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Case Report

Toll-Like Receptor 3 Deficiency in a Child with Recurrent Infections and Diabetes Mellitus

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Abstract

There are more than 400 different primary immune deficiencies worldwide. Amongst them, patients with humoral immunodeficiency are more common. Most of the innate immune defects, affect the phagocytic system. There are a few cases of toll-like receptor deficiency with innate immune defects, like TLR3 mutations, which usually present with Herpes simplex encephalitis. Herein, we report a two-year old boy with TLR3 deficiency, who was presented with recurrent infections and type one diabetes mellitus.

Keywords: Toll-Like Receptor 3 Deficiency; Diabetes Mellitus; Recurrent Infections; Skin Lesions

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Introduction

Innate immune responses are characterized by recognizing molecular components using the inborn receptors, named Pattern Recognition Receptors (PRRs) (1). Toll-like Receptor 3 (*TLR3*) is one of the receptors that can recognize double strand RNA. It principally expresses on circulating leukocytes, like natural killer cells and cytotoxic T cells. Other cell types expressing *TLR3* are mainly astrocytes, oligodendrocytes, neurons, pancreas cells, liver, lung and heart cells (2, 3). Deficiency of *TLR3* was reported in a few cases, they had been generally manifested as Herpes Simplex Encephalitis (HSE) (4-6). To our knowledge, diabetes mellitus as a sign of *TLR3* deficiency is rare. Although, some studies evaluate *TLR3* polymorphisms as a risk factor in the development of type 1 diabetes mellitus (T1DM) (7). However, although the exact mechanism is unknown, discovering such cases, whom are affected by a pathogenic mutation in the *TLR3* gene, can improve our knowledge regarding the relation between these two factors. Herein, we report a diabetic two-year-old boy with a history of recurrent infection and skin lesions, who is effected by a mutation in the *TLR3* gene.

Case presentation

A two-year-old boy was born from non-related parents. Since infancy, he suffered from recurrent fever, without any known origin since infancy. His weight gaining was slower compared to other children of the same age, he had spare hair and a delay in teeth growth (**Figure 1**). Although he could walk normally, he suffered from speech delay. At the age of fifteen months, he experienced three episodes of generalized tonic colonic seizure accompanied by a high fever. In the Cerebrospinal Fluid (CSF) examination, there were no white blood cells, but there were 200 red blood cells per dl. The Herpes Simplex Virus's (HSV) Polymerase Chain Reaction (PCR) was not tested. At the same time, there was a mild pneumonia, after four days, he was discharged in a good condition with a prescription of an oral phenobarbital. Two weeks later, he underwent an electroencephalography (EEG). The results were normal and the oral phenobarbital was discontinued. At the age of 20 months, he was referred to the hospital with a high fever and an uncontrollable coughing. In his chest sonography, there was an 18 mm pleural effusion with a consolidation in the right lung's base (**Figure 2**).

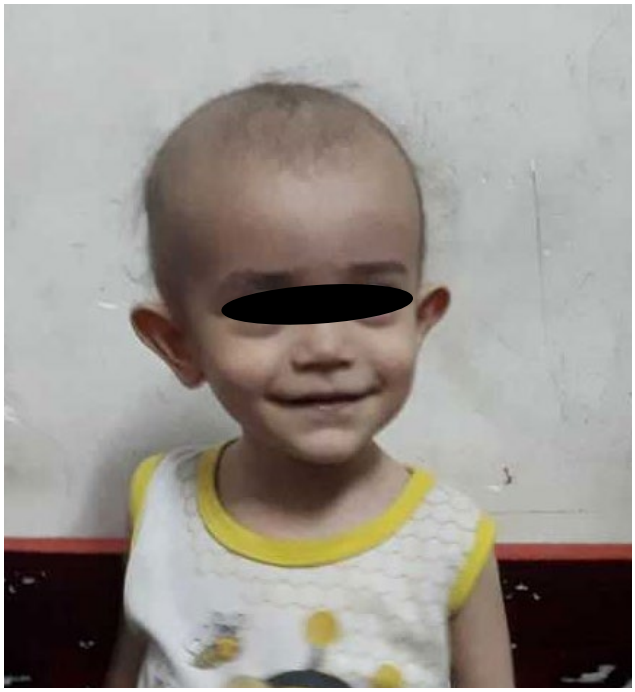


Figure 1. Spare hair in a twenty six months old boy, diagnosed with the TLR3 mutation, recurrent infections and diabetes mellitus.

