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Case Report

Rare Primary and Combined Immunodeficiency Disease: A Case Report from Paediatric Emergency Reception of Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

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I N F O

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A B S T R A C T

Combined immunodeficiency disease is a hereditary disease that evolves from the time of birth till the appearance of signs and symptoms at the age of six months specifically due to a weakened immune system and attack of infectious agents like bacteria, fungi, viruses, protozoans etc. An eight-year-old male child was admitted to the Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir repeatedly for intravenous administration of immunoglobulin. He was suffering from primary and combined immunodeficiency disease which is a rare condition that affects lymphocytes and leads to the weakening of the immune system. The patient was unable to defend his body from opportunistic infections. He was a child born to a consanguineous couple having birth order three. The impact of this disease was not only on the patient but on the family as well. The family was drained economically and mentally. This disease is not curable and can be managed only with palliative/ supportive care and with each passing day, the disability of the patient was increasing.

Keywords: Combined Immunodeficiency Disease, SKIMS, Case, X-linked, B and T Lymphocytes

Introduction

Combined immunodeficiency disease, also called combined immune deficiency (CID), is a hereditary disease (gene is inherited by the child from parents) that evolves from the time of birth till the appearance of signs and symptoms at the age of six months specifically due to a weakened immune system and attack of infectious agents like bacteria, fungi, viruses, protozoans etc. It is also called primary immunodeficiency. We must keep in mind that though CID is mild in nature, its acute type is serious and aggressive. It has been observed that this disease, maybe autosomal or X-linked, and may affect a neonate. This usually affects T and B cell functions or may lead to the deficiency of both T and B lymphocytes in the body. The child who is suffering from this inherited disease usually experiences recurrent infections caused by various microorganisms. In such cases, it has been observed that T cells and B cells are

either entirely absent or their function gets imbalanced. Thus due to these reasons, these patients are at higher risk of developing other diseases or getting misdiagnosed a number of times. Hence they may remain mislabelled for a few years of early life. This disease is one of the most deadly diseases that eventually lead to the death of a person if left untreated beyond 1 year of age. It is very fatal particularly in the first few years of life so the patients must receive immune boosting agents, particularly stem cells or immunomodulators.[1–3]

The normal function of the immune system is to protect our body by the formation of B and T lymphocytes, thereby fighting against the foreign invaders that attack the body. Here, in this disease condition, the immune system is unable to fight infections and diseases and thus an individual becomes highly susceptible to life-threatening diseases.[2]

Sometimes, it becomes very difficult for a clinician to differentiate between CID and other diseases occurring due to immunodeficiency and opportunism of other microbes. It is of utmost importance that this disease should be evaluated properly and diagnosed at an early stage of life so that treatment can be provided and necessary precautions can be taken to minimise the chances of infection and eventually take steps to boost the immune system of the individual.

Epidemiology

In the United States, there was a foundation known as the Jeffrey Model Foundation that implemented public awareness campaigns to identify primary immune deficiencies in the year 2003. Moreover, it was due to this organisation that severe combined immune deficiency diseases (SCID) were identified. The same organisation started screening the newborn population in order to identify SCID and T cell lymphopenia.[4,5]

In one of the reports in the United States, it was found that the incidence of CID was about 1:58000 live births. The same study depicted that due to higher incidences of autosomal recessive inheritance, the chances of SCID are more common in the offspring of consanguineous marriages. There are no records available at the national level regarding the incidence and prevalence of SCID in India, however, due to various reports and statistical projections, it has been estimated that there are more than a million cases of the disease at present in our country.[6]

Case Presentation

Being posted in the triage area of the Emergencies and Accidents Department of Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, we came across thousands of cases on a daily basis. The patient discussed in this report came to seek healthcare services in the paediatric emergency reception of SKIMS, Soura. SKIMS Soura, being the only tertiary care hospital near the Himalayan mountains, is the only hope for people residing in the valley and adjoining areas, particularly Leh and Ladakh. However, very rarely do we come in contact with such diseases in our clinical encounters that have less incidence in our population and are usually unreported. Hence in order to make our population and healthcare workers aware of this rare disease, we found it important to report this condition so that it can be brought to the notice of medical and nursing practitioners and its diagnosis is not missed or mislabelled.

