Case Report

Recurrent meningitis: an enigma: A Case Report

A Lois[1], S Save[1], N Narkhede[1], A De[2], N Chatterji[2], J Shastri[2]

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Abstract

Salmonella meningitis in children represents 13% of meningitis cases in developing countries. A case of recurrent *Salmonella* ser. Enteritidis meningitis in a 2.5 month old baby should alert the clinician for possibility of recurrence after successful antibiotic therapy and need to investigate for the possibility of immunodeficiency.

Keywords: *infant, immunodeficiency, recurrent meningitis, Salmonella meningitis*

Introduction

Salmonellosis is a global public health problem. It is an infection acquired by oral and faeco-oral routes. Risk factors for the development of gastrointestinal infection in children include contact with an infected member of the household, consumption of infant formula, visits to health centres and consumption of untreated water.[1]

Salmonella meningitis accounts for a very small proportion of all cases of bacterial meningitis and the incidence worldwide is less than 1% and 13% in developed and developing countries respectively.[2, 3] Salmonellae are facultative intracellular micro-organisms, and inadequate drug penetration may result in infection progression.[4] *Salmonella* meningitis should therefore be treated with a third-generation cephalosporin with an adequate duration of at least three weeks.[5] A very few cases of meningitis caused by *S.* Enteritidis have been reported in India and worldwide. We report a rare case of recurrent meningitis caused by *S.* Enteritidis in a two and half month old child with immunodeficiency.

[1] *Department of Paediatrics, Topiwala National Medical College, Mumbai, India*
[2] *Department of Microbiology, Topiwala National Medical College, Mumbai, India*

Address for correspondence: Dr. Sushma Save, Ajmera AEON,2002, North(B)Wing, Bhakti Park, Wadala (East) Mumbai 400037, India. Telephone: 91-9819096819 E-mail: *sushmasave73@gmail.com*

https://orcid.org/0000-0002-6498-7962

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Case report

A firstborn 2½ month old male child of non-consanguineous marriage was admitted with moderate grade fever for two days. He had one episode of a paroxysmal event in the form of up-rolling of eyeballs and frothing from angle of mouth, tightening of limbs, which lasted for about 5 minutes and subsided on its own. There was no history of vomiting, lethargy or irritability. The child was immunized only with the birth dose of BCG, OPV and hepatitis B. The child was fed with cow's milk in addition to breast milk because of the mother's perception of a low milk output. The cow's milk was pasteurized, boiled and cooled. The child was admitted at a private hospital where meningitis was suspected, and lumbar puncture done and CSF sent for routine tests and microscopy. He was then started on intravenous ceftriaxone 100mg/kg/day in two divided doses. The parents got the child discharged against medical advice due to financial constraints and got him readmitted at our hospital around four hours later.

On physical examination, the baby was active with a temperature of 39 °C, heart rate 140 beats/minute (normal for age), and respiratory rate of 44/minute. On general examination: Length: 62cm (between median and +1SD), Weight: 5.8 kg (between median and +1SD), Head circumference: 41cm (at median), Weight/length: between -1SD and -2SD, the anterior fontanelle was normal, measuring 2cm x 2cm. The child had an erythematous rash over the entire back which subsided on its own in 1-2 days. Central nervous system examination revealed extensor plantar reflexes. Rest of the systemic examination was normal.

Complete haemogram showed Hb: 9.1gm/dL (10.5-14), total leucocyte count of 13,600 cells/mm^3 (6000 - 14000), and platelets 3.1 x 10^6/mm^3 (1.5-4). CT brain was normal. CSF analysis revealed 8 mg/dL of glucose, protein 232.4 mg/dL, and white blood cells (WBC) 8990 cells/mm^3 with 82% neutrophils and 18% lymphocytes. Corresponding blood sugar was 76mg/dL. His serum potassium was 4mmol/L (3.5-5.6), serum sodium 140mmol/L (134-144), serum calcium 9mg/dL (8.8-10.8), serum creatinine 0.3mg/dL (0.6-0.8) and serum urea 6 mg/dL (5-18) which were all within normal limits.

The child was started empirically on intravenous ceftriaxone 100mg/kg/day in two divided doses, after the collection of blood sample for culture and CSF for cytological, biochemical, and microbiological evaluation. Blood and CSF culture grew *Salmonella* species. Blood culture was done using an automated blood culture BACTEC system, and conventional culture was used for CSF. Identification was carried out using standard biochemical tests. Slide agglutination using Salmonella polyvalent antisera and type specific antiserum confirmed the isolate to be *S.* Enteritidis. The antibiotic sensitivity of *Salmonella* in blood and CSF was done by modified Kirby Bauer disc diffusion method and Epsilometer strip test as applicable and instructed by CLSI 2018 guidelines.[6] Table 1 shows the antibiotic sensitivity pattern.

