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IMDDHH: A Contribution to the Understanding of the Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Inborn Errors of Immunity (IEI) is an extremely rare group of heterogenous disorders which are characterized by predisposition to severe unusual and recurrent infections, severe allergies, features suggestive of autoimmune conditions and sometimes malignancies. We report a two-year-old female child presented to our emergency department with complaints of a history of recurrent respiratory infections, recurrent skin infections and a recent history of purulent discharge from both ears. Clinical examination revealed acute otitis media, pneumonia, multiple healed skin lesions associated with soft non-tender hepatomegaly and normal cardiac findings. Elevated hepatic transaminases and hypogammaglobulinemia suggested the possibility of an inborn error of immunity. A whole exome sequencing study performed on the patient established a diagnosis of IMDDHH (Immunodeficiency, Developmental Delay, and Hypohomosyteinemia) by revealing a missense mutation in *the NFE2L2* gene of chromosome 2q31. Diagnosing such conditions with

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inborn errors of immunity requires a high index of suspicion combined with a comprehensive knowledge of the structure and function of both innate and adaptive immune systems. Recurrent skin and respiratory infections in a growing child belonging to a low-and-middle-income country like India is a common clinical scenario encountered frequently in pediatric clinic practice and is often ignored after attributing it to poor hygienic conditions. However, with careful history taking and examination, a sub-group of such patients may be isolated with a high probability of an underlying IEI, which can later be confirmed by genetic work-up.

Keywords: IMDDHH; immunodeficiency; developmental delay; hypohomocysteinemia; recurrent respiratory infections; recurrent skin infections.

1. INTRODUCTION

Inborn Errors of Immunity (IEI) is an extremely rare heterogeneous group of disorders which are predominantly diagnosed in infancy or in early childhood but may sometimes go unnoticed till late adolescence or adulthood [1]. Nearly 500 such disorders have been identified, most of them caused by single gene mutations and affect the normal immune system development and function. While individually rare, the collective prevalence of these conditions can be as high as 1-5 per 1000 population [2]. Classically characterized by recurrent infections and growth failure, IEIs can have multi-system involvement imparting significant morbidity and mortality to the pediatric population and also are a source of significant financial and emotional burden to the family members. While frequent, severe and unusual infections characterize the classical picture of a child with IEI, specific susceptibility to certain infectious agents, severe allergies, inflammatory processes, features suggestive of autoimmunity and certain malignancies are being reported as the presenting features of such patients [3]. We report a two-year-old female child who presented to our department with complaints of severe respiratory and skin infections and was later genetically confirmed to be a case of IMDDHH (Immunodeficiency, Developmental Delay, Hypohomocysteinemia), which is an extremely rare inborn error of immunity with only four cases reported till now in literature.

2. CASE REPORT

The propositus is a two-year-old female child who presented to the emergency room of our pediatrics department with complaints of pain in both ears with purulent discharge for the previous 10 days associated with high-grade fever, cough and progressive difficulty in breathing. On examination, the patient was confirmed to have bilateral acute otitis media, the features suggestive of pneumonia and evidence of recurrent skin infections in the past as evidenced by the multiple old scars with hyperpigmentation all over the body. (Figs. 1 and 2)