Health History

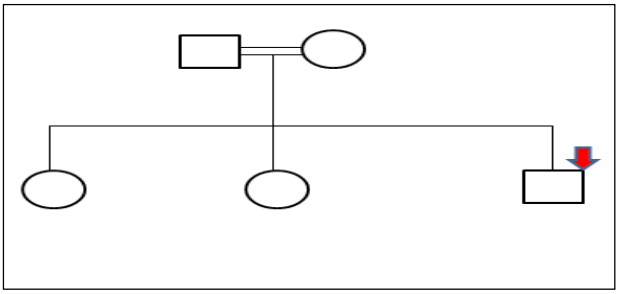

Figure 1. Genogram of the Client

The patient was an eight-year-old male child born in February 2014 to a consanguineous couple from 3rd progeny primarily suffering from congenital talipes equinovarus.

As per the father of the patient, the child was apparently well till 6 months of age, when he developed eczematous lesions over the face which gradually progressed to involve the complete body in about 3 to 4 months and were associated with severe itching. The symptoms had been relapsing and remitting for over 3 and a half years without a symptom-free period in between. The lesions used to increase in size with mucopurulent discharge. There was a history of skin peeling of fingers with past discharge from the lesions from 20 days in the year 2014. Moreover, the father of the client also complained that there were episodes of skin peeling from the lesions over the medial aspect of thighs and inner aspect of eyes for 15 days in the year 2014. However, the father stated that they are was no recurrent cough, chest infection or ear discharge.

The patient's father also added that there was no history of allergy, atrophy or similar complaints in the family and there was no bleeding manifestation in the past either in the family members or in the patient himself. The informant (father of the patient) also said that the patient had a history of allergic rhinitis on exposure to dust and pollen. He had been taken for treatment to various government hospitals in Jammu and Kashmir on an OPD basis. The patient was eventually taken to Jammu for better care and management and was treated as a case of atopic dermatitis with oral antihistamines and topical steroids from 2014 to June 2017. The patient was also given a course of cyclosporine

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for a year from June 2017 to 2018 and was symptom-free during that period of time. However, as per the father, once cyclosporine was stopped, the lesions eventually erupted with severity.

As per the father, the lesions were more severe and there was no relief for the patient, so they took him for better care to Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh in the year 2018. He was admitted as a case of suspected hyper IgE syndrome with secondary bacterial infection of hands, herpes labialis and molluscum contagiosum. Pus culture and sensitivity test were done which depicted that the bacteria present in the pus was Staphylococcus aureus. The report further showed the presence of herpes labialis and the presence of extensive molluscum with features of atopic dermatitis.

In 2019, the patient again complained of recurrent persistent oozing plaques over the face, hands, axila, and legs. He was again evaluated by a local dermatologist who labelled the condition as atopic eczema and amino deficiency syndrome. The local dermatologist asked for CD4 and CD8 counts, the results of which depicted a reversal of ratio. It was here that the patient was again re-advised for an array of tests that turned out to be normal again. The dermatologist also contacted one of the non-government organisations working on a project of a foreign university to get a mutation analysis done. The results of the report brought forth that he was suffering from CARMIL2 (capping protein, Arp2/3, myosin-I linker) defect which causes a defective CD28 co-signalling associated with impaired T-cell activation, differentiation, and function.

In the year 2020, the patient was again evaluated for a dystrophic nail with chronic mucocutaneous candidiasis. The clinician at that time suspected that the client must be followed up as he might be suffering from autoimmune polyendocrinopathy type I. Here the patient was advised to undergo a 24-hour urinalysis. The client had collected the urine and the amount was 800 ml. On analysis, no urinary protein or uric acid was detected in the sample.

In the year 2020, it became apparent that the patient was suffering from steroid-related growth retardation with features of Cushing syndrome and the patient had developed rickets due to hyperparathyroidism.

These features are somewhat similar to the symptoms reported in a related research paper on SCID that include the presence of the disease in the early months of life, fungal infections (recurrent/ persistent), candidiasis, growth retardation, lymphopenia, opportunistic/ recurrent infections, frequent use of antimicrobial agents, blood disorders like anaemia and low platelet count, autoimmunity, protozoal infections and inflammation of internal organs.[7]

Diagnosis

From 2014 to 2022, there were various investigations that were done at various healthcare centres where the patient visited. Some of the documented and available reports were:

The thyroid function test of the patient that was done in PGIMER depicted that T3 was 1.89, T4 was 8.1, and TSH was 1.45. The latest test was done in 2022 itself which showed the T3, T4, and TSH values to be 1.03, 8.91 and 1.64, respectively.