The child responded to intravenous ceftriaxone (100mg/kg/day) in two divided doses 12 hourly for three weeks. Though the baby's mother was asymptomatic, she was also investigated to look for a source of infection. Blood, urine, and breast milk of the mother sent for culture were negative. Stool cultures were however not done. The child was on pasteurized and boiled cow's

milk at home, hence testing of the cow's milk with which the baby was fed at home was not done. The child was discharged upon clinical improvement.

Table 1 – Antibiotic sensitivity of *Salmonella* in blood and CSF

Specimen	AIIMS identification	CIP	CTR	FIX	AMP	SXT	CHL	AZM
Blood	*S.* Enteritidis	S	S	S	S	S	S	S
CSF	*S.* Enteritidis	S	S	S	S	S	S	S

AIIMS- All India Institute of Medical Sciences, New Delhi, CIP - Ciprofloxacin, CTR - Ceftriaxone, FIX - Cefixime, AMP - Ampicillin, SXT - Trimethoprim/Sulfamethoxazole, CHL - Chloramphenicol, AZM - Azithromycin]

The child was readmitted one month after discharge with fever, refusal of feeds, and irritability for two days. During this admission the child had increased tone and brisk reflexes and extensor plantars. Other systemic examinations were normal. On admission, the Hb was 10.2gm/dL (normal range 10.5-14), and WBC 15,400 cells/mm^3 (normal range 6000-14000). Magnetic Resonance Imaging (MRI) of the brain was suggestive of diffuse meningitis. CSF glucose was 21mg/dL (blood sugar 85mg/dL), protein 120mg/dL, and WBC 736 cells/mm^3 (neutrophils 74%; lymphocytes 26%) were suggestive of pyogenic meningitis.

He was treated with intravenous ceftriaxone 100mg/kg/day in two divided doses, phenobarbitone 5mg/kg/day and levetiracetam 10mg/kg/day for the seizures which he eventually developed. Blood and CSF cultures again showed growth of *Salmonella* group D (*S.* Enteritidis), similar to the organism obtained one month previously during the first admission. He was treated with intravenous ceftriaxone (100mg/kg/day) in two divided doses for 28 days and intravenous ciprofloxacin (10mg/kg/dose 8 hourly) for 10 days along with supportive treatment. A primary immunodeficiency workup done during this admission showed decreased IgM levels. The child was discharged upon clinical improvement with proper neurodevelopmental assessment and regularly followed up for complications.

At seven months of age, the child had a discharge from the left ear, fever, rash and left axillary lymphadenopathy. Mendelian Susceptibility for mycobacterial disease[7] tested negative. Clinical Exome was done at nine months of age and a heterozygous two base pair duplication in exon 8 of the NLRP12 gene chr19:g.54301596_54301597dupGA; Depth: 106x that results in a frame shift and premature truncation of the protein 6 amino acids downstream to codon 944 (p.Arg944SerfsTer6; ENST00000324134.6) was detected suggestive of autosomal dominant familial cold auto inflammatory syndrome-2 (OMIM#611762) which is caused by heterozygous mutations in the NLRP12 gene (OMIM*609648); a variant of unknown significance, which requires parental testing for confirmation. However, this testing could not be done due to the limitations of COVID-19 pandemic in India.

The timeline of the disease is shown in Figure 1.

