Salmonella paratyphi B Sepsis with Secondary Hemophagocytic Lymphohistiocytosis in a Child

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Keywords

Salmonella paratyphi, *Salmonella typhi*, Hemophagocytic Lymphohistiocytosis, HLH, secondary Hemophagocytic Lymphohistiocytosis.

Abstract

Hemophagocytosis lymphohistiocytosis is a state of hyperinflammation with activated macrophages, cytokine storm and tissue destruction. It can be triggered by immune activation during infection. We report the case of an 8-year-old septic girl who presented with 8 days of fever, diarrhoea and splenomegaly. Laboratory abnormalities, blood and faeces cultures confirmed haemophagocytosis lymphohistiocytosis triggered by *Salmonella paratyphi B* infection, which has never been reported in children. We present a narrative review of the literature.

Introduction

HLH is a syndrome with high morbidity and mortality caused by excessive immune activation. In patients with HLH, a trigger, such as an infection, causes a state of hyperinflammation by activation of macrophages. In addition, natural killer cells and cytotoxic T-lymphocytes fail to eliminate these activated macrophages. This results in a cytokine storm, haemophagocytosis and multi-organ involvement or failure. HLH is subdivided into primary HLH and secondary HLH.

Patients with primary HLH have a gene mutation and usually present with HLH the first few years of life and a have positive family history of HLH. Even less aggressive infectious agents like enteroviruses can trigger HLH. In secondary HLH patients have no genetic predisposition and only invasive microorganisms can provoke HLH by uncontrolled immune activation. The presence of a malignancy or primary immunodeficiency contributes to a predisposition to develop HLH (1, 2). Treatment of secondary HLH caused by an infection, as in our patient, consists of

Figure 1: Literature search.