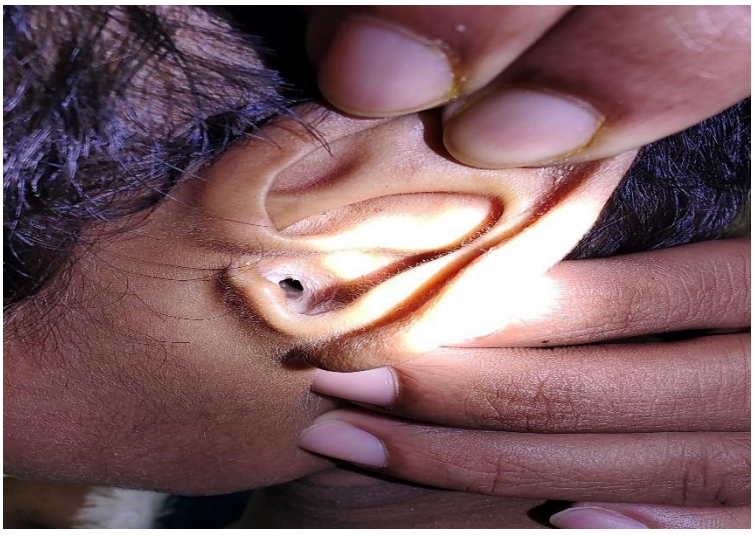

Fig. 1. Patient had recurrent episodes of bilateral otitis media

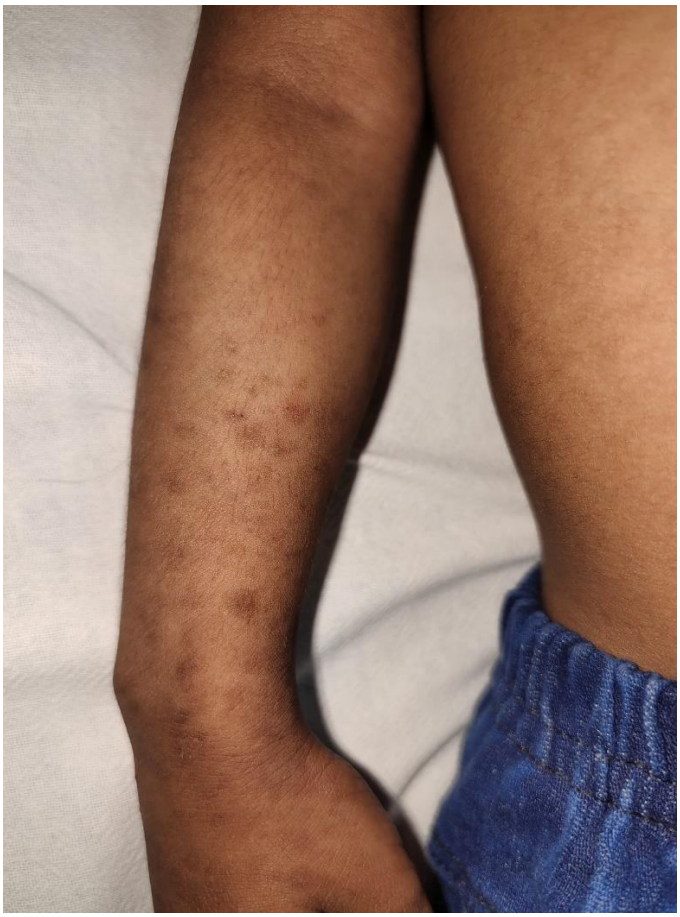

Fig. 2. Patient had multiple hypopigmented patches on skin all over the body indicating multiple healed skin infections of past

There was no history of any similar illness in any of the family members, no history of any pregnancy loss or sibling death and the immunisation history of the patient was up-to-date for age. There was mild developmental delay in the child in the domains of gross motor, fine motor and language skills. Anthropometry revealed both the weight for age and height for age to be between minus 1 and minus 2 SD (standard deviation). The liver span was 8cm indicating hepatomegaly which was soft & non-tender and was also associated with mildly increased transaminase levels. Suspecting the presence of an inborn error of immunity, an immunoglobulin profile of serum was performed which revealed decreased IgG levels. (Table 1).