Vitamin D levels were also done. It showed the value to be 10.65 which was far below the normal level.

Blood culture was done for the patient that depicted that there was no microorganism in the blood and it appeared sterile.

Pus culture and sensitivity report showed the presence of Staphylococcus aureus that was sensitive to cloxacillin, ciprofloxacin, clindamycin, vancomycin and teicoplanin.

Lymphocyte subset analysis was done in the same hospital, the results of which depicted normal levels for CD3+, CD19+, and CD56+ cells.

Ig profile was also done in the same hospital. Its results revealed that IgG was in the normal range (869), IgA level was 174, and IgM level was 106.

HIV serology was also done which was non-reactive.

Skin biopsy was also done for the patient and the tissue used for the biopsy was composed of cells that showed atopiform dermatitis.

Haemogram of the patient depicted that the patient's haemoglobin level was 7.0 with a haematocrit value of 25.9% and a mean corpuscular volume of 50.3 fl. The patient was thus suffering from severe anaemia.

Mutation Analysis Report

The patient got his gene analysis done via a research project from the Department of Paediatrics and Adolescent Medicine, The University of Hong Kong on October 23, 2019 with GenBank accession number NC 000016 [genomic DNA, NM 001013838 (mRNA)]. The results depicted that the patient had a mutation on homozygous nucleotide with substitution mutation in intron 21. The report further added that the patient's cDNA mutation G>A and substitution at intron 21 position+1, changing exon 21/intron 21 splice junction from AG/GT to AG/AT, IVS21 + 1G>A (nucleotide coding region c.2082+1G>A). In amino acid change, the report read as aberrant splicing which was further explained in the comment section that the variation is considered as previously unreported and is expected to cause the disorder.

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Management

From 2014 to 2017, the patient was managed with antihistamines and topical medicines in various hospitals of Jammu and Kashmir and was mislabelled as atopic dermatitis. In Jammu, the treatment was augmented with cyclosporine for the treatment of lesions which was a bit helpful.

While the patient was received in Nehru Hospital of PGIMER in 2018, the patient was started with cloxacillin (250 mg 4 times a day for 2 weeks), fluconazole (100 mg once a day for 10 days) and acyclovir (200 mg 3 times a day for 10 days). The patient was also advised to take syrup Septran (7.5 ml per day), which is available in a strength of 200 mg per 40 ml. The patient was advised to use mupirocin ointment for local application. The patient was prescribed syrup hydroxyzine HCL (5 ml 3 times a day), which is available in a strength of 1000 mg per 100 ml.

The patient was managed with the aforementioned treatment and was discharged from Nehru Hospital, PGIMER, Chandigarh in the year 2018.

In 2019, the report of mutation analysis was received which depicted that the patient was suffering from primary immunodeficiency disease and combined immunodeficiency -CARMIL2 defect.

After the diagnosis of CARMIL2 defect, the patient was advised to undergo intravenous immunoglobulin (IVIg) therapy every 6 months to boost his immune system. He was also provided with the option of a hematopoietic stem cell transplant.

The patient was admitted to the Department of Paediatrics at Sher-i-Kashmir Institute of Medical Sciences, Soura in the years 2020 and 2021 multiple times for intravenous immunoglobulin infusion. During his stay in the hospital, the condition of the patient was stable and there were no side effects noticed. He received 100 ml (5 g) of immunoglobulin intravenously for 3 to 4 hours.

The patient again visited Nehru Hospital, PGIMER, Chandigarh for follow-up. He was then advised to continue intravenous immunoglobulin therapy, however, that frequency was changed to monthly administration of 5 grams of intravenous immunoglobulin.

Conclusion

The incidences of congenital disorders like CID are increasing and are nowadays easily diagnosed by means of various investigations/ analyses. These techniques should be used so that each and every disease of this nature can be properly diagnosed as early as possible to start with specific treatment and delay complications that may arise from it. The clinicians should be abreast of knowledge that such diseases must not be confused with related diseases or opportunistic infections, so as to avoid mislabelling or pseudo-diagnosis of the problem.

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