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Pediatric neurolisteriosis: a diagnosis to consider even in the absence of immunodeficiency

Short title: Neurolisteriosis also affects immunocompetent children

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ABSTRACT

Neurolisteriosis is known to affect vulnerable groups for example, neonates or children with immunodeficiency. This is a key point of the current clinical guidelines regarding pediatric meningitis. We report a rare case of neurolisteriosis in an immunocompetent infant, without the typical signs of listeriosis, which led to a delay in administering the appropriate antibiotherapy. This case illustrates the clinical heterogeneity of neurolisteriosis and the relevance of appropriate polymerase chain reaction (PCR) tests when the clinical presentation differs from the current guidelines. This case also reminds us that raw or unpasteurized milk-based food products pose a risk even in immunocompetent infants or children.

KEY WORDS: listeria; meningitis; neurolisteriosis; PCR multiplex

1/ INTRODUCTION

Listeria monocytogenes (*L. monocytogenes*) is a Gram-positive bacillus transmitted via ingestion of contaminated food, causing lymphocytic meningoencephalitis leading to an uncertain outcome with high morbidity and substantial mortality (20–30%) [1].

Neurolisteriosis is known to affect vulnerable groups, for example, neonates or people who are immunodeficient. In immunocompetent patients, the diagnosis is frequently underestimated. Subsequently, the appropriate treatment is often delayed, which may lead to a poor outcome [1].

We report a rare pediatric case of neurolisteriosis in a 15-month-old immunocompetent infant. This case illustrates the clinical heterogeneity of neurolisteriosis and the relevance of appropriate polymerase chain reaction (PCR) tests when the clinical presentation differs from the current guidelines.

2/ OBSERVATION

A 15-month-old infant was admitted to the emergency room for febrile seizures in the context of acute otitis media treated with cefpodoxime for 24 h. Physical examination revealed a meningeal syndrome without purpura. Lumbar puncture (LP) showed a cloudy cerebrospinal fluid (CSF) with biological meningitis and a biological inflammatory syndrome (CSF: 1,250 leukocytes/mm³ with 74% neutrophils, glycorrachia 3.7 mmol/L, protein level 0.53 g/L; blood: C-reactive protein: 80 mg/L, leukocytes : 34.17 g/L, with 77% neutrophils). CSF quantitative PCR tests were negative for meningococcus, pneumococcus, bacterial DNA, herpes simplex virus (HSV), and enterovirus. A CSF culture was sterile. The initial intravenous antibiotic treatment (100 mg per kg per day [mg/kg/d] ceftriaxone, 5 mg/kg/d gentamicin, and 250 mg/m²/8 h acyclovir) was ineffective. Cerebral computed tomography scans were normal on day 3. On day 5, there was neutrophilic meningitis with negative results from a direct CSF examination along with an inflammatory syndrome. CSF culture and PCR results for HSV and enterovirus remained negative. The therapy was adapted to 300 mg/kg/d cefotaxime and 50 mg/kg/d vancomycin, which was rapidly followed by clinical improvement and a marked decrease in the signs of inflammatory syndrome.

However, on day 22, there was a relapse of febrile meningeal syndrome with increased inflammatory response. A third LP showed lymphocytic meningitis, again with negative results of the direct CSF examination. Magnetic resonance imaging only showed leptomeningeal enhancement. The last CSF culture was finally positive for *L. monocytogenes*. Listeria PCR test results, performed after the diagnosis, on the first CSF sample were consistently positive. Antibiotic treatment was adapted to 200 mg/kg/d amoxicillin for 21 days and 5 mg/kg/d gentamicin for 5 days. Clinical and biological improvement was rapid after 2 days accompanied by apyrexia and normalization of the

clinical state. The patient recovered fully with normal clinical, sensory, and neurophysiological outcome 6 months later. Retrospectively it was revealed that the infant consumed cheese made from unpasteurized milk 1 month earlier. This infant had no previous medical history and further immunological testing did not reveal any deficiency. In particular, there was no T or B cell deficiency and no immunoglobulin deficiencies. Moreover, the specific immune response was evaluated via vaccine responses, which were normal. Furthermore, secondary immunodeficiency due to HIV infection was excluded via HIV serology tests. Finally, the patient's development is still good after more than 4 years of follow-up without any serious infections.

3/ DISCUSSION

We report the case of *L. monocytogenes* meningoencephalitis in a 15-month-old immunocompetent infant. This case highlights that neurolisteriosis may be contracted after the neonatal period, even in immunocompetent children, and that a nonspecific clinical presentation requires PCR testing to allow for early and appropriate treatment.

Neurolisteriosis is not limited to vulnerable patients, i.e., neonates or people with immunodeficiency. According to the latest meta-analysis, the estimated number of cases of listeriosis was 23,150 worldwide in 2010, from newborns to the elderly [1]. Of all patients, 79.3% (75.4–83.3) were not in the perinatal age group, among which 30.7% (26.9–34.6) cases resulted in central nervous system infections. Of these patients with neurolisteriosis, 13.7% (2.4–25.1) developed neurological sequelae and 25.9% (21.9–29.9) of the non-perinatal patients died.

