


A Case Report of *Listeria monocytogenes* Meningitis in a Child With Hyper-IgM Syndrome in a Resource-Limited Setting

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Background

Acute pyogenic bacterial meningitis is the predominant form of central nervous system infection seen in children in low- and middle-income countries. In these cases, there is a significantly high case fatality rate associated with the presence of opportunistic infections.¹⁻³ Isolation of *Listeria monocytogenes* from the cerebrospinal fluid (CSF) is considered an opportunistic infection when it occurs outside infancy.^{1,3} The persistence or recurrence of symptoms of meningitis in a child despite appropriate treatment also raises questions about the competence of host immune function. In such instances, evaluation of cell-mediated immune and humoral immune status of the patient should be considered.^{3,4}

Case Presentation

A 3-year-old boy presented at our children's emergency unit with a 4-day history of fever and multiple generalized tonic-clonic seizures. Seven weeks earlier, he had a history of similar symptoms for which he was treated with intravenous ceftriaxone for 10 days at an outlying hospital. Further details on initial episode of illness were not known. Resolution of fever was complete with no residual neurologic deficit. There was no previous history of seizures. Of note, one sibling was managed for acute diarrheal disease 2 days prior to the onset of the patient's initial presentation. The family does not have poultry or keep cattle but they have a cat as a pet. The child rarely consumes dairy products.

The patient had never received prior immunosuppressive drugs and had no previous history of malignancy. Parents reported that the child was apparently healthy with normal growth and development. He does not sweat excessively and had no skin rashes. The child did have a positive history of frequent upper respiratory tract infections occurring more frequently than his siblings and

often needed treatment with antibiotics when his siblings did not.

Examination findings at presentation included a febrile child (temperature = 39°C) with normal facies and no rash. He was conscious with modified Glasgow Coma Score of 13 (E4V4M5). Speech was normal, neck was supple, and there were no obvious cranial nerve deficits or focal neurological signs. Motor strength was 3/5 in all extremities, deep tendon reflexes were brisk (3+), with sustained ankle clonus, and tone was normal to high in the limbs. His gait was unsteady but Romberg was not done.

Laboratory workup revealed a hematocrit of 30% (reference, 1-5 years = 31% to 44%), white blood cell count of 9.9×10^3 cells/mm³ (reference, 1-5 years = 6.5-13.2 $\times 10^3$), lymphocytes count of 30%, absolute lymphocyte count of 2970 cells/mm³ (reference, 1-5 years = 3.1-9.0 $\times 10^3$) with an estimated CD4 >200, neutrophils count 67%, absolute neutrophils count was 6633 (reference, 1-5 years = 1.9-7.5 $\times 10^3$), and monocytes count 2%, absolute monocytes count of 198 (reference, 1-5 years = 0.1-0.5 $\times 10^3$).⁵ Retroviral screening test using antibody test with HIV-1/2 Determiner (Abbott Laboratories, Chicago, IL) and HIV-1/2 Stat Pak^R Dipstick assay (Chembio Diagnostic System Inc, Medford, NY) was nonreactive for HIV 1 and HIV 2. Hemoglobin genotype was AA.

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The CSF appeared to flow briskly but opening pressure was not measured. The CSF glucose was 0.4 g/L, with concurrent blood glucose of 1 g/L. The CSF protein was 4.8 g/L; white blood cell count was 141/mm³ with neutrophils of 80% and lymphocytes of 20%. No red blood cells were seen. Cultures of both blood and CSF showed an isolate with hemolytic reaction on blood agar incubated aerobically. The isolate was a Gram-positive, short coccobacillus with positive catalase but oxidase negative. Christie Atkinson Munch-Petterson test was positive for the isolate.⁶ It demonstrated a tumbling motility on a hanging drop wet preparation and thus was identified as *L monocytogenes* (no automated/mechanized system of identification was available).

Listeria monocytogenes meningitis is unusual in our patient's age group and raises the concern of an immunosuppressive disease. This led us to embark on an immunodeficiency workup in this child. As cellular immunity seemed intact (based on absolute lymphocyte count, CD4, absolute monocytes count, and absolute neutrophils count), we performed an assay of the child's serum immunoglobulins on the sixth day of admission. Results of these revealed a reduction in immunoglobulin (Ig) G 1.24 g/L (normal range = 4.00-12.50 g/L), IgM 12.00 g/L (normal range = 0.41-2.00 g/L), IgA 1.18 g/L (normal range = 0.24-1.92 g/L), and marginally elevated IgE, 98.2 IU/mL (reference range for 3 years = 35 mean [119 + 1 SD, 405 + 2 SD] IU/mL).^{7,8} The reference values are based on the local laboratory reference values and published data.

