Disseminated Salmonellosis in a child with *IL12Rß1* deficiency – Case report and review of literature.

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Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of genetic disorders characterized by a defect in interferon γ (IFN γ)–mediated immunity, with predisposition to infections caused by atypical and low virulent mycobacteria and other intra-macrophagic organisms like Salmonella, Klebsiella, Listeria etc. A 10-year-old boy, second born of a consanguineously (third-degree) married Indian couple, presented with left inguinal and submandibular lymphadenopathy with low grade fever for 10 days. Past history was significant as the child had been unwell from infancy. At the age of 4 months and 5 years, he was diagnosed to have tubercular axillary lymphadenitis and was treated with anti-tubercular drugs on each occasion and he responded to the same. On examination, he had left submandibular and inguinal lymphadenopathy and mild splenomegaly. Chest radiograph showed enlarged mediastinal nodes. He underwent left inguinal lymph node biopsy that reported granulomatous lymphadenitis. However, culture from the biopsy showed a growth of *Salmonella enterica* sensitive to ceftriaxone. Genetic evaluation showed pathogenic homozygous mutation c.1791 + 2T > G in exon 15 of *IL12Rß1* gene by whole exome sequencing. A diagnosis of Mendelian Susceptibility to Mycobacterial Disease (MSMD) was established and he was treated with intravenous ceftriaxone followed by oral cefixime. He responded promptly and lymphadenopathy resolved. He is currently being maintained on azithromycin prophylaxis. Children and adults presenting with disseminated infections with atypical mycobacteria and salmonella must be evaluated for MSMD. Disseminated salmonellosis is a peculiar manifestation in IL12Rß1 deficiency. A detailed review of literature on IL12RB1 deficiency was performed. Index case has been discussed in light of the previously published literature.

Introduction

Mendelian Susceptibility to Mycobacterial diseases (MSMD), also known as Inborn Errors of IFN-γ immunity (IEI) are a group of innate immune defects, characterized by a predisposition to infections caused by atypical and low virulent mycobacteria, such as the Bacillus Calmette Guerin (BCG) vaccines & non-tuberculous environmental mycobacteria (EM). The term MSMD is a misnomer because these individuals are also vulnerable to infections caused by other intra-macrophagic organisms (Klebsiella, Listeria, nocardiosis), fungi (candidiasis, coccidioidomycosis, paracoccidiomycosis, histoplasmosis), parasitic infections (Toxoplasmosis, Leishmaniasis) and viral infections (Cytomegalovirus, human herpes virus 8, respiratory syncytial virus etc.) [1]. These defects have been localized to more than 17 genes and as many as 32 clinical phenotypes have been identified [2], and IL12Rß1 deficiency is the most common cause of MSMD.

We describe a 10-year-old Indian boy with MSMD with a mutation in *IL12Rß1* gene who presented with recurrent tuberculosis & disseminated salmonella infection.

Methods

The study was approved by the Ethical Committee of the institution and signed written informed consents were obtained from the parents. A retrospective review of clinical records was performed. A detailed clinical history including the age of presentation, symptoms, past history, family history and findings on physical examination, laboratory findings and details of treatment taken were recorded. Whole exome sequencing was performed on Next generation sequencing (NGS) platform. An extensive review of literature of the cases of MSMD with a mutation in *IL12Rß1* gene published from 2000 to 2021 was performed. Keywords like 'Mendelian susceptibility to Mycobacterial Disease', 'MSMD' and '*IL12Rß1*', were used to search literature on PubMed. Literature search showed a total of 25 publications including case reports and full access papers. The clinical profile, micro-organisms isolated, treatment given and outcome of 249 cases published was reviewed and data was compiled.