Table 1. Various biochemical parameters of the patient viz. Hypogammaglobulinemia

Investigation	Observed value	Normal range
Hemoglobin (g/dL)	10.4	11-13
Total Leukocyte Count (per mm^3)	4,196	4,000-11,000
Total Platelet Count (per mm^3)	2.21Lakh	1.5L-4.5Lakh
SGOT (IU/L)	117	10-40
SGPT (IU/L)	124	10-40
ALP (IU/L)	425	44-147
Total Bilirubin (mg/dL)	0.9	0.2-1
Protein (g/dL)	5.4	6-8
Albumin (g/dL)	3.9	3.5-5.0
Urea (mg/dL)	27	8-40
Creatinine (mg/dL)	0.5	0.6-1.0
IgG level (mg/dL)	125	600-1700

2D ECHO revealed no significant cardiac abnormality. After obtaining consent from parents, a whole exome sequencing study was performed which revealed a missense mutation in *NFE2L2* gene at exon 5 (variant c.1244C>G) of chromosome 2q31 (which results in amino acid substitution of Threonine by Serine at position 415) thus confirming a diagnosis of Immunodeficiency, developmental delay, hypohomocysteinemia (IMDDHH) (OMIM #617744), only the fifth reported case in the literature so far. The patient was started on luteolin and ascorbic acid tablets and asked for a follow-up. At 6-month follow-up, the patient continued to have recurrent episodes of lower respiratory tract infections with intermittent hemoptysis and bronchiectatic changes on chest imaging. The patient is being managed by supportive therapy.

3. DISCUSSION

Immunodeficiency, developmental delay, hypohomocysteinemia (IMDDHH) is an extremely rare multisystem disorder which is characterized by, as the name suggests, immunodeficiency, psychomotor delay, growth failure and hypohomocysteinemia. There is also a variable incidence of congenital cardiac defects and hepatic involvement in the patients affected by this condition. Only four cases have been reported till today in the literature [4].

Nuclear factor erythroid 2 related factors 2 (*NRF2*) belongs to the Cnc (*Cap 'n' Collar*) family of basic leucine zipper transcription factors that recognize the Antioxidant Response Element (ARE) present in the regulator region of the various genes involved in the cellular defence mechanism against several insults such as oxidative stress, infections, toxins and hypoxia [5]. Under the conditions of stress, *NRF2* migrates into the cellular nucleus and forms a heterodimer with the small *Maf* (Musculo Aponeurotic Fibrosarcoma) proteins, which in turn binds to and activates the AREs leading to the activation of the respective target gene [6]. At other times, *NRF2* is rapidly inactivated by degradation in 26S proteasome ($T_{1/2}$ = 20 minutes), by virtue of its binding to the *KEAP1* homodimers in the cellular cytoplasm. *KEAP1*, or Kelch-like ECH-associated protein 1, is a cysteine-rich protein that helps in the ubiquitination of *NRF2* by the *Cullin-RING E3 ligase* complex [7,8]. De novo missense mutations in *NFE2L2* affect the binding sites of *KEAP1* and lead to the accumulation of *NRF2* resulting in the increased expression of genes regulated by *NRF2* [4].

IMDDHH is caused by a heterozygous mutation in *the NFE2L2* gene on chromosome 2q31 and is inherited in an autosomal dominant manner. Huppke *et al.* have reported 4 unrelated cases between 1 year 8 months and 14 years afflicted with this condition [4]. The patients characteristically have failed to thrive, ultimately leading to short stature. The presence of immunodeficiency leads to recurrent respiratory and skin infections in the form of pneumonia, otitis media etc. which may require repeated hospitalizations imparting a severe psychological and financial burden on the family. A work-up often reveals hypogammaglobulinemia, IgA deficiency and sometimes defective NK cell function [4]. The delayed acquisition of fine motor skills and speech development further complicates the lives of the affected patients.

Ascorbic acid and luteolin are two therapeutic options for IMDDHH described in the literature so far, as they have been shown to decrease the levels of *NRF2* and have no serious adverse effects [9]. Ascorbic acid has anti-oxidant effects and can suppress levels of *NRF2*, and has been utilized in the treatment of Imatinib-resistant chronic myelogenous leukaemia by virtue of this mechanism of action [10]. Luteolin is a polyphenolic flavonoid and has potent *NRF2* inhibitor activity. It is found in high concentrations in celery, parsley and green pepper [11]. Treatment with luteolin and ascorbic acid has demonstrated normalization of the hepatic function, reduction in the incidence of respiratory infections and improvement in the scholastic performance of patients with IMDDHH [4].