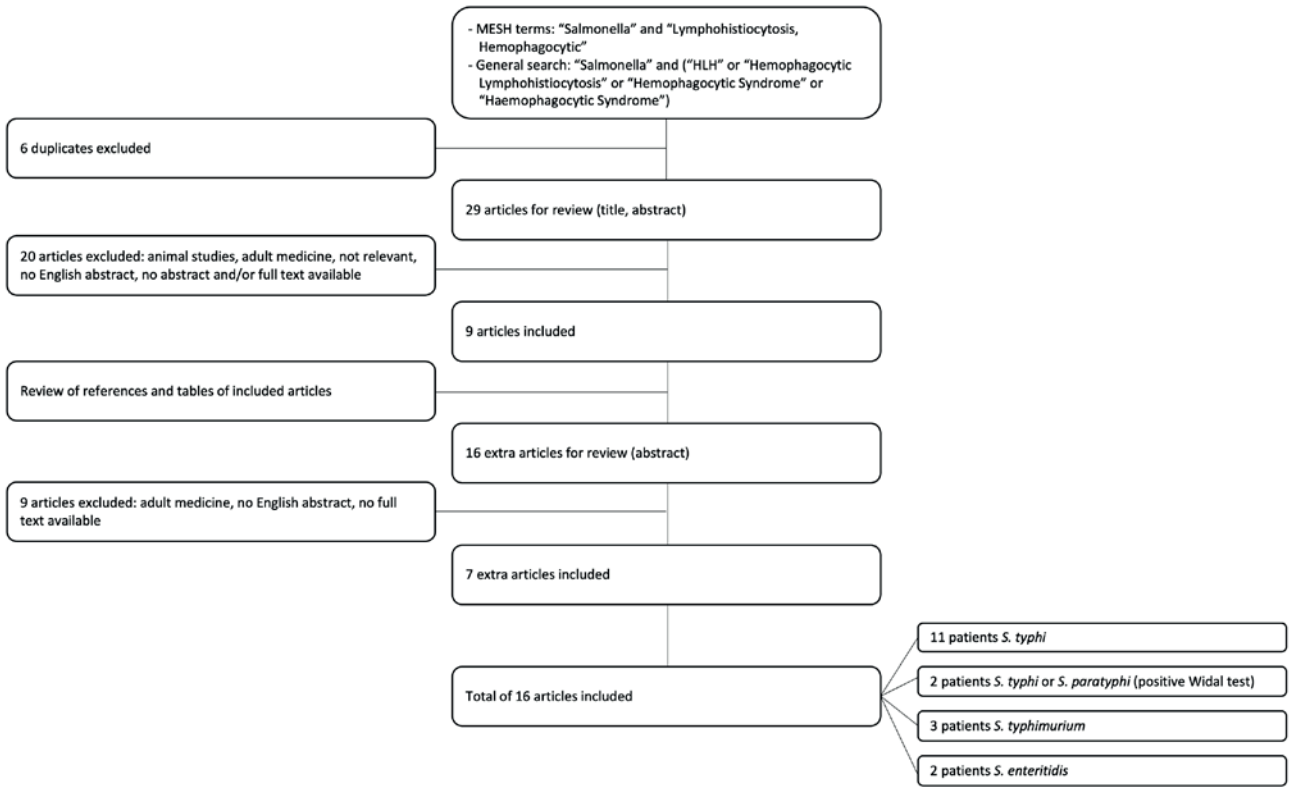

Table 1: Main blood laboratory parameters on presentation to the emergency department.

Laboratory parameter	Laboratory value	Normal value[1]
Haemoglobin	6,6 mmol/L (↓)	7,2-9,6 mmol/L
Leucocytes	2,9 10E9/L (↓)	4-11 10E9/L
Absolute lymphocytes	0,6 10E9/L (↓)	1-5 10E9/L
Thrombocytes	50 10E9/L (↓)	150-400 10E9/L
APTT	32,6 s	24-37 s
PT	12,8 s	10-13,5 s
D-dimers	>128000 ng/mL (↑)	<500 ng/mL
Fibrinogen	1,93 g/L (↓)	2-4,5 g/L
pH	7,47 (↑)	7,32-7,43
pCO2	4,3 kPa (↓)	5,5-6,8 kPa
Bicarbonate	24 mmol/L	23-29 mmol/L
Base excess	0,4 mmol/L	-3 - 3 mmol/L
Lactate	0,9 mmol/L	0,5-2,2 mmol/L
Glucose	6,4 mmol/L	4-7,8 mmol/L
Urea	4,3 mmol/L	2,5-6 mmol/L
Creatinine	58 µmol/L	15-72 µmol/L
Uric acid	0,25 mmol/L	0,15-0,40 mmol/L
Sodium	124 mmol/L (↓)	135-145 mmol/L
Potassium	2,5 mmol/L (↓)	3,6-5 mmol/L
Calcium	2 mmol/L (↓)	2,2-2,7 mmol/L
Gamma GT	14 U/L	<40 U/L
ASAT	201 U/L (↑)	<31 U/L
ALAT	40 U/L (↑)	<35 U/L
LDH	1466 U/L (↑)	< 350 U/L (2-12 years)
CK	932 U/L (↑)	<145 U/L
Hs-Troponin T	11 ng/L	<12 ng/L
NT-Pro-BNP	17,3 pmol/L (↑)	<9,8 pmol/L
Triglycerides (non-fasting)	3,87 mmol/L (↑)	<2 mmol/L
Ferritin	12986 µg/L (↑)	8-110 µg/L
Haptoglobin	<0,1 g/L (↓)	0,3-2 g/L
CRP	157 mg/L (↑)	<10 mg/L
Albumin	37 g/L	35-50 g/L
Soluble IL-2 Receptor	>7500 U/mL (↑)	158-623 U/mL

[1] Normal values as reported by the local laboratory of the Elisabeth-Tweesteden Hospital Tilburg.

adequate treatment of the underlying infection in combination with corticosteroids (3). However, if the patient does not respond within 24-48 hours, a full HLH therapy including chemotherapy such as etoposide as proposed in the HLH 2004 guidelines, may be necessary (1, 4).

Case report

An 8-year-old girl with no relevant medical history presented to the emergency department of the Elisabeth-Tweesteden Hospital (ETZ) in the Netherlands with a fever of 8 days' duration. Her parents reported that she had an average of three watery stools per day and she was suffering from extreme fatigue. A conjunctival injection of the left eye which they had initially observed, had resolved. There were no sick contacts at home or at school. She had received all the recommended immunizations. The last time she had travelled to the north of Iraq, her country of origin, had been 4 months ago. Her medical history was otherwise uneventful. On presentation, monitoring of her vital signs showed a free airway, respiratory rate of 28/min (normal value 15-25/min), oxygen saturation of 98% (normal value >95%), heart rate of 135 beats/min (normal value 70-120 beats/min), normal blood pressure of 105/59 mmHg (systolic blood pressure 50th percentile 90-110 mmHg) and body temperature of 36.9°C (normal value 36.5-37.5°C) (5).

