Case report

CMV Infection as a Possible Cause of Chronic Diarrhea in Patient With Autosomal Recessive Hyper IgE Syndrome

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ABSTRACT

Hyper IgE syndrome especially the autosomal recessive genotype caused by DOCK8 mutation is not rare immunodeficiency disorder in Saudi Arabia due to high consanguinity. DOCK8 disruption will alter the normal immune function leading to higher susceptibility to viral infection and allergic diseases. Chronic diarrhea in AR-HIES is extremely rare; thus, we are reporting a 5-year old DOCK8 mutation who had chronic severe diarrhea explained only by cytomegalovirus infection and died despite intensive management.

1. Introduction

Autosomal recessive hyper IgE syndrome (AR-HIES) is a multisystemic immunodeficiency disease characterized by eczema, recurrent bacterial infection and over production of IgE caused by mutation in the DOCK8 gene[1] Other clinical presentations have been reported including bronchial asthma, food allergy, failure to thrive (FTT), diarrhea, malignancies like squamous cell carcinoma and lymphomas, skeletal and dental abnormalities.[2,3,4] Infections such as osteomyelitis, meningitis, enteritis, and progressive multifocal leukoencephalopathy (PML) were seen in few cases.[4,5,6] Cutaneous viral infections frequently seen in AR-HIES included human papillomavirus (HPV), herpes simplex and varicella zoster.[4-6] In single center experience of 25 patients in Saudi Arabia, Epstein-Barr Virus (EBV) and/or cytomegalovirus (CMV) infection reported in 10 patients (40%); one of them was critically ill with severe diarrhea, eosinophilic pneumonia, bronchiolitis and spondylohepatitis requiring stem cell transplantation; their statistical analysis found that CMV infection was the only significant predicting factor for a poor prognosis and early death.[2] Similar study was done in Kuwait including 9 DOCK8 deficient patients; two CMV infection was documented and one of them died due to CMV sepsis.[7] In this paper we are reporting a 5-year-old patient with AR-HIES diagnosed by gene study who had unexplained severe chronic diarrhea and CMV viremia but died despite intensive treatment.

Case report:

A 5-year-old female, diagnosed early in her life with Hyper-IgE syndrome based on clinical picture of recurrent skin and sinopulmonary infection s, bronchiectasis and chronic otitis media with effusion confirmed by homoygous gene mutation in DOCK8 gene. She was started on monthly IVIG and prophylactic Sulfamethoxazole & Trimethoprim. She was admitted in our intensive care unite with septic shock (Staphylococcus aureus bacteraemia, Streptococcus pyogenes and Staphylococcus haemolyticus from multiple skin abscesses and Serratia fonticola from ear culture). She found to have chronic diarrhea, progressive weight loss and severe failure to thrive.

She was admitted on March 15, 2017 for more than one month with very complicated course. She was intubated on inotropes and treated with antibiotics, antifungal, IVIG replacement, steroid, multiple PRBC transfusion due to severe low hemoglobin and received low molecular weight heparin due to bilateral lower limb deep venous thrombosis. Besides that she found to have continuous loose bowel motion from the first day of admission which was watery and in large amount reach more than 1 Litre per day. No previous history of diarrhea according to the mother but there was history of progressive weight loss over the last six months. Patient was initially NPO started on TPN with nutrition support until bowel control was achieved. No previous history of diarrhea according to the mother but there was history of progressive weight loss over the last six months. Patient was initially NPO started on TPN with nutrition support until bowel control was achieved. 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crucial factors for the formation of burns during electrocautery. For that purpose, calculations were carried out for DC argon discharges having in mind that the main advantage of argon coagulation is constant, a minimum depth of the thermal effect. The emphasis was put on generation of sparks between various electrode arrangements (cylinder-cylinder, sphere-sphere cylinder-sphere, cylinder-cone, sphere-cone, and cone-cone). Electrocautery sparks have been distinguished both for the positive and negative cycles. It was found that mechanisms of electrical spark formation are not equal in both directions introducing the electrical asymmetry.