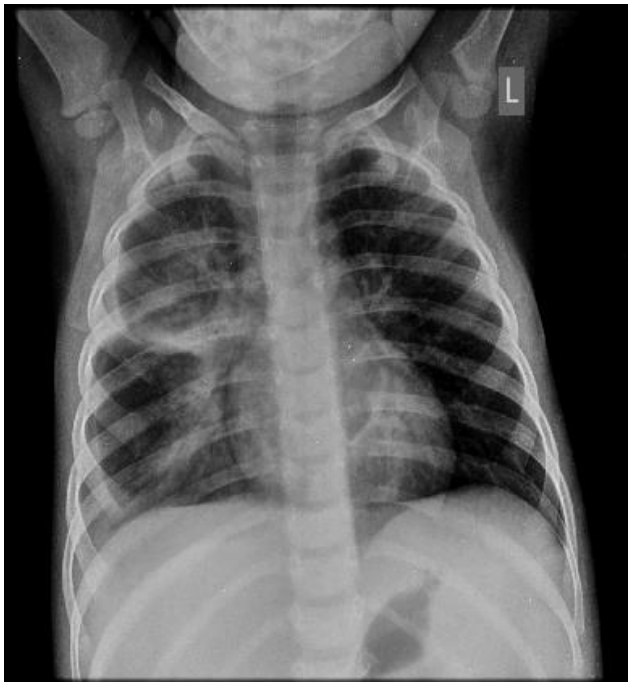
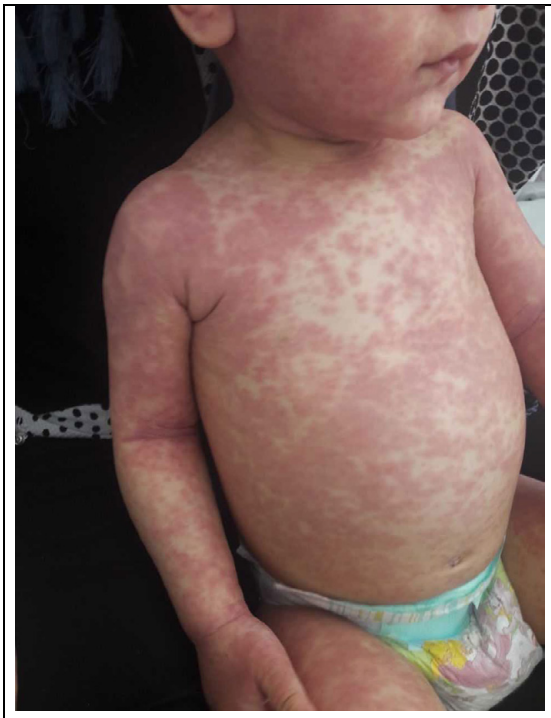
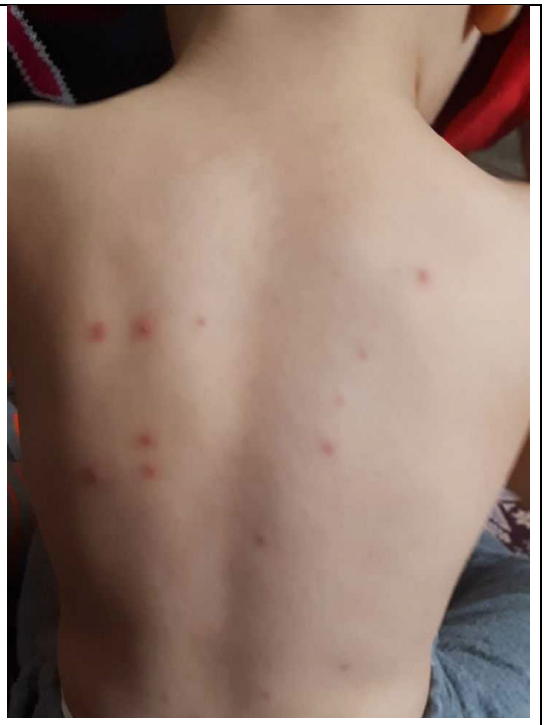


Figure 2. Radiography of twenty months old boy with the TLR3 mutation, suffering from a fever and cough.



erythematous maculopapular rash in a twenty months old boy



After discontinued prednisolone and ursobil

Figure 3. skin lesions of a patient with the *TLR3* mutation, recurrent infections and diabetes mellitus.

After a few days of antibiotic therapy, he suffered from an erythematous maculopapular rash and a high-grade fever (**Figure 3**). In the abdominal sonography, there was a gallbladder edema, and also hepatomegaly. He was diagnosed with elevated liver enzymes, the hepatomegaly and skin lesions as drug reaction with Eosinophilia and Systemic Symptoms (DRESS), then was discharged with a prescription of Ursobil and a 7.5 mg prednisolone per day. Even so, his skin lesions could not be controlled. At the age of twenty-two months, he suffered from polyuria and polydipsia. After a few weeks, he was admitted to the emergency department while he was suffering from vomiting, anorexia and tachypnea. In the laboratory evaluation, there were signs of metabolic acidosis and a high blood sugar level. He was diagnosed with a mild diabetic ketoacidosis. The use of prednisolone was discontinued and then the insulin was prescribed. Skin lesions decreased after a few weeks (**Figure 3**). At the age of twenty two months, the whole-exome sequencing shows a heterozygous mutation in the exon 5 of the *TLR3* gene (c.2656_2657insTAGG, p.A888fs*5). now he is on an insulin treatment, and despite the regular treatments, his blood sugar could not be controlled. And due to recurrent skin herpetic lesions, he is on regular prophylactic dose of acyclovir. While despite it, he frequently experiences mucosal herpetic lesions. Details of his laboratory examinations are seen in **Table 1**.

