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Disymptomatic Wiskott Aldrich Syndrome: Overcoming a Diagnostic Challenge

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1. Abstract

Background: There are three main forms of the Wiskott Aldrich syndrome, the classic severe form, the disymptomatic form without cutaneous signs (Harzheim and colleagues, 1965) and a milder variant X-linked thrombocytopenia and neutropenia. The aim of this paper is to describe the very rare occurrence of disymptomatic form of Wiskott Aldrich syndrome in two Iraqi brothers and the diagnostic challenge associated with such cases.

Patients and methods: The case of two Yezidis brothers referred because each boy had two different medical reports from Hevi Teaching Children Hospital in Dohuk, Kurdistan Iraq. Two of these medical reports recommended sending them outside Kurdistan or outside Iraq for the diagnosis and management of their illnesses. Each of these medical reports was signed by a committee that included four consultant doctors.

Results: The two brothers had chronic illness of more than two years duration characterized by thrombocytopenia, leucopenia, splenomegaly, draining ear (more prominent in the older brother) and chronic liver disease (more prominent in the younger bladder). The parents were consanguineous. The father was apparently healthy, but the mother was having allergic skin disorder. The boys had an older brother who died at the age of thirteen. The two patients have four healthy sisters aged 18, 15, 10 and 8 years respectively.

Conclusion: This paper demonstrates that when it comes to the diagnostic challenges associated with rare disorders, obscurity, uncertainty and complexities can be transformed to a crystal-clear diagnosis in the hands of the expert.

2. Keywords: Rare disorders; Disymptomatic form; Wiskott Aldrich syndrome; Yezidis; Iraq

3. Introduction

Wiskott Aldrich syndrome is an X-linked hereditary disorder that was first reported in 1937 by Alfred Wiskott (Figure 1), a German pediatrician who described three brothers presented shortly after birth with thrombocytopenia, bloody diarrhea, eczema and recurrent ear infections. All the three patients died early in life from intestinal bleeding and sepsis. Wiskott thought that the origin of the hemorrhagic diathesis is a dysfunction in the line of the platelets. The three brothers had sisters who showed no symptoms [1,2].

In 1954, Robert Anderson Aldrich (Figure 2) and

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colleagues studied a family of a six-month-old infant with thrombocytopenic purpura. Sixteen of 40 male infants in the family had died and ten of them, including the proband were experiencing draining ears, eczematoid dermatitis and bloody diarrhea. A X-linked recessive gene was thought to be responsible for the fatal disorder in the family [2,3].

Figure 1: Dr. Alfred Wiskott (1898-1978), a German pediatrician who first reported the syndrome in 1937.

Figure 2: Robert Anderson Aldrich (1917-1998), an American pediatrician who described the disease in a family of Dutch-Americans in 1954.

Wiskott Aldrich syndrome is classically associated with thrombocytopenia commonly causing bloody diarrhea, susceptibility to infections, eczema and an increased risk of autoimmune disorders. The platelets in the classic Wiskott Aldrich syndrome are small with reduced mean size, but the presence of large platelets (macro-thrombocytopenia) is well recognized [2].

There are three main forms of the Wiskott Aldrich syndrome, the classic severe form, the disymptomatic form without cutaneous signs (Harzheim and colleagues, 1965) and a milder variant X-linked thrombocytopenia and neutropenia [2,4]. The aim of this paper is to describe the very rare occurrence of disymptomatic form of Wiskott Aldrich syndrome in two Iraqi brothers and the diagnostic challenge associated with such cases.

4. Patients and Methods

The case of two Yezidis brothers who had normal development and facial appearance and undiagnosed chronic illness were studied. They were referred because each boy had two different medical reports from Hevi Teaching Children Hospital in Dohuk, Kurdistan Iraq. Two of these medical reports recommended sending them outside Kurdistan or outside Iraq for the diagnosis and management of their illnesses. Each of these medical reports was signed by a committee that included four consultant doctors. The first medical report of the older brother aged 14 years, stated that the child had chronic aplastic anemia of unknown cause. The second medical report stated that he had features of paroxysmal nocturnal hematuria. The medical report of the younger brother, aged 11 years, stated that the child had chronic hepatitis of unknown cause. The second medical report stated that he had features of paroxysmal nocturnal hematuria.

