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Research Article

A Case Report on Disseminated Candida Lusitaniae Infection and Tuberculous Lymphadenitis in Patient with Compound Heterozygous Pair of Mutations of CYBA Chronic Granulomatous Disease

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Abstract:

Chronic granulomatous disease (CGD) is an unusual hereditary chief immune- deficiency disease, which is characterized by nicotinamide adenine dinucleotide phosphate oxidase (NADPH) system malfunction. In this type of disease the phagocytic cells could not be able to destroy the pathogens at the time of development of an infection. This will result in patient's susceptibility to recurrent and intractable microbial infections. The disease is considered to be a genetically heterogeneous having equal susceptibility among all the ethnic groups. Patients with (CGD) suffer from persistent, fatal fungal and bacterial infections of theskin, the lymph nodes, airways, brain, liver, and bones. Whenever there is an infection with any odd microorganisms the susceptibility for CGD rises.

In our article we aim to report a case study of a 4 months old female with disseminated candidiasis Tuberculosis lymphadenitis in details. The infant was treated successfully with antifungal voriconazole and broad spectrum antibacterial agents as well as anti-mycobacterial medications. When the patient was followedup later, it showed regression of the abnormal reports. But later developed CNS Candida and disseminated tuberculous with sequalae. Diagnosis was confirmed as heterozygous CYBA forp22phox, defect by genetic analysis. P22phox is an omnipresent protein which is coded by thegene CYBA located on the long arm of chromosome16. P22phox it is crucial factor of the enzyme superoxide-generating (NADPH) oxidase.

Infection with bacteria, Candida lusitaniae is maximum among the patients whoare suffering with haematological malignancies. The chance of the infection rises when the patient is receiving chemotherapy. This type of infection usually occurs among the patients who are presenting fungal infection that has already spread throughout the blood and among them only 7.3% of the patients are showing the symptomatic manifestations of peritonitis. However, the most difficult point is that the laboratory culture is not the answer for the growthof the particular microorganisms as these organisms are extremely difficult to culture or separate.

Key Words: cgd; cyba; disseminated candida lusitaniae; bcgitis

Introduction:

Chronic granulomatous disease (CGD) is considered to be a disease that can be inherited and it occurs due to the disorder of the superoxide-generating phagocyte NADPH oxidase system. 1 That is the reason why patients who are suffering from the CGD are much more prone to infection caused by catalase positive bacteria and also fungus such as Burkholderia cepacia,Aspergillus, Nocardia sp., Serratia marcescens, and Staphylococcus aureus. Moreover, it is also well known that CGD patients are also more susceptible to infectivity caused by sentinel micro-organisms along with heightened risk for pyogenic microorganisms [1].

Here we are going to present a case study with Chronic granulomatous disease (CGD)showing the symptomatic manifestations of lymphadenitis

caused by disseminated Candida lusitaniae and TB(BCG)lymphadenitis. The term disseminated Candida lusitaniae means either the invasive form of candidiasis or immense fungal infection with Candida which surely rapidly spreads up to several visceral organs like kidney, liver, heart, brain, eyes or spleen etc[1, 2]. CGD is also being referred to as "Bridges–Good syndrome". This is an inherited disease where our lymphatic system cannot produce the Reactive Oxygen Species (ROS). Now CGD is caused mainly due to the mutations observed among one of the five alleles namely CYBA, CYBB, NCF1, NCF2, or NCF4 and these alleles codes for the varied subunits of the enzyme named as NADPH oxidase, which plays a significant responsibility within our immune system [2]. As it is a genetic disorder, therefore it can be observed among the children as it affects the important roles of the certain cells and also to build up immunity against varied germs by our immunity. This particular disorder is treated with antibiotics like antibacterials or the antifungals but it cannot cure the condition [2].

In general, signs and symptomatic manifestations of the CGD are presence of fever, pain in the chest while inhalation or exhalation, inflamed and sore lymph glands, irritation of the skin and the constant running of the nose, rash or swollen redness in the mouth or in the skin [2]. As the infections are associated with the formation of the "granuloma" therefore, the nameCGD, however, only a handful of microorganisms cause "granulomas" [3]. Among the bacteria, Mycobacteria, i.e., that causing tuberculosis and also fungi causes formations of granulomas throughout the world [2, 3].