On physical examination she appeared ill. She had a pale skin colour, minimal cervical lymphadenopathy, dry cracked lips, mild splenomegaly (1cm below the left costal margin) and a painful abdomen without guarding on palpation. The initial laboratory findings are shown in Table 1. There was marked pancytopenia, haemolysis, hyponatremia, hypokalaemia, elevated transaminases, elevated creatinine kinase, hypertriglyceridemia, hypofibrinogenaemia, elevated D-dimers, high inflammatory markers and elevated soluble interleukin-2 (IL-2) receptor. The chest x-ray was unremarkable. Abdominal ultrasound confirmed a mild splenomegaly of 13 cm (normal < 10,5 cm (6)) with some free intraperitoneal fluid collection and no hepatomegaly. After taking blood and faeces culture, we started empirical treatment with intravenous ceftriaxone and fluid challenge with 20 ml/kg normal saline 0.9% for impending circulatory shock. Sodium and potassium depletion was corrected. She was transferred to the regional paediatric intensive care unit (PICU) for further, diagnostic evaluation and management.

Additional serological and molecular testing during the PICU admission revealed negative infectious serology (negative immunoglobulin (Ig) G and IgM for parvovirus B19, cytomegalovirus and Ebstein-Barr virus, negative anti-streptolysin titre and anti-DNAse B and negative Leishmania DNA). A bone marrow examination was performed. It showed a moderately cell-rich bone marrow with mildly reduced erythropoiesis and lymphohistiocytic infiltration. There was no evidence of neoplasia or haemophagocytosis. Blood and faeces cultures were positive for *Salmonella paratyphi B*. Since the patient's fever persisted after 3 days of antibiotic treatment, other alternative diagnoses, such as haemophagocytic lymphohistiocytosis (HLH) were considered. Despite a bone marrow without signs of haemophagocytosis, the patient fulfilled at least 5 of the 8 clinical and laboratory diagnostic criteria as proposed by the HLH-2004 guidelines study: fever, splenomegaly, hypertriglyceridemia, high ferritin and a high soluble IL-2 receptor (1). Pancytopenia was also present, but the deficiencies were too mild to fulfil this criterion. Natural killer cell (NK-cell) activity was not tested.

Ceftriaxone therapy was continued intravenously for 10 days. To be on the safe side, because of the possibility of *S. paratyphi* drug resistance to ceftriaxone because of persistent fever after 48 hours, we pragmatically added oral azithromycin for 5 days, while waiting for the result of the antibiogram. We considered the patient's recent travel to Iraq and the possibility that she had been infected there. However, the susceptibility results showed sensitivity to ceftriaxone. In addition to ceftriaxone and azithromycin, we added intravenous dexamethasone at a dose of 0,15mg/kg for 5 days due to persistent fever after 48 hours. Due to another fever spike on the 5th day of intravenous dexamethasone treatment, we prolonged the treatment orally for 3 days at a dosage of 5 mg/m2. After this, the patient had no more fever. Despite the absence of bleeding, the patient presented with depleted serum fibrinogen (reported as too low by our laboratory) which required suppletion with 3 g intravenous fibrinogen (Haemocomplettan®) (7). Thereafter, there was a rapid clinical and laboratory improvement. All laboratory parameters normalised. She was discharged after 14 days of hospitalisation, including 7 days in the PICU. Immunological tests conducted during outpatient follow-up at 6 weeks after discharge showed a transient low CD-19 cell count of 197 x106/L (normal range: 300-700 x106/L). This normalised spontaneously after 5 months. There was no depletion of other lymphocytes, including NK-cells: 441 x106/L (normal range: 100-600 x106/L).

We concluded that this patient suffered from a secondary form of HLH triggered by the infectious agent, *S. paratyphi B*. The elevated liver enzymes and lipase were believed to be related to the multiorgan involvement caused by either the HLH or *Salmonella* sepsis, or both. However, it is not unthinkable to consider the side effects of ceftriaxone.

Literature search

To our knowledge there are no similar reports of secondary HLH caused by *Salmonella paratyphi B* in children. We, therefore, conducted

Table 2: Literature review.