5. Results

The two brothers had chronic illness of more than two years duration characterized by thrombocytopenia, leucopenia, splenomegaly, draining ear (more prominent in the older brother) and chronic liver disease (more prominent in the younger bladder). The parents were consanguineous. The father was apparently healthy, but the mother was having allergic skin disorder. The boys had an older brother who died at the age of thirteen after hospitalization because of an illness characterized by diarrhea and vomiting. The illness that caused the death of the older brother was not diagnosed precisely and postmortem examination was not performed. The two patients have four

healthy sisters aged 18, 15, 10 and 8 years respectively.

The older brother was known to have mild thrombocytopenia before about one year and splenomegaly (13-15 cm) was shown on more than one abdominal ultrasound examination before more than 18 months. The ultrasound examination also showed normal sized kidneys and pelvi-calceal systems, but both kidneys showed increased echogenicity in the second ultrasound examination. He also had intermittent hematuria without pyuria or with evidence of infection for more than one year. Urinalysis was sometimes showing a trace of albumin and calcium oxalate and amorphous urate crystals. About two weeks before referral, leukocyte count was within the normal range, but the patient continued to have thrombocytopenia (Table 1).

Table 1: The white blood counts, the differential counts, red blood cell counts, red blood cell indices, platelet counts, and mean platelet volume of the older brother performed before referral.

	Earlier test	Few weeks before referral	Latest tests before referral	Latest tests before referral	Normal values
ESR				**22 mm/L**	
Hemoglobin	**13.1 g/dL**	**12.6g/dL**	**12.3 g/dL**	**12.9 g/dL**	**11.5-16.5 g/dL**
Hematocrit (HCT)	**37.6%**		–	**35.95**	**35-55 %**
WBC	**5.7x10^9/L**	3.1 x10^9/L	4.9 x10^9/L	5.39 x10^9/L	**3.5-10 x10^9/L**
Neutrophil		58 %		66.2%	
Granulocyte	69.3 %		67.8 %		35-80.3 %
Lymphocyte	24 %	36 %	26.1%	20.9 %	15-50 %
Monocyte		4%		8.2%	
Eosinophil		2%		3.49%	
Basophile		0%		0.066%	
RBC	4.04 x10^{12}/L	4.12x10^{12}/L	**3.93 x10^{12}/L**	**4.19 x10^{12}/L**	3.5-5.5 x10^{12}/L
Mean corpuscular volume (MCV)	92.9 FL	89.8 FL	87 FL	85.7 FL	75-100 FL
Mean corpuscular hemoglobin (MCH)	32.4 pg	30.6 pg	31.3 pg	30.7 pg	25-35 pg
Mean corpuscular hemoglobin concentration (MCHC)	34.8 g/dL	34.1 g/dL	36 g/dL	35.8 g/dL	31-38 g/dL
Red blood cell distribution width (RDW)	14.4%	14.9%	14.3 %	14.5 %	11-16%
Reticulocyte				2.3%	
Platelet count	**109 x 10^9/L**	**68 x 10^9/L**	**93 x 10^9/L**	**78.3 x 10^9/L**	**100-400 x 10^9/L**
Mean platelet volume (MPV)	9.5 FL		10.2 FL	11.6 FL	8-11FL

Plateletcrit (PCT): amount of blood occupied by platelets	0.10 %		0.1		0.01-9.99%
Large platelets concentration ratio (LPCR)	27.1%				0.1-99.9%

Bone marrow aspiration and biopsy examination was performed few weeks before referral at Hevi Pediatrics Hospital in Dohuk which is located in Kurdistan region of Iraq. The marrow aspiration showed cellular and hypocellular marrow smears and fragments with good megakaryocytes. Erythropoiesis was present with all stages of maturation and granulopoiesis was also present. No foreign cell was seen. The bone marrow biopsy showed heterogeneous patches of cellular and hypocellular tissue and reduced hematopoietic tissue of erythropoiesis and granulopoiesis. Adequate number of megakaryocytes with no abnormal tissue seen. Serum was tested for ceruloplasmin level and it was 26 mg/dL (Normal: 20-60 mg/dL).