The assays that actually helps in the diagnosis of the granulomas are the neutrophil function test (NFT), and the genetic test that identifies the particular mutations, and dihydrorhodamine reduction assay. The NFT determines that how efficiently the white blood corpuscles (WBC) are tasking throughout our body [3].

The genes of the five NADPH oxidase components are CYBB (located on the X chromosome) encoding gp91phox, and the autosomal genes CYBA encoding p22phox, NCF2 encoding p67phox NCF1 encoding p47phox and NCF4 encoding p40phox. Moreover, 70% of the CGD patients reveal mutation within the CYBB gene (among them mostly are hemizygousmales, whereas few are heterozygous females with distorted expression of their mutation).2 mutations in the CYBA gene that encodes for p22phox and also mutations in NCF2 gene, are considered to be very unusual and as per the past scientific evidence about 6% of total CGD cases identified throughout the globe) and lead to AR220CGD. 3 The protein p22phox is expressed from CYBA gene that is present upon chromosome 16q24. Any of these mutant genes can result in the development of CGD. [4]

Case report:

Patient was a 4-month-old female a product of full-term gestation. She was previously well. She was admitted with history of progressive abdominal distension and fever for the last 2 weeks, no other complains. Patient received BCG vaccine however there are positive familyhistory of TB. No index case of primary immunodeficiency or early death, no consanguinity. Looks sick mild distress, not pale not jaundice, no dysmorphic feature, severe abdominal distension, with generalized tenderness and dilated veins with umbilical hernia, no organomegaly the rest of examinations within normal. All septic, Radiological and Immunological work were done.

Ultrasound test was done and it showed, diffuse increased echogenicity of the visualized bowel loops associated with mild bowel wall thickening and hyperaemia, findings are worrisome for enterocolitis for high clinical concern. Mild to moderate free fluid was notedin the abdomen associated with internal septations predominantly in the sub hepatic region, highly worrisome for superimposed infection /early fluid collection.

CT scan for Chest, Abdomen, and Pelvis (Figure 1) The impression multiple mediastina, hilarand axillary lymph nodes noted some of them showing central necrosis. Tree in bud airspace opacities, hilar opacities associated with bilateral mild pleural effusion were also noted. Extensive innumerable variable size diffuse scattered abdominal necrotic lymph nodes were noted in a background of severe mesenteric fat stranding, mild ascites with no drainablecollection was reported. Differentials may include TB infection, other granulomatous infection;less likely Differentials may include underlying malignancy. After 6 weeks ultrasound repeatedshow, there are remarkable improvements.