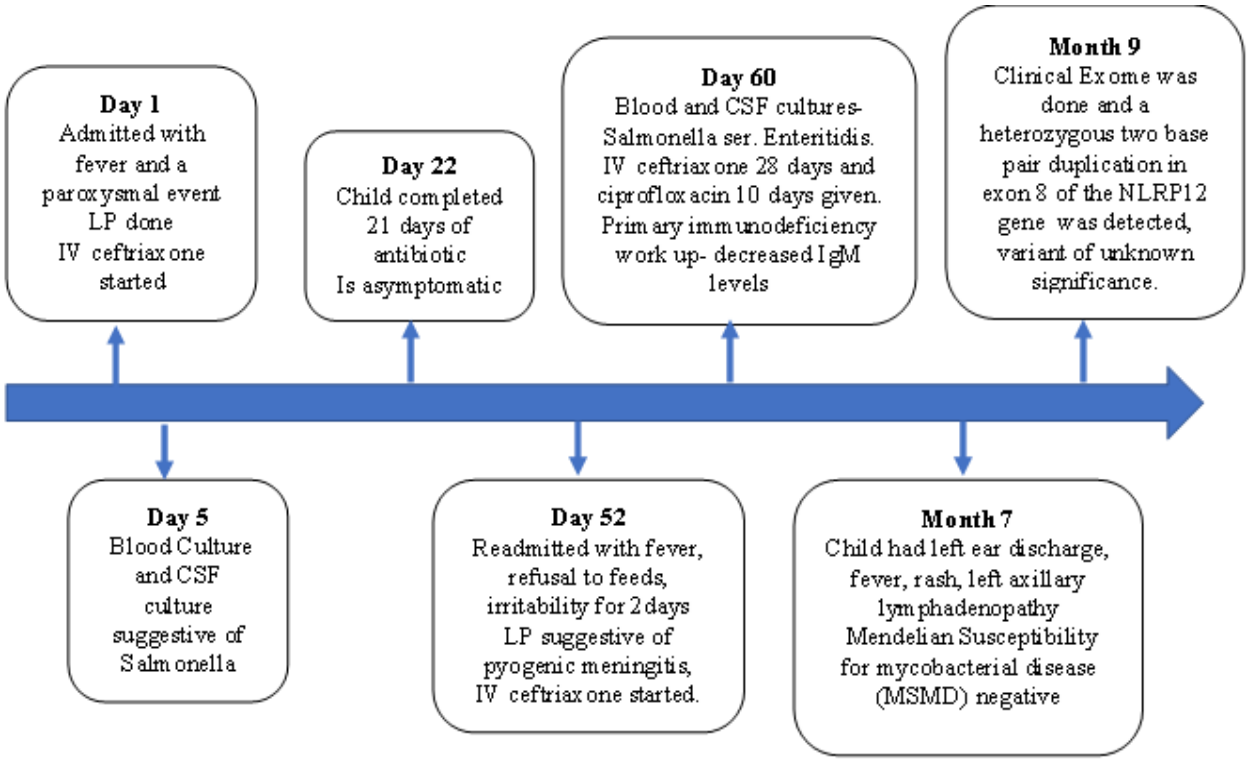

Figure 1: Timeline of the disease

Discussion:

Salmonella meningitis in infants has a wide spectrum of morbidity and complications, leading to a complicated hospital course and a high prevalence of permanent adverse outcomes.[3] Thus early recognition of acute complications of *Salmonella* meningitis and a follow-up plan for early developmental assessment of the survivors is vital.

The genus *Salmonella* is a Gram-negative bacillus of the family Enterobacteriaceae. The most recent classification of *Salmonella* includes two species: *Salmonella ser. Enterica* and *Salmonella ser. Bongori, S.* Enteritidis belongs to serogroup D and corresponds to *S. Enterica*, subspecies *enterica*, serovar *enteritidis.*[9,10] Non-typhoidal *Salmonella* (NTS) causes a self-limiting enterocolitis in immunocompetent individuals.[11] Primary NTS bacteraemia can occur in the immunocompromised, and mortality is significantly higher in this group (up to 21% in some case series).[11] There is increased risk of *Salmonella* meningitis in infants less than 6 months of age.[11]

The drug of choice for treatment of *Salmonella* meningitis is a third-generation cephalosporin such as ceftriaxone which has intracellular penetration, and intracellular activity is dependent on the extracellular concentration achieved.[12] Thus, for successful treatment, third-generation cephalosporin should be used in the dose that crosses the blood brain barrier, and continued for 4 weeks to ensure complete killing of the organism and to prevent relapse.[13] A combination of

ciprofloxacin and ceftriaxone or cefotaxime has been suggested too by Prince EH et al[14] and the American Academy of Pediatrics.[15]

Complications during the acute phase of *Salmonella* meningitis include prolonged seizures (100%), hydrocephalus (50%), subdural collection (42%), stroke (33%), ventriculitis (25%), empyema (13%), brain abscess (8%) and cranial nerve palsy (8%).[2] Long term follow-up is mandated to look for motor sequelae, epilepsy, language delay and cognitive delay.[2]

NLRP-12 is a key suppressor of innate immune signaling in salmonellosis. Any mutation in NLRP-12 gene may affect the Nuclear Factor Kappa B (NFKB) mediated destruction of *Salmonella*. Hence modulation of NLRP 12 expression and activation might help in prevention and treatment of *Salmonella*.[16]

NLRP12 Autoinflammatory disease (AID) is a rare autosomal dominant disorder caused by germline mutations in the NLRP12 gene and may have clinical manifestations of primary immune deficiencies (PID).[17] Monarch-1 is involved in the inhibition of the inflammatory response. Mutations in the NLRP12 gene appear to reduce the ability of the monarch-1 protein to inhibit inflammation which contributes to caspase activation and hyperproduction of interleukin-1β. The role of NLRP12 in the pathogenesis of infectious diseases remains a subject of investigation. Treatment of NLRP12-AID is usually based on the use of NSAIDs or short-term course of corticosteroids, with only some patients requiring sophisticated targeted drugs.[18]

Conclusion:

Timely diagnosis of *Salmonella* meningitis, along with appropriate antibiotics for an adequate duration will reduce the mortality and morbidity. Early recognition of acute complications and a follow-up plan for early developmental assessment of survivors are vital. Immunodeficiency work up needs to be done in a case of recurrent *Salmonella* meningitis.

Declarations

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