Case

A 10-year-old boy, second born of a consanguineously (third-degree) married Indian couple, presented with left inguinal and submandibular lymphadenopathy with low grade fever for 10 days. Past history was significant as the child had been unwell from infancy. At the age of 4 months and 5 years, he had developed left and right axillary lymphadenopathy respectively, associated with low grade fever. He had been vaccinated with BCG (Bacillus Calmette Guerin) vaccine at birth. He was well until the age of 4 months, when he developed left axillary lymphadenopathy, however, it was not associated with any BCG site reaction. He underwent a lymph node biopsy that showed features suggestive of tubercular lymphadenitis and modified Ziehl Neelsen (ZN) stain for acid fast bacilli was positive. He was diagnosed to have BCG adenitis elsewhere and treated with isoniazid & rifampicin for 6 months and he responded to the same.

At the age of 5 years, he developed isolated right axillary lymphadenopathy with low grade fever. Lymph node biopsy reported features of tubercular lymphadenitis with presence of acid fast bacilli and he was treated with a course of anti-tubercular therapy (ATT) for a duration of 6 months, to which, he responded promptly. He also reported intermittent rashes over face and trunk from the age of 8 that had been treated with topical medications. He had now presented with recurrence of lymphadenopathy and low grade fever.

On examination, left submandibular and inguinal lymph nodes were enlarged (5x 6 cms), firm, mobile and tender. He also had mild splenomegaly. Chest radiograph showed enlarged mediastinal nodes. Considering tuberculosis as a possibility, he underwent left inguinal lymph node biopsy that reported granulomatous lymphadenitis (Figure S1,S2), however, tissue Gene X-pert and ZN stain were negative. The biopsy culture on Matrix Assisted Laser Desorption Ionization-Time Of Flight (MALDI-TOF) reported growth of Salmonella enterica subspecies enterica; sensitive to ceftriaxone.

Immunological evaluation showed hypergammaglobulinemia with preserved oxidative burst (Table S1). Genetic evaluation showed pathogenic homozygous mutation c.1791 + 2T > G in exon 15 of *IL12Rß1* gene by whole exome sequencing. A diagnosis of Mendelian Susceptibility to Mycobacterial Disease

(MSMD) was established and he was treated with intravenous ceftriaxone (4 weeks) followed by oral cefixime (4 weeks). He responded promptly and lymphadenopathy resolved over a period of 4 weeks. He is currently maintained on azithromycin prophylaxis.

Discussion

Mendelian susceptibility to mycobacterial is a clinical syndrome, first described in 1951, that predisposes apparently healthy individuals to infections caused by weakly virulent mycobacteria, such as BCG and EM. However, these patients are also susceptible to infections by more virulent Mycobacterium tuberculosis [3]. These diseases are caused due to a defect in the IL-12/IL-23/ISG15-Interferon-γ axis, which is the principal immunological pathway for intra-macrophagic pathogens. The defect in Interferon γ (IFN γ) - mediated signalling is characterized by decreased production or reduced response to IFN γ.

IL12Rß1 deficiency is the most common cause of MSMD and accounts for 44% of the known genetic etiologies. Mycobacterial infections are the most common infections observed in patients with IL-12Rβ1 deficiency (BCG, M.avium, M. avium intracellulare complex, M. chelonae, M. fortuitum etc.) [1]. Vaccination with BCG is known to protect against subsequent infections with EM and recurrent infections with BCG were reported to be relatively rare in these patients. Among the patients who were BCG-vaccinated, 78% patients developed BCG disease [4]. The time period between the BCG vaccination and the development of lymphadenitis in a case series of 10 patients was found to be 2 to 22 months [5]. Index case was vaccinated with BCG at birth and presented at 4 months with enlarged left axillary lymph node diagnosed to be tubercular in origin, possibly BCG lymphadenitis.

IL12 pathway is also involved in protection against Salmonella species, and non-typhoid salmonellosis is the second most common infection described in patients with *IL12Rß1* deficiency [6]. A recent study of patients with IL-12Rβ1 deficiency reported salmonellosis in 33.3% of the patients [7]. Staretz-Haham, et al described a case who had six episodes of asymptomatic Salmonella bacteremia who was treated with ceftriaxone on all occasions except for the last episode in which ciprofloxacin was added for 6 weeks [8]. Another case report of a young girl with 4 episodes of salmonella gastroenteritis was treated with third generation cephalosporins during each episode and duration of therapy ranged from 7–14 days. During the fourth episode a course of ciprofloxacin was given for 4 weeks followed by prophylaxis with trimethoprim & sulfamethoxazole [6]. Salmonella bacilli was isolated from the lymph node biopsy in our patient who presented only with low grade fever and lymphadenopathy in the absence of gastrointestinal symptoms. He was treated with third generation cephalosporins for a prolonged duration of 8 weeks and stool culture done prior to discontinuing antibiotics was reported sterile.