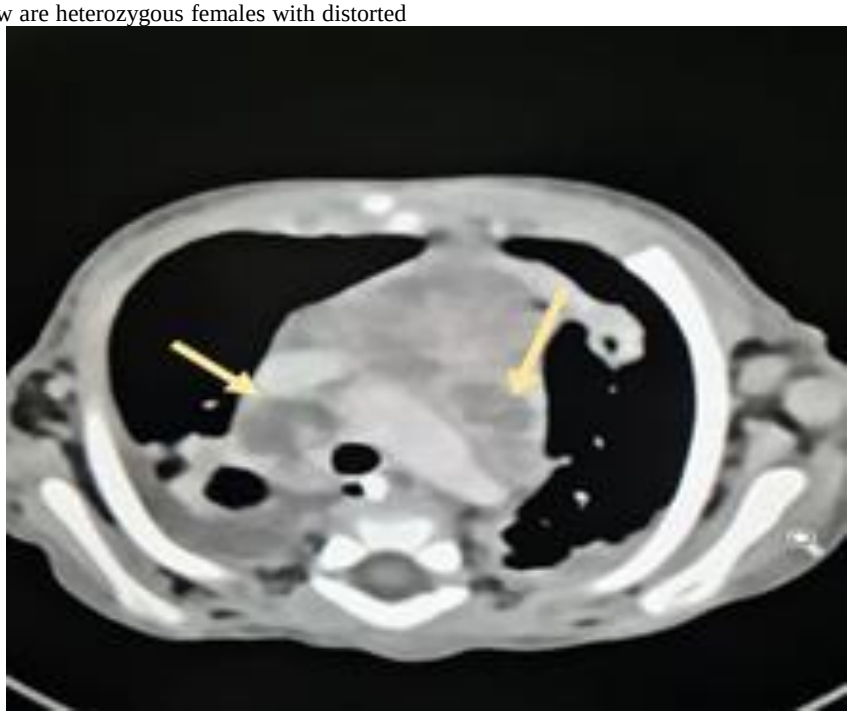

Figure 1: *Ct chest with contrast showed multiple necrotizing hilar and mediastinal lymph nodes, in case of pulmonary TB.*

After 4 weeks from admission left an axillary lymph-node biopsy showed: chronic nonnecrotizing granulomatous lymphadenitis. Refer Figure: 2 Culture for positive AFB, Ziehl- Neelsen stain positive for Acid Fast Bacilli consistent with tubercular lymphadenitis, NegativeGrocott methylamine silver (GMS) stain for fungal identification (Refer Figure 3).

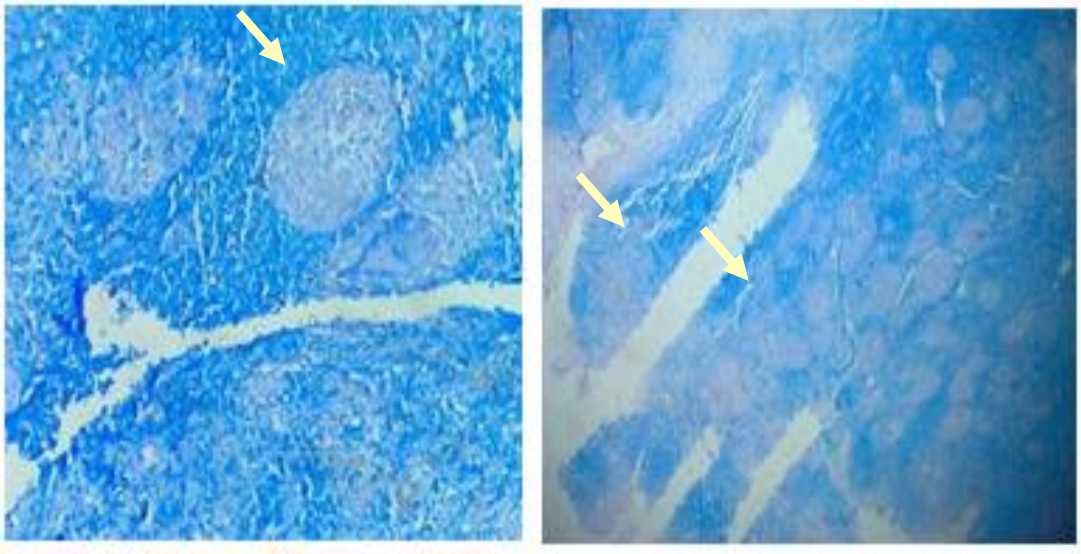

Figure 2: *Lymph node excisional biopsy with ziehl-neelsen stain which is positive for acid fast bacilli consistent with tubercular lymphadenitis*