First author	Year publication	Country	Patient details	Cultured *Salmonella species*	HLH criteria mentioned (HLH-2004 study)	Treatment	Comments
Benz-Lemoine (8)	1984	France	7-year old, boy (with CGD)	*S. typhimurium* (blood culture)	Fever, splenomegaly, cytopenia(s), BME showing haemophagocytosis.	NA	Case report.
Udden (9)	1986	United States	17-year old, boy	*S. typhi* (blood culture)	Fever, pancytopenia, BME showing haemophagocytosis.	NA	Case report.
Fame (10)	1986	United States	13-year old, girl	*S. typhi* (stool and blood culture)	Fever, splenomegaly, pancytopenia, BME showing haemophagocytosis	Ampicillin IV switch to amoxicillin PO switch to trimethoprim-sulfamethoxazole IV then PO	Case report.
Mallouh (11)	1987	Saudi Arabia	3 children	*S. typhi*	Fever, cytopenia(s), BME showing haemophagocytosis	NA	Case series.
Stéphan (12)	2001	France	1 child	*S. enteritidis*	Fever, splenomegaly, hypofibrinogenaemia, hypertriglyceridaemia	NA	Retrospective study.
Caksen (6)	2003	Turkey	6-year old, boy	Positive Widal test for *S. typhi*	Fever, splenomegaly, pancytopenia, BME showing haemophagocytosis	Chloramphenicol PO	Case report.
Pandey (14)	2012	India	10-year old, boy	Positive Widal test	Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis	Ceftriaxone IV	Case report.
Pande (13)	2016	India	13-year old, girl	Positive Widal test, *Salmonella* (blood culture)	Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis	Cefeperazone+sulbactam IV switch to piperacillin+tazobactam IV, prednisolone IV and PO	Case report.
Abbas (15)	2018	Pakistan	4-year old, girl	*S. typhi* (blood culture)	Fever, pancytopenia, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia, BME showing haemophagocytosis	Ceftriaxone IV switch to tazobactam IV	Case report.
Uribe-Londono (16)	2018	Colombia	8-year old, girl	*S. typhi* (bone marrow and blood culture)	Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia	Piperacillin-tazobactam IV with switch to ciprofloxacin, IVIG	Case report and literature review.
Sánchez-Moreno (17)	2019	Spain	7-year old, boy	*S. typhi* (stool and blood culture)	Fever, splenomegaly, pancytopenia, elevated ferritin, hypofibrinogenemia	Ceftriaxone IV, methylprednisolone	Case report and literature review.
Yasar (18)	2019	Turkey	14-year old, girl	*S. typhi* (blood culture)	Fever, pancytopenia, elevated ferritin, hypofibrinogenemia, BME showing haemophagocytosis	Ceftriaxone IV, dexamethasone, IVIG	Case report.
Banday (19)	2020	India	12-year-old, boy	Positive Widal test, *S. enteritidis* (bone marrow and blood culture)	Fever, splenomegaly, cytopenia, elevated ferritin, hypofibrinogenemia, BME showing haemophagocytosis	Ceftriaxone IV with switch to meropenem IV, dexamethasone IV	Case report and literature review.
Durmus (20)	2020	Turkey	9-year old, boy	*S. typhimurium* (blood culture)	Fever, splenomegaly, cytopenia, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia	Ceftriaxone IV, IVIG	Case report.
Wei (21)	2020	China	3-year old, boy (with CGD)	*S. typhimurium* (bone marrow and blood culture)	Fever, splenomegaly, pancytopenia, elevated ferritin, elevated soluble CD25, hypofibrinogenemia, decreased NK cell activity, BME showing haemophagocytosis	Meropenem IV, methylprednisolone	Case report.
Dange (22)	2021	India	5-year old, girl	Positive Widal test, *S. typhi* (cerebrospinal fluid and blood culture)	Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis	Ceftriaxone IV, dexamethasone, etoposide	Case report.
Waeterschoot (our report)	2022	The Netherlands	8-year old, girl	*S. paratyphi B* (stool and blood culture)	Fever, splenomegaly, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia, elevated soluble CD25	Ceftriaxone IV, azithromycin PO, dexamethasone	Case report and literature review.

a literature search in PubMed on 30th of March 2023, with the following search terms: "*Salmonella*" AND "Lymphohistiocytosis, Hemophagocytosis" as MeSH search terms or "*Salmonella*" AND "HLH" OR "Hemophagocytic Lymphohistiocytosis" OR "Hemophagocytic Syndrome" OR "Haemophagocytic Syndrome". The summary of the results of our search is shown in Figure 1.

Of the 29 original articles we identified, 20 were excluded for the following reasons: animal study, disease onset > 18 years of age, irrelevant to the research question, no English abstract available, no abstract and full text available. The remaining 9 articles were all case reports or case studies. Screening of these papers based on the same criteria led to the inclusion of 7 extra articles, resulting in a total of 16 included articles.