Interestingly, there are a few reports of patients with salmonella enteritidis infection who had skin biopsy proven leukocytoclastic vasculitis that responded to antibiotic therapy [4, 9, 10]. Index case presented with intermittent rashes over the face and trunk responsive to topical steroids, possibly a form of cutaneous vasculitis.

Previous case series have reported varied clinical spectrum in patients with IL-12Rβ1 deficiency. Infections with various other intracellular organisms like Nocardia, Klebsiella, Candida, Cryptococcus,

Paracoccidiomycosis etc have also been reported in these patients [4, 5, 11]. The profile of previously reported patients with IL-12Rβ1 deficiency has been tabulated in Table S2.

Prognosis of patients with IL-12Rβ1 deficiency is variable and cannot be completely attributed to the underlying immune deficiency. The overall mortality in these patients is 26% and is dependent on several factors such as the age of presentation, the infectious agent and the therapeutics used. Early age of presentation was found to be associated with poorer prognosis compared to patients presenting at a later age. Infection with Salmonella species was found to be associated with a higher mortality rate up to 52% compared to infections with EM (7%) [1]. Individuals with IL-12Rβ1 deficiency treated with prolonged courses of antibiotics and exogenous IFN γ were less likely to undergo surgical resection of the affected areas. Hematopoietic Stem Cell transplantation (HSCT) though a curative option, is not indicated in all patients and be considered in selected cases, especially in those in which there is an HLA-compatible donor available within the family and in settings where IFN γ treatment is not readily available [1, 12]. It must be noted that IFN γ therapy is not readily accessible in resource-limited settings like ours and the index case is doing well on azithromycin prophylaxis.

Conclusions

Children and adults presenting with disseminated infections with atypical mycobacteria and salmonella must be evaluated for MSMD. Disseminated salmonellosis is a peculiar manifestation in IL12Rß1 deficiency. These patients need aggressive and long-term antibiotic therapy to eradicate Salmonella infection.

Declarations

> Funding- None

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> Authors' contributions-

Dr.Rachna Shanbhag Mohite- Initial Draft of manuscript, review of literature.

Dr. Rajeshwari - Assessment of Microbiology specimens.

Dr. Vidya - Assessment of histopathology specimen.

Dr. Sagar Bhattad- Patient management, final draft.