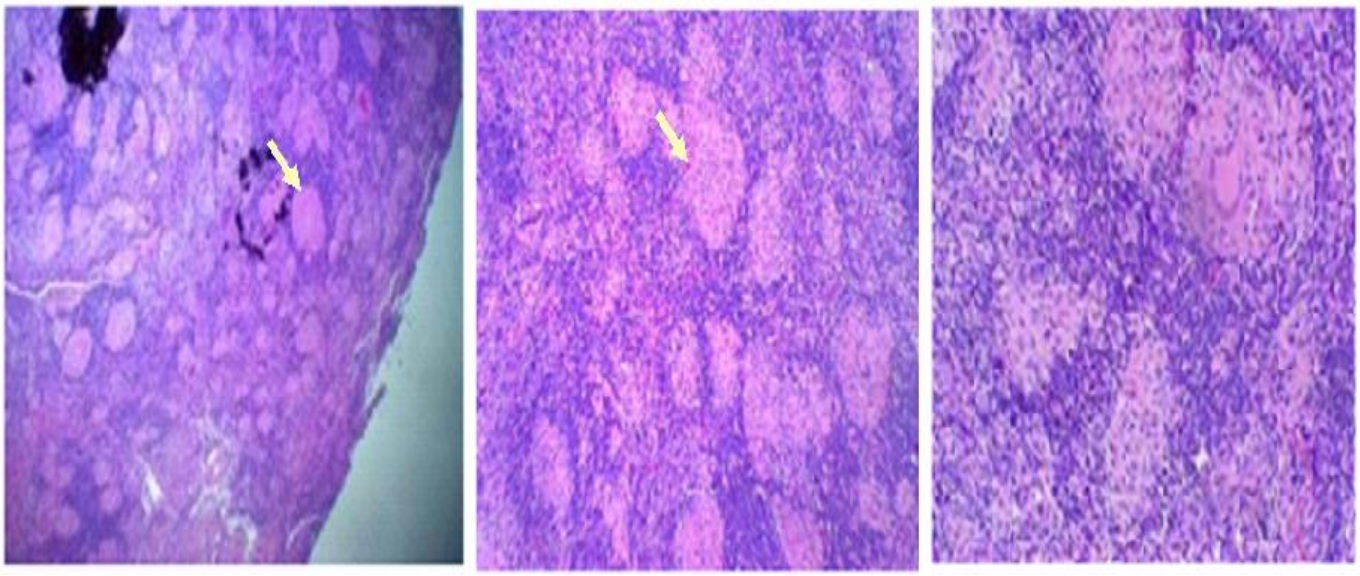

Figure 3: *Lymph node excisional biopsy showed chronic non necrotizing granulomatous lymphadenitis*

She was started on antibiotics amikacin, rifampicin, ethambutol, isoniazid, pyridoxine,methylprednisolone was added. Soon after the start of the antibiotics, patient graduallyimproved [4]. Follow up of abdominal US showed minimal free fluid noted in the pelvis region. Her medications were later switched to oral, and Amikacin was discontinued and levofloxacinwas added. She was having on/off vomiting after feeding, so she was started on omeprazole as well she was discharged on anti-mycobacterial medications.

One month later, patient readmitted with lethargy decreased feeding with vomiting anddehydration and had left facial palsy, hemiplegia. During admission, she developed seizures; she was seen by neurosurgery team and an External Ventricular Drain (EVD) inserted, initial cerebrospinal fluid (CSF) Gram stain and bacterial culture were negative, and polymerase chainreaction (PCR) for mycobacterial tuberculosis also negative [5]. Three weeks later she developedEVD related Candida Lusitania infection where EVD was changed and started on Voriconazolesince the patient's culture report reported the same Candida from urine and abdominal paracentesis.

She was initially on Keppra, phenobarbitone and lorazepam, still had breakthrough seizures, lorazepam was changed to Diazepam, and seizures were controlled [5]. CT brain was done initially showing showed hyperdense small shadow in the left periventricular posterior occipital horn medially, called tuberculosis granuloma (Figure 4).