Discussion

Patients with Primary Immunodeficiency (PID) are in danger of recurrent infections, autoimmune disorders and malignancies. There are some other clues like, the failure to thrive, recurrent or permanent skin lesions and positive family history of PIDs (8). Humoral immunodeficiency is most common among people diagnosed with PIDs. Even so, defects in innate immunity such as toll-like receptors deficiency, can cause many complications for affected patients (3). Accordingly, due to the recent pandemic infection of SARS-CoV2, there is an increasing concern about such immunity systems' errors. Also, current evidences have shown that the COVID-19 patients with PIDs, may show a very different reaction, from very mild to life-threatening conditions. so prompt recognizing of these patients could be very helpful(9). To our knowledge, most of the reported defects in the *TLR3* gene, are associated with herpes encephalitis. However, there are a few reports of

Table 1. Laboratory data of a patient suffering from the TLR3 mutation, recurrent infections and diabetes mellitus.

Laboratory data	at age 15 months	at age 20 months	at age 22 months
White blood cell	7600	13.09	7190
- Neutrophil	63%	33%	54%
- Lymphocyte	30%	49%	40%
- Monocyte	6%	10%	5%
- Eosinophil	1%	8%	1%
Red blood cell	4730000	3820000	4240000
Platelet	176000	121000	346000
Urinary analysis			
- Specific gravity		1010	1010
- WBC	-	4-5	2-3
- RBC		20-25	3-4
- Ketone		-	+
Blood sugar		115	549
Ig G total	-	1179	-
Creatinine		0.4	0.9
Urea		10	35
Random Urine creatinine		20	-
Uric acid		4.1	-
HbA1c		-	6.77
Insulin		-	5.46
TSH		-	0.2
T 4		-	14.4
Anti TPO		-	10
Anti-GAD		-	< 1
Islet cell antibody	-	-	0.56
Ammonia		221	149.4 ---71
Lactate			14.1
blood gas			
- PH		7.44	6.94 ---7.47
- PCo2		22.2	10.6 ---30.1
- Po2		72.6	85.4 ---38.7
- HCO3		19.7	6.7 ---23.8
- O2 sat		95.4	93.7 ---77.5
AST		687 ---329---74	25
ALT		420----414----114	40
ALP		736----395	268
LDH		1104	-
Triglyceride		206	-
Cholesterol		107	-
CSF analysis			
- Wbc	0		
- RBC	200		
- Sugar	76		
- Protein	16		
- LDH	26		

GAD, glutamic acid decarboxylase

this mutation in diabetic patients, especially the ones with type 1 diabetes mellitus (7, 10, 11). At the age of fifteen months old, our patient presented numerous conditions such as, the CNS infection with an unknown HSV status, a complicated and very difficult to treat pneumonia, erythematous maculopapular rash at twenty months of age and a final diagnosis of diabetic ketoacidosis at the age of twenty-two months. His diabetes mellitus was difficult to control and a higher dose of insulin was required.

Type 1 diabetes is a chronic disease that affects all the aspects of life in children. It is estimated that there are approximately 542,000 children under the age of fifteen, with type 1 diabetes worldwide. Approximately, 86,000 new cases are diagnosed each year and numbers are rising between 3-5% per year (12). The age of onset of diabetes was shifted

to an earlier age to infancy. The etiology of diabetes showed that environmental agents in genetically susceptible people, can trigger the autoimmune destruction of the pancreases' beta cells. Indeed, several viruses have been associated with T1DM in humans(13). There is a documented correlation between the Coxsackievirus (CVB4) and pediatric type 1 diabetes. One of the mediators of a viral damage, is the double-stranded RNA (dsRNA), generated during replication and transcription of the viral RNA and DNA. The Toll-like Receptor 3 (*TLR3*) gene, plays an important role in the innate immune responses triggered by a viral infection. The binding of the dsRNA to the *TLR3*, triggers the release of pro-inflammatory cytokines such as interferons, which exhibit potent antiviral action; thus, protecting the uninfected cells and inducing apoptosis of infected ones. Therefore, the *TLR3* gene is a good candidate for the development of the T1DM (7, 14). One study reported a significant association between the risk of T1DM and the *TLR3* polymorphisms. The rs3775291 and rs13126816 polymorphisms of the *TLR3* genes, are associated with the risk of T1DM, whereas the rs5743313 and rs11721827 polymorphisms, are associated with the age of the T1DM diagnosis and a poor glycemic control. The number of risk alleles of the five *TLR3* polymorphisms in the haplotypes, seems to influence the risk of T1DM, suggesting that these polymorphisms might interact in the susceptibility of the disease(7).

Conclusion

The authors conclude that the presentation of a defect in the *TLR3* gene can be very confusing. There are serious concerns about the occurrence of the diabetes mellitus type 1 in these patients. So, evaluation of this mutation in patients suffering from recurrent infections, skin and hair abnormalities and simultaneous diabetes mellitus can be very helpful.

Conflict of interest

The authors declare that there is no conflict of Interest.

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