Tetralogy of Fallot is an Uncommon Manifestation of Warts, Hypogammaglobulinemia, Infections, and Myelokathexis Syndrome

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Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency disorder. We report three patients with WHIM syndrome who are affected by Tetralogy of Fallot (TOF). This observation suggests a possible increased risk of TOF in WHIM syndrome and that birth presentation of TOF and neutropenia should lead to suspect WHIM syndrome. *(J Pediatr 2012;161:763-5)*

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency disorder characterized by warts, hypogammaglobulinemia, infections, and abnormal retention of mature neutrophils in the bone marrow (myelokathexis).[1,2] This neutropenia, which is associated with a B and T lymphopenia and hypogammaglobulinemia, results in an increased risk for bacterial infections. Patients with WHIM syndrome present major and selective susceptibility to human papillomavirus that may manifest as cutaneous warts and genital dysplasia and cancer. The real prevalence of the disease is unknown but ~40 cases have been reported.[3] Autosomal dominant heterozygous mutations of the gene encoding the CXC chemokine receptor 4 (CXCR4) have been associated with the syndrome[4] and lead to a gain of CXCR4 function.[5,6] CXCR4 is a G protein–coupled receptor with a unique ligand, CXCL12 (previously named SDF-1).[7,8] This signaling axis orchestrates leukocyte trafficking and is involved in the regulation of bone marrow homeostasis, hematopoiesis, and organogenesis.[9-11] Notably, besides hematopoietic and central nervous system defects, mice deficient for *CXCR4* or *CXCL12* exhibit cardiac defects, indicating a role for this axis in ventricular septum formation.[12,13]

Tetralogy of Fallot (TOF) is a congenital heart disease characterized by: (1) pulmonary outflow tract obstruction; (2) ventricular septal defect; (3) overriding aortic root; and (4) right ventricular hypertrophy. The first 3 features are the result of abnormalities occurring during embryogenesis, and the fourth one is the consequence of the obstruction to pulmonary blood flow. The etiology is multifactorial. To date, some genetic alterations, the most frequent being represented by microdeletions of chromosome 22, have been associated with TOF but pathogenesis still remains unclear. The incidence is of 3 of every 10 000 live births, which represents approximately 10% of all congenital defects.[14-16]

TOF	Tetralogy of Fallot
WHIM	Warts, hypogammaglobulinemia, infections, and myelokathexis

Results

We report the cases of 3 patients with WHIM syndrome who are affected by TOF (**Figure**). Taking into consideration the relatively poor prevalence of the two disorders, in the present report we show that patients with WHIM syndrome display an increased risk to develop TOF.

The first patient is a 19-year-old man with a history of WHIM syndrome identified at age 2.5 years, manifesting as severe neutropenia and recurrent pneumonias, resulting in bronchiectases (**Table**). There was no evidence of hypogammaglobulinemia and warts. The bone marrow analysis showed myeloid hypercellularity with the presence of mature neutrophils. These hematologic and clinical findings led to the suspicion of WHIM syndrome and thereby to *CXCR4* gene sequencing that revealed S338X mutation. The congenital heart disease was suspected at birth and was characterized by the anatomic variant of TOF associated with pulmonary atresia and with anomalies in branch pulmonary arteries. Of note, the patient presented with agenesis of the left-hand fingers with homolateral hypoplasia of the radius. The patient has been maintained on daily subcutaneously administered granulocyte-colony stimulating factor therapy since 2 years of age.

In the second case, the patient had TOF associated with the presence of patent ductus arteriosus documented at birth; the heart disease was surgically corrected at the age of 2 years (**Table**). This patient is a 15-year-old girl who has

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Supported by eRare (grant to F.B. and R.B.), Fondazione Cariplo, PRIN 2009, and Telethon Italia (GGP10170A to R.B.). F.B. was supported by AP-HP (*Assistance Publique-Hopitaux de Paris*) and ANR (*Agence Nationale de la Recherche*) (ANR-07-MRAR-029) and is a member of the Laboratory of Excellence LERMIT (*Laboratory of Excellence in Research on Medication and Innovative Therapeutics*) (Investissements d'Avenir). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2012.05.058

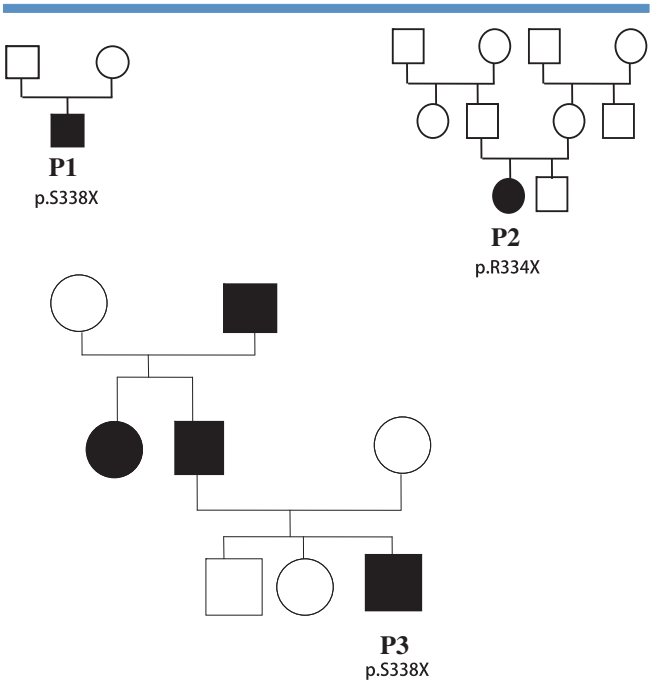

Figure. Pedigree trees of the three WHIM patients, who are affected by TOF.