Results

All the 16 included papers were case reports or case studies, with 1 to 3 patients reported (4, 8-22). They included a total of 18 paediatric patients. Only 3 papers included a review of the literature. The microbiological diagnoses of included patients were *Salmonella typhi* [11], *Salmonella typhimurium* [3], *Salmonella enteritidis* [2] and *S. typhi* or *S. paratyphi* [2] (based on positive Widal tests). These studies are summarised in Table 3.

Discussion

To our knowledge, this is the first paediatric report of HLH in which *S. paratyphi B* was cultured in both blood and stool.

Considering the pathophysiology of enteric fever, the *S. (para)typhi* organism penetrates the intestinal epithelium after ingestion of contaminated food or water. Within the endothelial cell, proliferation and subsequent hypertrophy of Peyer's patches occurs through recruitment of mononuclear cells and lymphocytes. Further dissemination and replication in the reticuloendothelial system causes hepatosplenomegaly and generalised sepsis. Activation of phagocytes plays a crucial role in the body's defence against enteric fever. However, if this is not appropriately regulated there is a risk of developing HLH (1, 23, 24).

Although infections with *Salmonella* species have been implicated as triggers of HLH, only a few cases have been reported so far in the literature (see Table 3). Our literature search did not yield any report of paediatric patients with HLH triggered by *Salmonella paratyphi* infection. In 2013, Nath et al. reported the case of an 18-year-old male with clinical criteria for HLH and a positive *S. paratyphi* A blood culture (25). His bone marrow examination showed haemophagocytic changes. He was successfully treated with a 10-day course of intravenous ceftriaxone and dexamethasone. Our case differs from this case not only in age, but also in the *S. paratyphi* serotype and in the absence of haemophagocytic changes in the bone marrow. However, it should remembered that this morphological hallmark of HLH is quite often absent in the bone marrow or lymph nodes, especially in the early stages of HLH (26).

The literature search identified 5 patients (4, 13, 14, 19, 22) in whom the diagnosis was based on a positive Widal test. The Widal test is a serological test for the detection of agglutinating antibodies to the O and H antigens of *S. typhi* and *paratyphi*. However, the World Health Organization doesn't recommend this test for diagnosis since it is time-consuming and unreliable due to low sensitivity (false-negative results due to hypoproteinaemia or weak and delayed antibody response in non-endemic areas) and specificity (false-positive results in vaccinated or previously infected patients) (27).

The incidence of HLH is unknown although it is associated with high morbidity and mortality. It is more common in children than in adults. The highest incidence is seen in children less under the age of 3 months (28).

The Netherlands is a low endemic country for typhoid and paratyphoid fever, both accounting for 0.36 cases per 100.000 persons in 2017 (latest available statistics from the European Centre for Disease Prevention and Control, ECDC) (28, 29). This number has been stable over the period 2013-2017, with a seasonal distribution and predominantly being a travellers' disease. Most of the reported cases were from travellers from endemic regions such as India and Pakistan (28). It is intriguing that the girl described in our case did not travel abroad in the three months preceding her illness. Regarding the distribution of patients with a *S. typhi* or *S. paratyphi* infection, the ECDC reported the following percentages in 2017: 68% S. typhi, 20% *S. paratyphi* A, 10% *S. paratyphi B*, 0,6% S. paratyphi C and 2% S. paratyphi unspecified (28). *S. typhi* and *S. paratyphi* show some similarities in epidemiology, pathogenesis, mode of transmission and clinical signs. Paratyphoid fever often has a milder course and is less likely to lead to a chronic carrier status (29, 30). The incubation period is between 1-10 days. It has been observed that the onset of travel-related infection can occur up to months after the end of travel (31). In this case chronic stool carriership was not determined in the girl's household members.

Finally, it is important to note that the diagnosis of HLH in a patient with enteric fever can be challenging, as mild pancytopenia, persistent fever and splenomegaly may be related to both the enteric fever itself and HLH (4). Maybe the suspicion of HLH in this case would have been low in a high-endemic low-income country due to the scarcity of sophisticated diagnostic test methods such as soluble IL-2 receptor, NK cell activity and a bone marrow examination. Perhaps the diagnosis would have been severe enteric fever. This is different in our low-endemic high-income country, with less exposure to severe enteric fever, but more availability of advanced diagnostic methods to confirm the diagnosis of HLH (32).

Conclusion

This case illustrates the importance of considering a *Salmonella* infection in the differential diagnosis of HLH in patients with severe infection of enteric origin, without a history of recent travel to an endemic area.

Disclosures

The authors have no conflicts of interest or funding to disclose.

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