Although certain hyperspecialized immunoassays were been performed, we assume that the infant in our case report does not suffer from any immune deficiency. The control of listeria infection is dependent on both innate and adaptive immune responses. Nevertheless, innate

1 responses are the first and probably the most important responses after listeria exposure [2].
2 In particular, phagocytic disorders can cause a sensitivity to listeria infections. In the present
3 case, we did not examine the innate immune responses because the symptoms, the context,
4 and the progression did not suggest phagocytic disorders and because these are not first-line
5 examinations.

6 Furthermore, a deficiency of the adaptative immune response as in combined
7 immunodeficiencies was ruled out for several reasons. First, combined immunodeficiencies
8 are not usually associated with listeria infection [2]. The symptoms of combined
9 immunodeficiencies are characterized by an early onset (first week or month of life) with
10 severe infections such as chronic diarrhea and interstitial pneumonia in the context of growth
11 failure. The infant in the present case report was 15 months old when she was admitted for
12 meningitis, without any previous medical history of infection. Moreover, the first
13 immunologic analysis of this patient did not reveal any T or B cell or immunoglobulin
14 deficiencies. Finally, the specific immune response was evaluated by vaccine responses,
15 which were normal; however, T or B cell function was not studied because it was not
16 justified in this context.

17 Secondary immunodeficiency, such as HIV infection, was also excluded.

18 To conclude, the patient's favorable outcome without any serious infection over the follow-up
19 period of more than 4 years has allowed us to rule out the diagnosis of severe immune
20 deficiency.

21 In France, between November 2009 and July 2013, 252 neurolisteriosis cases were identified
22 among the 818 listeriosis cases reported (30.8%) [3]. Also in France, from 2001 to 2006, *L.*
23 *monocytogenes* was responsible for 0.7% (18/2539 cases) of all the bacterial meningitis cases
24 in the 0- to 18-year-old population [4]. Noteworthy, only two children were immunodeficient
25 in all the neurolisteriosis pediatric cases [4]. Therefore, immunodeficiency is likely to be an

exception in the pediatric age, in contrast to what is known in adulthood and unlike previous reports [1, 4]. Thus, clinicians should be aware that listeriosis may occur in immunocompetent children and that the central nervous system is the preferred target of this microbial agent in nonvulnerable populations [5], as found in the present case.

As a foodborne infection, listeriosis represents a public health concern. However, sanitary food rules relate to a number of nonmedical issues. The American Academy of Pediatrics endorses a ban on cheese made from unpasteurized milk [6]. However, there are no specific guidelines in this regard in France, where consumption of unpasteurized-milk cheese is common during childhood. The role of the food product may be difficult to determine without bacteriological analysis. In our case, the consumption of high-risk food was identified but after a longer delay than the 14 days of incubation usually considered for neurolisteriosis, and the cheese presumably responsible for the infection was not analyzed.

Following the current guidelines, the clinical arguments for treating a case as neurolisteriosis is the progressive onset of febrile meningitis associated with rhombencephalitis and/or cerebellar syndrome [7]. As shown in the present case and in the latest French listeriosis prospective report, neurolisteriosis presentations may be subtler and often misleading [3]. Moreover, the first CSF analysis in our case revealed cloudy fluid with a predominance of neutrophils and not lymphocytes. Updated guidelines including these facts should promote an improved evidence-based therapeutic algorithm.

The present case shows that early diagnosis of listeria meningitis remains a challenge in childhood. In addition to a poorly specific clinical presentation, only two of the last 18 French pediatric reported cases had positive results on direct CFS analysis. For the others, diagnosis was made by CSF culture or listeria PCR [4]. The sensitivity of Gram-staining is below 50% for *L. monocytogenes*. In addition, CSF culture, despite being considered the reference method, suffers from a low sensitivity: It depends directly on the sample

1 transportation conditions and on the bacterial load, which may even be decreased by the
2 administration of antibiotics before LP [8]. Given such limitations, PCR for the *L.*
3 *monocytogenes* genome seems to be a particularly useful test [9]. Moreover, new multiplexed
4 nucleic acid tests (multiplex PCR) have now proven their significant efficacy in presumed
5 bacterial meningitis [10]. The use of such multiplex PCR in meningitis with negative
6 bacterial culture facilitated the diagnosis of neurolisteriosis in a recently reported case [11].
7 The current French guidelines recommend testing for listeriosis and tuberculosis in cases of
8 bacterial-like worsening meningitis under antibiotic treatment, especially when a second LP
9 shows features of bacterial meningitis [7]. In neurolisteriosis, the sooner the diagnosis is
10 made, the better the prognosis. Multiplex PCR, now available in most pediatric emergency
11 departments, is likely to reduce the delay to appropriate treatment and thereby improve the
12 outcome.

14 **4/ CONCLUSION**

15 Beyond neonates and vulnerable patient populations, listeria meningitis may occur in
16 immunocompetent children. It should be considered in every child presenting with aseptic
17 meningitis especially when appropriate antibiotic therapy fails to relieve the symptoms. The
18 clinical presentation of listeria meningitis has poor specificity. Specific PCR testing is the key
19 to rapid and appropriate therapeutic choices that will directly influence the prognosis.

21 **Conflicts of interest: none**

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