The older brother was also experiencing draining ear during the previous year and culture of ear swab revealed growth of proteus that was sensitive to largely to cephalothin, pipracillin and gentamicin, but resistant to Co-trimoxazole and clindamycin. Before referral, several tests were performed to rule out possible infections including Brucella agglutination test and Widal test (S. typhi-O, S. typhi-H, S. typhi B-O and S. typhi B-H), Epstein Barr VCA IgM, tests for HCV and all were negative. A doctor from Dohuk thought that the child might have mucopolysachridosis and skeletal survey was performed. Radiographs of the wrist, foot, cervical spine, lumber spine, skull and pelvis were taken and all showed no bony lesion and no abnormality could be detected.

The thrombocytopenia in the case of the older brother was presenting mainly as hematuria, but he developed an episode of epistaxis. Renal function tests showed normal findings in more than one occasion. The older brother also had ultrasonographic evidence of liver involvement, but he didn't develop clinical jaundice. However, his total bilirubin was mildly elevated to 2 mg/dL few months before referral.

Few weeks before referral, the older brother experienced more reduction in platelet count in association with the development of leucopenia, mainly neutropenia. He also had some reduction in the hemoglobin level. The red blood cells were normochromic normocytic with anisocytosis and thrombocytopenia was associated with some large platelets (Table 2).

Table 2: Blood counts and cell indices of the younger brother performed few weeks before referral.

ESR			**41mm/hr**
Hemoglobin	**12.7 g/dL**	**12.5 g/dL**	**11.7 g/dL**
Hematocrit (HCT)	**37.1%**	**35.1%**	**32.5%**
WBC	6.3 x10^9/L	5.8 x10^9/L	5.97 x10^9/L
Granulocyte	61.6 %	66.2%	_
Neutrophil	_	_	59.3
Lymphocyte	32.5 %	26.9 %	29.6 %
Monocyte	_	_	7.97%
Eosinophil	_	_	2.34%
Basophile	_	_	0.787%
MID	5.9%	6.9%	_
RBC	**4.07x10^{12}/L**	**4.04 x10^{12}/L**	**x10^{12}/L**
Reticulocyte	_	_	1.8%
MCV	91 FL	86.9 FL	85.7 FL
MCH	31.2 pg	30.9 pg	31 pg
MCHC	34.3g/dL	35.5 g/dL	36.2 g/dL
RDW	15.1 %	13.1 %	14.5 %
Platelet	**111 x 10^9/L**	**107 x 10^9/L**	**87.6 x 10^9/L**

MPV	11.9 FL	11.8 FL	14.5 FL
PCT	0.13 %	0.12 %	
LPCR	40.7 %	42.6 %	

The clinical picture of the11-year younger brother was dominated by chronic liver disease. However, he was also having thrombocytopenia with easy bruise ability especially of the legs for more than two years duration. Mild thrombocytopenia was detected more than 18 months before referral. Few weeks before referral, he was having jaundice, enlarged spleen and elevated ESR (28 mm/hour) and thrombocytopenia.

Abdominal ultrasound performed about two years before referral showed normal findings, the liver and spleen were not enlarged. However, abdominal ultrasound performed three months later showed mild splenomegaly, the spleen was 12.5 cm in length. The liver was normal. However, abdominal ultrasound showed normal findings about one year before referral.

Laboratory tests performed before referral included serum ceruloplasmin 28 mg/dL (Normal 20-60), serum copper 123 µg/dL (Normal 30-150 µg/dL), SGOT 200 iu/L (Normally less than 37 iu), SGPT 171 iu/L (Normally less than 42 iu) and serum ferritin 111.1 ng/ml (Normal 15-300).