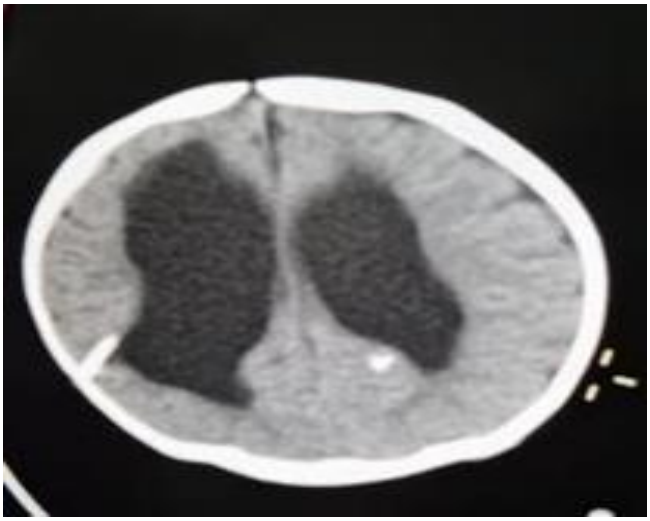

Figure 4: *Brain CT scan showed hyperdense small shadow in the left periventricular posterior occipital horn medially, called tuberculosis granuloma*

Followed by (MRI) brain &spine showed diffuse infective process involving both cerebral hemisphere with two pockets of abscess in addition to the diffuse thick meningeal enhancement in addition to the moderate communicating hydrocephalus seen supra or infratentorial most like representing infective process as diffuse meningitis representing a picture of central nervous system (CNS) tuberculosis and communicating hydrocephalus, spineshow upper cervical disseminated infective process TB vs. pyogenic infection (Figure 5, 6, 7) .

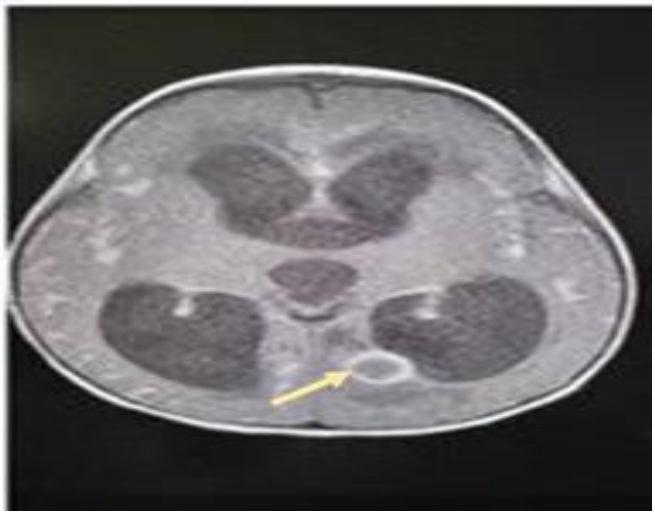

Figure 5: *Abnormal multiple ring enhanced intraparenchymal lesion, brain abscesses*

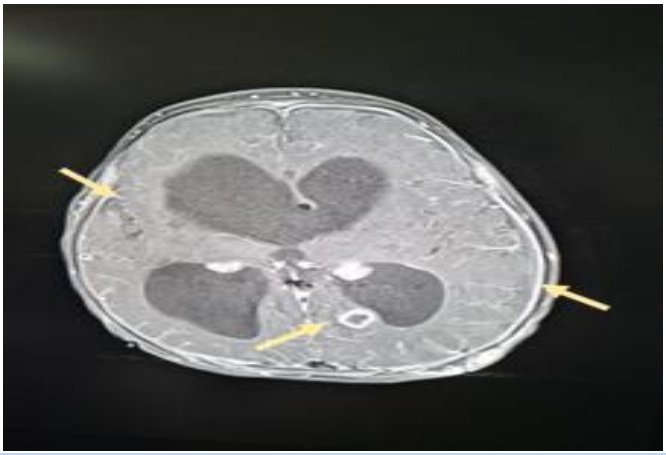

Figure 6: *Axial brain MRI showed redemonstration of multiple enhanced ring shape intraparenchymal brain lesions with interval of mildly decrease in size compared to previous study which is indicate mild regression in size of brain abscesses, called tuberculosis granuloma, with diffuse thick meningeal enhancement representing diffuse meningitis*