Based on the result of our patient's antibiotic susceptibility testing, intravenous amoxicillin and amikacin were administered for 3 weeks. His seizures were controlled with phenobarbitone, which was stopped on the 12th day on admission. He was discharged following completion of his antibiotic treatment and a 4-day period without fever or seizures. He had no other neurologic symptoms at discharge except for a persistent unsteady gait.

Intravenous immunoglobulin was offered, but the parents could not afford the cost. However, protein-conjugated *Pneumococcal* and *Haemophilus* vaccines were given in addition to trimethoprim-sulfamethoxazole prophylaxis. The patient was followed-up in the outpatient clinic. During the follow-up visits, his gait progressively improved. At 6 months post presentation, he was walking normally with no other neurologic deficits.

Subsequently, the family moved and was unable to attend clinic visits. However, regular telephone contacts with the mother assured doctors that the child remained healthy with no further seizure activity off phenobarbitone and with a normal neurological status. Parents were instructed that if he had another episode of bacterial

meningitis, additional studies including a genetic evaluation of IgM genotype would be indicated.

Discussion

Immunoglobulins (IgM, IgG, IgA, IgE, and IgD) are antibodies produced by B-lymphocytes and plasma cells in response to the presence of foreign antigens. The B-cell has many surface receptors among which are cluster of differentiation (CD), *CD79* and *CD40*, and membrane-bound IgM or IgD antibodies receptors that are useful in cell-cell interaction with antigens.⁷ When a B-cell recognizes an antigen, it internalizes it and presents it on the major histocompatibility complex-II molecules. The helper T-cell (CD4+) will bind to the presented antigen to express *CD40* ligand on its surface, which stimulate production of cytokines and interleukins.^{7,8} This complex interactions activate the B-cell to produce specific antibodies, for example, IgM or IgE as required and mediate class switching. Class switch recombination allows the class of antibody produced by an activated B-cell to change through a process called isotype or class switching. In event of impaired switching of IgM to other forms of antibodies, production of IgM persists at the expense IgG, IgA, or IgE types. As a result, patients with this disease would have decreased levels of IgG, IgA, IgD, and IgE, but normal or elevated levels of IgM in the blood.

A few of the genetic disorders associated with hyper IgM syndrome (HIGMS) are X-linked recessive disease due to mutation of the *CD40* ligand gene (it affects T-cells' ability to stimulate and activate B-cell). Other autosomal recessive forms of HIGMS includes mutations of *CD40* gene which result in loss of surface expression of *CD40* on B cells and a defect of enzyme activation-induced cytidine deaminase (AID); an enzyme that helps to recombine genetic material. These defects result in impaired Ig isotype switching for heavy chain production in B-cells. There may also be a mutation in the Uracil Glycosylase DNA (UNG) gene responsible for the production of enzyme that helps with class switching in B-cell.

HIGMS may be suspected when there are normal B-cells, depressed serum IgG, IgA, IgE, and IgD, but normal or increased IgM levels. Clinical features that may suggest this syndrome includes large tonsils, lymphoid hyperplasia, and poor IgG response to vaccines. Flow cytometric assay is a screening test and subsequent sequence analysis of *CD40L*. Lymph node histologic may show feature abortive germinal center with phenotypic abnormality of follicular dendritic cells.

Recurrent or persistent bacterial meningitis in a child warrants further workup for proximate or concomitant

causes such as anatomic/structural defects and autoimmune or immunodeficiency syndromes (congenital or acquired). Questions to ask include a detailed review of past medical history to determine if the child has had frequent/recurrent pneumonias, sinus, ear, or skin infections (with pyogenic bacteria, fungal, or *Pneumocystis jirovecii*), recurrent/severe bouts of diarrhea (especially with enterovirus, giardia, or cryptosporidium), head trauma, or the presence of autoimmune diseases such as lupus, rheumatoid arthritis, type 1 diabetes disease, or inflammatory bowel disease. The caregiver should be asked about any delayed growth and/or development, recurrent anemia, thrombocytopenia, or other blood disorders.^{1,3,4}

In Nigerian children, *L monocytogenes* is a rare finding particularly beyond infancy and hence raises the suspicion of an immunocompromised state.² In our patient, the positive history of recurrent respiratory tract infections severe enough to warrant repeated treatment with antibiotics in combination with an unusual isolate and negative past medical history for other obvious causes prompted us to entertain other rare conditions such as an immunodeficiency syndrome. Apart from the above history, our patient did not bear any physical stigmata of known immune deficiency syndromes such as sparse hair or conical teeth.