**MATERIALS AND METHOD**

Cautery can be operated in a monopolar or bipolar configuration as illustrated in Figure 1 [21,22]. In the monopolar configuration, an electrical circuit is completed between the generator, cables, surgical electrodes, and return electrode [23,24]. The surgical current is dissipated from the surgical electrode through the patient to the return electrode completing the path to the cautery generator. Although the monopolar electrocautery is easy to use, it can cause a large volume of tissue injured and interfere with pacemakers. Bipolar configuration, however, is composed of two closely spaced electrodes serving as the surgical electrode and return electrode [25,26]. The current is restricted to a small volume of tissue close to or between the electrode pair. Advantages of bipolar configuration encompass a small volume of tissue injured and less risk of burn injury albeit it requires more skills.

**Discussion:**

Primary immunodeficiency diseases (PID) are heterogeneous group of inherited genetic defects of the immune system. Up to 200 phenotypes of PID are well-known but it is believed that more potential diseases have not been identified yet and more gene causing immune diseases are emerging due to advance molecular genetic testing.[8] In the Middle Eastern Countries, a high incidence and prevalence of immune disorders inherited as autosomal recessive pattern due to high rate of consanguinity reaching more than 50%.[9,10] Prolonged diarrhea, failure to thrive and recurrent infections are potentially warning signs for PID.[11] Prolonged diarrhea that persists for more than 2 weeks, fails to respond to conventional treatment and requires parenteral nutrition is defined as severe protracted diarrhea (SD).[12] Most of the SD found to be due to infectious cause and the usual detectable organisms include salmonella, pseudomonas, E.coli, cryptosporidium, coxsackie virus and CMV.[11] While Chronic diarrhea is defined as loose stools, increased stool frequency, or urgency for more than 4 weeks duration in it is rarely to be due to infection.[13] In Hyper IgE syndrome (HIES), Chronic diarrhea unlike SD is extremely rare and only 2 cases were mentioned in the literature.[14] HIES is triad of eczema, recurrent infection and elevated IgE. However, the genetic etiology divided in to autosomal dominant (AD-HIES) where is STAT3 mutation is major cause; and autosomal recessive (AR-HIES) which causes either by homozygous or compound heterozygous mutation in DOCK8.[3] SD had been reported in AD-HIES in which the patients had 5-6 episodes per year with average 6 bowel motions per day and lasting for 15-20 days.[11] Similarly, SD was seen in DOCK8 deficient patients; frequently with salmonella enteritis and Giardiasis.[16] DOCK8 disruption leads to severe cellular immunodeficiency characterized by impaired T-cell activation and natural killer (NK) cell functions, abnormal eosinophil homeostasis and IgE over production; which are predisposing to viral infection and allergic disease.[4,17] Allergic disease is very common among AR-HIES patients includes allergy to food or drugs, urticaria, asthma and allergic rhinitis.[2,6] In large study including 136 DOCK8 deficient patients, allergy found in 71% and more than 80% of those to food allergens.[6] Similarly in Saudi Arabia, the commonest allergic disorder was food hyper sensitivity with percentage of 70% of AR-HIES patients.[2] Hint, food allergy can explain the prolonged diarrhea in HIES.[14] Endoscopic histological evaluation of those patients with SD, the finding of erythematous edematous mucosa is suggestive for intestinal inflammation thus; the persistent intestinal inflammation due to the pathology of the disease itself can play a major role than infection, reflecting poor response to specific antimicrobial treatment and support the theory of food hypersensitivity.[11]

AR-HIES patients with DOCK8 mutation can present with prolonged diarrhea but the cause whether it is due to infection or food hyper senstivity still not clear. CMV infection can be seen in AR-HIES but associated with high mortality.

**Conflict of interest:**

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

**Abbreviations:**

IVIG: intravenous immunoglobulin IgE: immunoglobulin E
DOCK8: Dedicator of cytokinesis 8
HIV: human immunodeficiency virus
NGT: nasogastric tube
DNR: do not resuscitate
PCR: Polymerase chain reaction
TPN: total parenteral nutrition

**References:**

[8] Abadel, B. (2020). "Primary immunodeficiency diseases (PID) are heterogeneous group of inherited genetic defects of the immune system. Up to 200 clinical phenotypes of PID are well-known but it is believed that more potential diseases have not been identified yet and more gene causing immune diseases are emerging due to advance molecular genetic testing." In: Int J Biol Med Res. 11(4): 7176-7178.


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