Tru-cut liver biopsy was also performed before referral. A single core of tissue (18 mm long and 0.8 mm thickness) was obtained. Histopathologic examination showed marked distortion of the liver lobular architecture associated with marked mononuclear inflammatory cell infiltration of all portal tracts. There were moderate lobular focal inflammation and Kupffer cell hyperplasia suggesting widespread extensive inter-phase hepatitis. There was also marked portal fibrosis. The bile ducts were identifiable in the portal tracts and they were not involved in the inflammatory injury. Histopathologic examination showed neither steatosis nor choleastasis. Intra-cytoplasmic eosinophilic globule and glass ground change were not seen. There was no vascular alternation of cytoplasm or pigment accumulation in the H and E stained section. The pathologic diagnosis made by the histopathologist was active chronic hepatitis in transition to cirrhosis that could be attributed to autoimmune hepatitis and Wilson disease. Slit lamp examination showed normal findings and serum levels of ceruloplasmin was 28 mg/dL

A doctor from Dohuk thought that the child might have mucopolysaccharidosis and skeletal survey was performed on the eighth of November. Radiographs of the wrist, foot, cervical spine, lumber spine, skull and pelvis were taken and all showed no bony lesion and no abnormality could be detected.

Jaundice was gradually lessening, but he still having elevated bilirubin and liver enzymes. Abdominal ultrasound performed about one month before referral showed splenomegaly, spleen 15 cm in length. The liver was enlarged to about 17.5 cm and echo texture was normal and no focal lesion was present.

On referral, the younger brother had high ESR (41 mm/1hour), thrombocytopenia 87.6 and reticulocyte count was 1.8% (Table 3).

Table 3: The main features Disymptomatic Wiskott Aldrich syndrome in this study.

ETHNICITY
The affected brothers are Yezidis. Yazidis is an ethnically Kurdish religious community or an ethno-religious group indigenous to northern Mesopotamia They lives primarily in the Nineveh Province of Iraq.
FAMILY HISTORY
The parents are consanguineous. The father was apparently healthy, but the mother was having allergic skin disorder. The boys had an older brother who died at the age of thirteen after hospitalization because of an illness characterized by

diarrhea and vomiting. The two patients have four healthy sisters aged 18, 15, 10 and 8 years respectively.
THROMBOCYTOPENIA
Both brothers have chronic thrombocytopenia manifested as intermittent hematuria and epistaxis in the older brother and easy bruising in the younger brother.
LEUCOPENIA
Leucopenia occurred in the older brother during the period of observation.
DRAINING EAR
Draining ear occurred in the older brother during the period of observation.
CHRONIC LIVER DISEASE
Chronic liver disease was more prominent in the younger brother.
SPLENOMEGALY
BONE MARROW
Bone marrow showed adequate number of megakaryocytes with no abnormal tissue seen.

Laboratory tests also showed direct hyperbilirubinemia and elevated hepatic enzymes.

6. Discussion

The occurrence of disymptomatic form of Wiskott-Aldrich syndrome has been reported as early as 1965 by Harzheim, Stechele and Künzer [4]. The involvement of the liver and the occurrence of hepatosplenomegaly have been recognized as early as 1960 [5].

Puck et al. (1990) emphasized the diagnostic difficulties in sporadic cases presenting without skin involvement. They reported two unrelated males with sporadic congenital thrombocytopenia associated with immunologic abnormalities as infants including episodic neutropenia in one patient and multi-system autoimmune disease at the age of two years in the second patient [6].

Difficulties are experienced in reaching a diagnosis of a rare genetic syndrome. Experience and mastering the skills of clinically approaching a genetic disorder can not only change all the assumptions, but may transform the complexities, obscurity and uncertainty to simplicity and a confident diagnosis will emerge promptly when it comes to the masters of approaches in clinical medicine. All the desperation, inconvenience experienced by the patients and their guardians can be changed to relief, hopes and certainty when it come to the experts.

7. Conclusion

This paper demonstrates that when it comes to the diagnostic challenges associated with rare disorders, obscurity, uncertainty and complexities can be transformed to a crystal-clear diagnosis in the hands of the expert.

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