Listeria monocytogenes accounts for only 0.4% of community-acquired meningitis.² However, the majority of these cases occur in newborns, pregnant women, the elderly, and people with compromised immune function.³ The rarity of *L monocytogenes* meningitis beyond infancy makes the isolation of the bacteria in our patient's CSF strongly suspicious of immune dysfunction.

Globally, most reported cases of *L monocytogenes* meningitis beyond infancy are seen in immunocompromised patients with comorbidities of childhood malignancy, diabetes mellitus, HIV infections, steroid therapy, and tuberculosis.^{9,10} Congenital cellular, humoral, or combined immunodeficiency syndromes have also been reported with *L monocytogenes* meningitis.^{3,9,10}

The clinical features of *L monocytogenes* in our patient were similar to those previously reported in other patients with immunodeficiency but without HIGMS.¹¹ In the series reported by Simpson,¹¹ convulsions were one of the earliest features of *L monocytogenes* meningitis. Furthermore, 40% of the patients had no altered mental status. Two of the 6 patients had unsteady gait similar to features seen in our child.¹¹

There is paucity of literature on children with HIGMS presenting with *L monocytogenes* meningitis. Tsai et al⁴ reported 2 cases of HIGM among Taiwanese children who had recurrent upper respiratory tract infections (as seen in our patient), bouts of bronchopneumonia, occipital cellulitis, recurrent otitis media, and *Pneumocystis jirovecii* pneumonia.⁴ Analysis of 9 reported cases of

HIGMS among the Taiwanese children described features of chronic diarrhea, bronchiectasis, ileal perforation, sclerosing cholangitis, hypoxia ischemic encephalopathy, perianal abscesses, and acute respiratory distress syndrome.⁴ No patients were reported to have a combination of HIGM and *L monocytogenes* meningitis.⁴

Immunological assays of immunoglobulins in the Taiwanese study⁴ showed either elevated or low IgM levels with reduced levels of serum IgA, IgG, and IgE as seen in classic HIGM. In our child, the IgM level was 6-fold above the upper normal reference range for age while IgG was low, IgA and IgE levels were within normal limits suggesting one of the many variants of HIGMS phenotypes documented in the literature.^{12,13} In a high-income setting, further investigations such as genetic sequencing looking for specific mutations would have been recommended as next step in evaluation of this unusual patient.

Finally, definitive identification of *L monocytogenes* in the basic laboratory can be difficult due to gram variability and because *Listeria* can resemble diphtheroids, cocci, or diplococci.¹⁴ It is recommended that biochemical, immunological, molecular, or mass spectrometry testing be performed on a single colony from a pure culture.¹⁴ Definitive diagnosis in high-income countries would include a real-time polymerase chain reaction (PCR)-hly6 on the CSF, a test not available in most low- to middle-income country laboratories. However, Le Monnier et al⁶ demonstrated a 100% concordance rate between a real-time PCR-hly and positive *Listeria* culture of 214 CSF samples in their study.⁶ Thus, the identified *Listeria* bacteria from multiple body fluids in our patient likely would have the same concordance/correct identification rate vis-à-vis high-income country laboratories. In this patient, a gram-positive bacilli, *Bacillus* spp was considered but this was discarded due to the coccobacilli shape of the isolate. Facility for PCR is not available in our center and such facilities are hard to obtain in a resource-limited setting like ours.

Recommendations

- Children beyond infancy with *L monocytogenes* meningitis warrant a comprehensive evaluation for underlying immunodeficiency if other causes have been excluded.
- *Listeria monocytogenes* should be suspected by laboratories and care providers when initial testing is inconsistent with more common organisms.

Conclusion

The presence of recurrent/persistent meningitis and isolation of atypical organisms outside expected age norms should raise the suspicion of impaired immune function.

Whereas *L monocytogenes* meningitis beyond infancy is often seen in impaired cell-mediated immunity, humoral immunity with the assay of immunoglobulins should be considered as well.

Author Contributions

MAA: Substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SM: Critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

TMS: Contributed to design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AJ: Contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DAG: Contributed to design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical Approval

This case report was approved by the Bowen University Teaching Hospital Health Research Ethics Committee (Approval No. NHREC/12/04/2012).

Informed Consent

Written informed consent was obtained from the parent of the child for the publication of this case report.

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