> Ethics approval- Waiver obtained

> Consent to participate- Obtained

> Consent for publication- Obtained

References

1. Bustamante J, Boisson-Dupuis S, Abel L, et al. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol. 2014;26:454–70.
2. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020 Jan;40(1):24–64.
3. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol. 2002;20:581–620.
4. De Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, et al. Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries. Medicine. 2010 Nov;89(6):381.
5. Doğruel D, Gündeşlioğlu ÖÖ, Yılmaz M, Alabaz D, Altıntaş DU, Kocabaş E. Clinical findings and genetic analysis of the patients with IL-12Rβ1 deficiency from southeast Turkey. The Turkish journal of pediatrics. 2019 Mar 1;61(2):174-9.
6. Ozen M, Ceyhan M, Sanal O, Bayraktar M, Mesci L. Recurrent Salmonella bacteremia in interleukin-12 receptor beta1deficiency. J Trop Pediatr. 2006;52(4):296–8.
7. Moradi L, Cheraghi T, Yazdani R, Azizi G, Rasouli S, Zavareh FT, et al.Mendelian susceptibility to mycobacterial disease: Clinical and immunological findings of patients suspected for IL12Rβ1 deficiency. Allergologia et immunopathologia. 2019 Sep 1;47(5):491-8.
8. Staretz-Haham O, Melamed R, Lifshitz M, et al. Interleukin-12 receptor beta1 deficiency presenting as recurrent Salmonella infection. Clin Infect Dis. 2003;37:137–40.
9. Van de Vosse E, Ottenhoff TH, de Paus RA, Verhard EM, de Boer T, van Dissel JT, et al. Mycobacterium bovis BCG-itis and cervical lymphadenitis due to Salmonella enteritidis in a patient with complete interleukin-12/-23 receptor β1 deficiency. Infection. 2010 Apr 1;38(2):128 – 30.
10. Filiz S, Kocacik Uygun DF, Verhard EM, van Dissel JT, Uygun V, Bassorgun C, et al.Cutaneous Leukocytoclastic Vasculitis due to Salmonella enteritidis in a Child with Interleukin-12 Receptor Beta-1 Deficiency. Pediatric dermatology. 2014 Mar;31(2):236–40.
11. Jirapongsananuruk O, Luangwedchakarn V, Niemela JE, Pacharn P, Visitsunthorn N, Thepthai C, et al. Cryptococcal osteomyelitis in a child with a novel compound mutation of the IL12Rß1 gene. Asian Pac J Allergy Immunol. 2012 Mar 1;30(1):79–82.
12. Wang L-H, Yen C-L, Chang T-C, Liu C-C, Shieh C-C. Impact of molecular diagnosis on treating Mendelian susceptibil- ity to mycobacterial diseases. J Microbiol Immunol Infect. 2012;45:411–7.

13. Aksu G, Trpan C, Çavusoglu C, Soydan S, Altare F, Casanova JL, et al. Mycobacterium fortuitum-chelonae complex infection in a child with complete interleukin-12 receptor beta 1 deficiency. The Pediatric infectious disease journal. 2001 May 1;20(5):551-3.
14. Sakai T, Matsuoka M, Aoki M, Nosaka K, Mitsuya H. Missense mutation of the interleukin-12 receptor β1 chain–encoding gene is associated with impaired immunity against Mycobacterium avium complex infection. Blood, The Journal of the American Society of Hematology. 2001 May 1;97(9):2688-94.
15. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, et al.Low Penetrance, Broad Resistance, and Favorable Outcome of Interleukin 12 Receptor β1 Deficiency Medical and Immunological Implications. The Journal of experimental medicine. 2003 Feb 17;197(4):527–35.
16. Lichtenauer-Kaligis EG, de Boer T, Verreck FA, van Voorden S, Hoeve MA, Vosse EV, et al. Severe Mycobacterium bovis BCG infections in a large series of novel IL–12 receptor β1 deficient patients and evidence for the existence of partial IL–12 receptor β1 deficiency. Eur J Immunol. 2003 Jan;33(1):59–69.
17. Fieschi C, Bosticardo M, de Beaucoudrey L, Boisson-Dupuis S, Feinberg J, Santos OF, Bustamante J, Levy J, Candotti F, Casanova JL. A novel form of complete IL-12/IL-23 receptor beta1 deficiency with cell surface-expressed nonfunctional receptors. Blood. 2004;104(7):2095–101.
18. Sanal O, Turul T, De Boer T, Van De Vosse E, Yalcin I, Tezcan I, Sun C, Memis L, Ottenhoff TH, Ersoy F. Presentation of interleukin-12/-23 receptor β1 deficiency with various clinical symptoms of Salmonella infections. J Clin Immunol. 2006 Jan;26(1):1–6.
19. Haerynck F, Holland SM, Rosenzweig SD, Casanova JL, Schelstraete P, De Baets F. Disseminated Mycobacterium avium infection in a patient with a novel mutation in the interleukin-12 receptor-β1 chain. The Journal of pediatrics. 2008 Nov 1;153(5):721-2.
20. Ehlayel M, de Beaucoudrey L, Fike F, Nahas SA, Feinberg J, Casanova JL, et al.Simultaneous presentation of 2 rare hereditary immunodeficiencies: IL-12 receptor β1 deficiency and ataxia-telangiectasia. Journal of Allergy and Clinical Immunology. 2008 Dec 1;122(6):1217-9.
21. Luangwedchakarn V, Jirapongsaranuruk O, Niemela JE, Thepthai C, Chokephaibulkit K, Sukpanichnant S, et al. A novel mutation of the IL12Rß1 gene in a child with nocardiosis, recurrent salmonellosis and neurofibromatosis type I: first case report from Thailand. Asian Pacific journal of allergy immunology. 2009 Jun;27(2–3)(1):161.
22. Pedraza-Sánchez S, Herrera-Barrios MT, Aldana-Vergara R, Neumann-Ordoñez M, González-Hernández Y, Sada-Díaz E, et al. Bacille Calmette–Guérin infection and disease with fatal outcome associated with a point mutation in the interleukin-12/interleukin-23 receptor beta-1 chain in two Mexican families. International Journal of Infectious Diseases. 2010 Sep;1;14:e256-60.
23. Gruenberg DA, Añover-Sombke S, Gern JE, Holland SM, Rosenzweig SD, Torgerson TR, et al. Atypical presentation of IL-12 receptor β1 deficiency with pneumococcal sepsis and disseminated nontuberculous mycobacterial infection in a 19-month-old girl born to nonconsanguineous US residents. Journal of Allergy and Clinical Immunology. 2010 Jan 1;125(1):264-5.