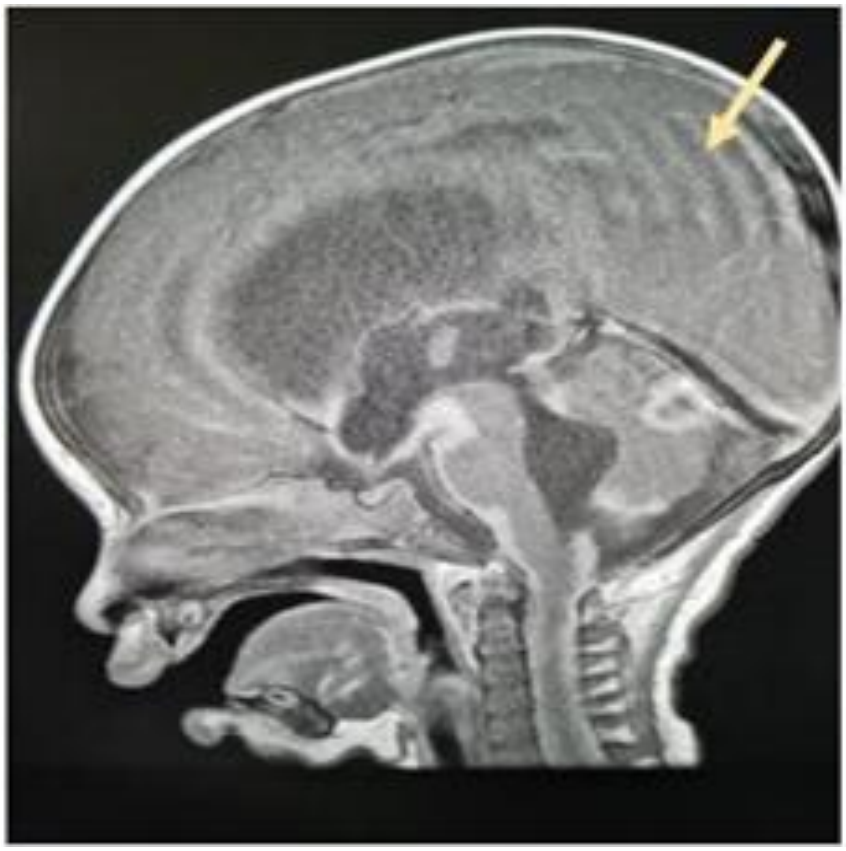

Figure 7: *This is the sagittal cut showing communicated hydrocephalus, all ventricles are dilated above and below tentorial with no obstruction*

Neurosurgeons were consulted, External Ventricular Drain (EVD) was inserted and theCSF culture grew Candida Lusitaniae with the following sensitivity pattern (sensitive to voriconazole and caspofungin but resistant to fluconazole and Amphotericin B). Patient was kept on Voriconazole for 6 weeks were the patient showed clinical improvement repeated CSFstudy parameters normalized and culture showed no growth [5]. The previous MRI brain imagingfindings was resolved, so Ventricular Peritoneal shunt (VP) was inserted. Patient showed slowly progressive improvement from ascites, and complete resolution of all her symptoms. Due to recurrent ascites which it was believed to be due to VP shunt, patient underwent VP Shunt removal and VA insertion. After the surgery she developed persistent vomiting and lethargy and she went to PICU. She developed seizures, was started lorazepam was changed toDiazepam, seizures were controlled for a while then again break through seizures so Keppra dose increased and Topamax added and weaning phenobarbitone started [5]. As because of the patient's persistent ascites, ascitic paracentesis were done frequently. The patient became lethargic had abdominal distension and vomiting, looks dehydrated. She was seen by neurosurgeon and the impression shunt failure revealed by CT scan showed communicating hydrocephalus with right subdural collection. Soon after choroid plexuses cauterization and endoscopic 3rd ventricular cystostomy with EVD done and admitted for two days in PICU. Once the patient become more stable, reassess by neurosurgeon VP inserted and observed for any sign of high IC or ascites. Patient clinical stable and discharge in good condition.