had recurrent respiratory infections since early childhood. Severe neutropenia was discovered at age of 2 years, and on that occasion, an analysis of the bone marrow revealed myelokathexis with mature neutrophils presenting morphologic abnormalities consistent with apoptosis. Granulocyte-colony stimulating factor therapy was started at 5 years of age to maintain circulating neutrophil count in the normal range. Because of the occurrence of repeated pneumonia episodes, she has been maintained on antibiotic prophylaxis. In the following years, the observation of hypogammaglobulinemia suggested WHIM syndrome and genetic confirmation of the diagnosis was obtained at age 5 by detection of the R334X mutation in the *CXCR4* gene. In the following years, the patient has developed a plantar wart.

The third patient is 7 years old and presented shortly after birth with a heart murmur that led to the discovery of a TOF characterized by ventricular septal defect, overriding aorta, and pulmonary infundibular stenosis. The congenital heart disease was surgically corrected in the first months of life. Neutropenia, lymphopenia, and hypogammaglobulinemia were present since infancy, and the analysis of bone marrow showed myelokathexis. Three other family members have had neutropenia and recurrent infections, but none of them had a congenital heart defect. The genetic analysis of *CXCR4* revealed the same mutation (S338X) in the 4 subjects. The child underwent treatment with intravenous immunoglobulins, obtaining a satisfactory control of infectious episodes.

Discussion

Although TOF is the most common form of cyanotic congenital heart disease, its occurrence in 3 unrelated patients with WHIM syndrome is much higher than expected; the normal occurrence in the general population is 3 of every 10 000 live births. Because of the low number of patients whom we have observed, we cannot draw a correlation between the development of the heart defect with a specific mutation. The detection of the same mutation (S338X) in a family with 4 members affected by WHIM syndrome with only 1 showing TOF rules out the hypothesis that the heterozygous gain-of-function mutation of *CXCR4* directly leads to the development of the cardiac defect. Instead, our observations suggest that the WHIM syndrome–associated *CXCR4* truncating mutation might increase the risk that this combination of cardiac defects may develop during the formation of the fetal heart. Beyond a role for CXCL12 and CXCR4 in heart, nervous system, and blood vessel development,[17] studies show that CXCR7, the recently described second receptor for CXCL12,[18,19] has also a role in fetal

Table. Features of WHIM syndrome in reported patients

Feature	Patient 1	Patient 2	Patient 3
Mutation *(CXCR4)*	S338X	R334X	S338X
Age at molecular diagnosis	19 y	5 y	Birth (neutropenia and affected father)
Clinical manifestations at onset	TOF	TOF	TOF; neutropenia
Neutropenia (age at onset)	+ (2.5 y)	+ (2 y)	+ (20 d)
Myelokathexis	+	+	+
Hypogammaglobulinemia (age at onset)	–	+ (5 y)	+ Not really assessable as early IVIG at the onset
Recurrent infections	Pneumonia	Pneumonia	–
Warts	–	+*	–
Pulmonary outflow obstruction	Pulmonary valve agenesis	Pulmonary infundibular stenosis	Pulmonary infundibular stenosis
Overriding aorta	+	+	+
Ventricular septal defect	+	+	+
Right ventricular hypertrophy	+	–	–
Age at surgical correction	1 y	2 y	2.5 mo
Medical treatment	G-CSF; antibiotic prophylaxis	G-CSF; antibiotic prophylaxis	IVIG

G-CSF, Granulocyte-colony stimulating factor; *IVIG*, Intravenous immunoglobulins.
*One episode without relapse.

endothelial biology and heart development—in particular, ventricular septum and heart valve development.[20,21] Its germline deletion results in perinatal lethality, and its mutation affects semilunar valve development, contributing to aortic and pulmonary valve stenosis and, in some cases, septal defects.[22] Recent findings support the view that CXCR7 modulates CXCR4 function by acting as a scavenger for CXCL12[23] and forming heterodimers with CXCR4.[20,24,25] In vitro studies on endothelial progenitor cell function show a role for both CXCR4 and CXCR7 in regulating the response of the cells to CXCL12 and, thus, angiogenesis.[21] This suggests that interactions between the 2 chemokine receptors may be required for proper valve morphogenesis.

Our observations demonstrate that TOF can be a presenting manifestation of WHIM syndrome and that this rare inherited disease should be suspected in children with a congenital heart defect and neutropenia. The recognition of this manifestation of WHIM syndrome might help to prevent the diagnostic delay in the identification of this rare genetic disease.

A prompt diagnosis should facilitate the management of leucopenia, which might include in the future CXCR4-targeted therapy as supported by 2 recent studies indicating that the specific CXCR4 antagonist plerixafor may be effective in restoring the cellular blood counts to normal.[26,27] ■

We are grateful to Virginia Gulino for critical discussion.

Submitted for publication Dec 21, 2011; last revision received Mar 20, 2012; accepted May 24, 2012.

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