24. Schejbel L, Rasmussen EM, Kemp HB, Lundstedt AC, Nielsen KR, Obel N, et al. Combined IL-12 Receptor and IgA Deficiency in an Adult Man Intestinally Infested by an Unknown, Non-Cultivable Mycobacterium. Scand J Immunol. 2011 Dec;74(6):548–53.
25. Boisson-Dupuis S, El Baghdadi J, Parvaneh N, Bousfiha A, Bustamante J, Feinberg J, et al. IL-12Rβ1 deficiency in two of fifty children with severe tuberculosis from Iran, Morocco, and Turkey. PloS one. 2011 Apr;13(4):e18524. 6(.
26. Schepers K, Schandené L, Bustamante J, Van Vooren JP, de Suremain M, Casanova JL, et al. IL-12Rβ1 deficiency and disseminated Mycobacterium tilburgii disease. Journal of clinical immunology. 2013 Nov 1;33(8):1285-8.
27. Gimenez-Sanchez F, Cobos-Carrascosa E, Sanchez-Forte M, Martinez-Lirola M, Lopez-Ruzafa E, Galera-Martinez R, et al. Different penetrance of disseminated infections caused by nontuberculous Mycobacteria in Mendelian susceptibility to mycobacterial disease associated with a novel mutation. The Pediatric infectious disease journal. 2014 Mar 1;33(3):328 – 30.
28. Senanayake MP, Kumararatne DS, Doffinger R, Barcenas-Morales G. Disseminated BCG in an infant with interleukin-12 receptor B1 (IL12Rß1) deficiency. Paediatrics and international child health. 2015 Feb 1;35(1):69–71.
29. Al-Kzayer LA, Yassin AK, Salih KH, Shigemura T, Sano K, Al-Simaani RB, et al. Syrian refugee in Iraq diagnosed as a case of IL12Rß1 deficiency in Japan using dried blood spots. Frontiers in immunology. 2019 Jan 25;10:58.
30. Mahdaviani SA, Mansouri D, Jamee M, Zaki-Dizaji M, Aghdam KR, Mortaz E, et al. Mendelian Susceptibility to Mycobacterial Disease (MSMD): Clinical and Genetic Features of 32 Iranian Patients. J Clin Immunol. 2020 Aug;40(6):872–82.
31. León-Lara X, Hernández-Nieto L, Zamora CV, Rodríguez-D'Cid R, Gutiérrez ME, Espinosa-Padilla S, et al. Disseminated Infectious Disease Caused by Histoplasma capsulatum in an Adult Patient as First Manifestation of Inherited IL-12Rβ1 Deficiency. J Clin Immunol. 2020 Oct;40(7):1051–4.

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