders. This then moves slowly to progressive encephalopathy with psychomotor regression convulsions and spastic tetraparesis. Retractions of joint, minimal facial features and cutaneous abnormalities are often associated. Creatine deficiencies are disorders recently described, associating variably severe mental retardation, autistic traits, behavioral signs, and epilepsy.<sup>27</sup> Autism is sometimes observed in some organic acidurias, especially propionic aciduria. Finally, purine metabolism disorders, the Smith Lemli Opitz syndrome (abnormal cholesterol synthesis), succinic semialdehyde dehydrogenase deficiency, and some cases of mitochondrial diseases have also been linked to autism.<sup>27,28</sup>

A systematic investigation of metabolic disorders associated to autism is necessarily incomplete and very often negative if not oriented by clinical suspicion and so should not be performed. A more rational approach is to recommend a metabolic

investigation in each case, taking into account clinical data for each patient.<sup>27</sup>

Our patient was previously healthy, with adequate psychomotor development until this infectious episode. Additionally, newborn screening and metabolic tests performed on the admission were negative (normal values for ammonia and lactate) and MRI images do not suggest metabolic disorders. Finally and most importantly, she had a favorable outcome with improvement in all skills and development quotient enhancement. These features do not support an inborn error of metabolism, which are characteristically progressive and lead to severe mental retardation.

This case describes the emergence of massive regression, autistic features, and recovery in a previously healthy youngster following an episode of enterovirus encephalitis. It provides further evidence that autistic symptoms as well as loss of other developmental skills can emerge following an external event such as an infection. The role played by disturbance caused by infection in frontal and temporoparietal left lobes network seems clear.<sup>22</sup> To our knowledge, there are no other published studies linking this possible association between enterovirus encephalitis and massive regression and autistic features, with good recovery in a 2-year period.

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## Author Contributions

FM undertook data collection, drafting of the manuscript, and literature research. All authors took responsibility for the care and treatment of the patient during hospitalization. MJB, MC, MP, and AM critically revised the manuscript for intellectual content. MJB and AM gave final approval of the version submitted for publication

## Declaration of Conflicting Interests

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## Ethical Approval

This case report was appreciated and approved for publication by the Ethics Committee of Dona Estefânia Hospital, Lisbon.

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