Total White Blood Cell (WBC): 20.08 (10^9/L); neutrophils 59.2 %; lymphocytes 33 %; haemoglobin is 9.3 g/dl (MCV: 80.9 MCH: 24.3 RDW: 17.6) and the platelet count is 818(10^9/L). The biochemical report of the patient also showed that the level of urea: is 1.31 mmol/L, creatinine is 25.5 umol/L, serum albumin is 22.9 g/L, lactic acid is 2.05 mmol/L, aspartate amino-transferase (AST) is 43.22 U/L, alanine amino-transferase (ALT) level is

39.95 U/L, and the C-reactive protein (CRP) is 127 mg/L. he following leucocyte markers were reported as follows: T Lymph (CD3+): 46.74%, CD3 Abs Count: 1616.38, B Lymph (CD19+): 32.64%, CD19 Abs Count: 1128.99, NK-lymph(CD1656 Abs Count: 19.35%, CD16+CD56 Abs Count: 669.13, CD3+CD4 Abs Count: 962.39, T suppressor (CD3+CD8+): 18.95%, CD3+CD4 Abs Count: 655.36, T Helper (CD3+CD4+): 27.83%, T Helper, T Suppressor ratio: 1.47%.

Neutrophil oxidative burst test showed reduced in activity.

Influenza A Virus, Corona Virus, Para-influenza Virus, Respiratory Syncytial Virus A/B, Human Metapneumovirus A/B, Adenovirus, Boca virus, Rhinovirus / Enterovirus, Mycoplasma pneumoniae, Legionella pneumophila, Bordetella pertussis were conducted.

A heterozygous likely pathogenic variant was identified in the CYBA gene. Also, a heterozygous pathogenic variant was identified in the CYBA gene. This like consistent with agenetic diagnosis of Autosomal receive chronic granulomatous disease type 4. Parental carriertesting is needed to identify the phase of the detective variants.

Gene	Varirant Candidates	Amino Acid Change	SNP Identifier	Zygosity	In Silico Parameters	Alelle Frequencies	Type & Classification
CYBA	NM_000101 3:c 261C>A	p. (Tyr87*)	N/A	heterozygous	polyPhen:N/AAlign-GVGD:N/A SHIFT:N/A MutationTaster: Conversation_nt:high Conversation_aa: N/A	gnomAD: -ESP: -1000 G. CentoMD-	Nonsense Pathogenic (class1)
CYBA	NM_000101. 3c.203+1G>C		N/A	heterozygous	Polyphen: N/A Align-GVDGD: N/A Shift: N/A MutationTaster Disease causing Conservation_nthigh Conservation_aa: N/A 2/2 likely spliceeffect	gnomAD:-ESP 1000 G:- CentoMD	Splicing Likely Phatogenic (class 2)

Discussion:

In the case report, it was hypothesized patient suffered from CGD the case is supported by both laboratory and radiological findings.

We had sent sample for the mother, to the Laboratory of Human Genetics of Infectious Diseases, France. DNA extraction was carried out of whole blood by the desired protocol.

This variant has previously been described as disease causing for chronic granulomatous disease heterozygous pair of mutations of CYBA where many of the previous were homozygous [5, 6]. In several cases, the heterozygous parents are observed with respect to the mutations that indicate consanguinity within the family [7-11]. Depending on the prevalence of CGD throughout the globe it is 1 out of 200,000–250,000 live births. The real incidence may be even higher than the predicted incidence, in countries with a higher consanguinity rate, such as Saudi Arabia, Oman and Medial East in general. Therefore, we can find more cases of AR CGD [16].