4. CONCLUSION

Having a high index of suspicion is extremely important while diagnosing and managing cases suspected of having inborn errors of immunity. Contrary to common belief, the incidence of such conditions may be significantly higher than expected and the low reported incidence can be attributed to the lack of definitive investigations needed to diagnose such rare conditions. A clinical picture characterized by recurrent respiratory and dermatological infections is not uncommon in pediatric practice and is most often attributed to poor sanitary conditions in a developing country such as India. But when

probed upon such cases may reveal an underlying immune disorder, such as IMDDHH, which can have therapeutic options and can significantly improve the quality of life both of the patient and his/her family.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Khalilzadeh S, Boloorsaz MR, Baghaie N, Sadeghi SM, Hassanzad M, Velayati AA. Primary immunodeficiency in children: Report of seven years study. Tanaffos. 2011;10(2):38-43.
   PMID: 25191361; PMCID: PMC4153139.
2. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507.
   DOI: 10.1007/s10875-022-01289-3
   EPUB: 2022 Jun 24. PMID: 35748970; PMCID: PMC9244088.
3. Picard C, Bobby Gaspar H, Al-Herz W, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018; 38(1):96-128.
   DOI: 10.1007/s10875-017-0464-9
4. Huppke P, Weissbach S, Church JA, Schnur R, Krusen M, Dreha-Kulaczewski S, Kühn-Velten WN, Wolf A, Huppke B, Millan F, Begtrup A, Almusafri F, Thiele H, Altmüller J, Nürnberg P, Müller M, Gärtner J. Activating de novo mutations in NFE2L2 encoding NRF2 cause a multisystem disorder. Nat Commun. 2017;8(1):818.
   DOI: 10.1038/s41467-017-00932-7
   PMID: 29018201; PMCID: PMC5635015.
5. Kobayashi M, Yamamoto M. Nrf2-Keap1 regulation of cellular defense mechanisms against electrophiles and reactive oxygen species. Adv Enzyme Regul. 2006;46:113-40.
   DOI: 10.1016/j.advenzreg.2006.01.007
   Epub 2006 Aug 2. PMID: 16887173.
6. Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, Oyake T, Hayashi N, Satoh K, Hatayama I, Yamamoto M, Nabeshima Y. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun. 1997;236(2):313-22.
   DOI: 10.1006/bbrc.1997.6943
   PMID: 9240432.
7. Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD, Yamamoto M. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes Dev. 1999;13(1):76-86.
   DOI: 10.1101/gad.13.1.76
   PMID: 9887101; PMCID: PMC316370.
8. Furukawa M, Xiong Y. BTB protein Keap1 targets antioxidant transcription factor Nrf2 for ubiquitination by the Cullin 3-Roc1 ligase. Mol Cell Biol. 2005;25(1):162-71.
   DOI: 10.1128/MCB.25.1.162-171.2005
   PMID: 15601839; PMCID: PMC538799.
9. No JH, Kim YB, Song YS. Targeting nrf2 signaling to combat chemoresistance. J. Cancer Prevent. 2014;19:111–117.
   Available:https://doi.org/10.15430/jcp.2014.19.2.111
10. Tarumoto T, Nagai T, Ohmine K, Miyoshi T, Nakamura M, Kondo T, Mitsugi K, Nakano S, Muroi K, Komatsu N, Ozawa K. Ascorbic acid restores sensitivity to imatinib via suppression of Nrf2-dependent gene expression in the imatinib-resistant cell line. Exp Hematol. 2004;32 (4):375-81.
    DOI: 10.1016/j.exphem.2004.01.007.
    PMID: 15050748.
11. Tang X, Wang H, Fan L, Wu X, Xin A, Ren H, Wang XJ. Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung

carcinoma A549 cells to therapeutic drugs. Free Radic Biol Med. 2011;50(11):1599-609. DOI:10.1016/j.freeradbiomed.2011.03.008. Epub 2011 Mar 12. PMID: 21402146.

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