Mutation analysis of CYBA revealed 12 different mutations, including three novel mutations of CYBA gene in four of 22 Iranian patients with AR-CGD were found [25]. Other study for genetic analysis show in 32 patients with CGD, 4 (17.4%) carried CYBA variants, and 3 (13%) carried NCF2 variants [26]. In Upper Egypt it was observed that many of the usual mutations are within the CYBA gene [27]. In India cohort study, 41 different mutations were observed where 9 novel mutations were found within the CYBB gene and 2 novel mutations each in the CYBA, NCF1, and NCF2 genes. CGD cases frequently manifested severe and deep-seated infections of the lung, liver skin, brain, and lymph nodes [22, 23]. The majority of infections in CGD are due: S. aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia species, Aspergillus species, Salmonella, Candida Lusitaniae, Bacille Calmette Guerin (BCG) and tuberculosis are also important [23,24]. As the disease is considered to be a primary immune disorder, it affects our WBC of immune system, such as the neutrophils, monocytes and eosinophils and the macrophages [30]. As mentioned earlier the patient is unable to resist the infections caused by certain specific bacteria and thereafter it develops a chronic infectious and inflammatory disorder [30]. The disorder can affect many parts of the body such as lungs, skin and the bones and other inflamed tissues which are actually very sparsely distributed throughout the parts of the body. The symptomatic manifestations of this particular disorder generally start at the stage of the infancy, however those children who have mild form of this disease will not develop the signs and symptoms till childhood or teenage [30]. The major mechanism of action behind the disease that it fails to produce an enzyme or produces faulty enzyme that could help in the process of killing of microorganisms by the white blood cells (WBCs) [30]. According to the prevalence of this particular disorder, the disease affects the male counterparts more often than the female gender [31]. According to the study of the North America and Europe the disease has affected approximately two third of the individuals who are suffering from the X linked recessive form of the disorder. Therefore, it is also estimated that out of a million about 4 to 5 children are suffering from the CGD [31]. Infection of VP shunts varies between 2 to 27% [12, 13]. Similar cases C. lusitaniae isolated from lymph node [14]. C. lusitaniae which was isolated previously were observed to be resistant to antibiotic amphotericin B [15]. Many CGD patients exhibits regional lymphadenopathy after the BCG vaccination (BCGitis), while the case of disseminated disease (BCGosis) is less frequent [17]. However, study in Saudi Arabia estimated a rate from 0.1 to 4.3 per one million in vaccinated children [18].

As per previous scientific data, 50-76 % of BCG-infected patients mostly shows the symptomatic manifestation of immunodeficiency [19, 20]. CGD, severe combined immunodeficiency disease (SCID), Mendelian susceptibility to mycobacterial disease (MSMD) and hyper-IgM syndrome are the most common PIDs linked with unpleasant events after the vaccination [21].

Since the risk of fatality is more among CGD of all varieties, therefore identification of mutations is necessary for the diagnosis and genetic counseling especially in our country with high consanguinity prevalence 57.7%. 29 CGD treatment usually includes various modalities of treatments, and prophylactic antifungals and antibiotics. Prophylactic recombinant human interferon-γ, immunosuppresses or immune modulators may be, supportive. However, hematopoietic stem cell transplantation and gene therapy are recently developed options for the treatment cure of CGD [29].

Thus, CGD patients receive the prophylaxis for the antibacterial and the antifungal. In general, the antibiotic that is prescribed to the patient of CGD is the trimethoprim- sulfamethoxazole, and it is generally given for the antibacterial infections. Past data have revealed that this particular antibiotic is generally given to the patients of the CGD as they have the activity against the majority of the antibacterial infections.

The pathological condition of the CGD have revealed that the condition may often include the following areas of the physiological system such as pneumonias, liver abscesses, skin infections such as skin abscesses, lymphadenitis and osteomyelitis. Moreover, it should be noted that there is a high proneness to CGD, when infections occur with Candida lusitaniae, and Mycobacterim tuberculosis and these organisms are not considered to be sentinel organism for the diseased condition of CGD.

However, this also proved that new-borns should be potentially screened for the CGD.

Conclusion:

Chronic granulomatous disease (CGD) is a disorder which is inheritable and this actually happens due to disorder of the superoxide-generating phagocyte NADPH oxidase system. In this paper a case study has been detailed of a 4 months old female case patient with all the related laboratory and radiological findings. From the past scientific literatures, it has been confirmed that infection with bacteria, Candida lusitaniae is maximum among the patients who are suffering with haematological malignancies. Moreover, the disease is considered to be a genetically heterogeneous having equal susceptibility among all the ethnic groups. It has been observed that whenever there is an infection with any rare microorganisms the susceptibility for the disease rises.

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