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First Case of X-Linked Moesin Deficiency Identified After Newborn Screening for SCID

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To the Editor

Population-based screening of newborns can effectively identify infants with genetic defects of the immune system leading to severe combined immunodeficiency (SCID) [1]. Early diagnosis of SCID prompts intervention before life-threatening infections and improves the clinical outcome [2]. SCID newborn screening is based on PCR quantification of T cell receptor excision circles (TRECs) in neonatal dried blood spots. TRECs are a DNA by-product of T cell receptor rearrangement and a biomarker of thymic output of naïve T cells. Identification of babies with undetectable or abnormally low TREC levels prompts diagnostic follow-up to confirm and define the severity of immune deficiency and to identify the underlying cause. Newborn screening also identifies infants with forms of T cell lymphopenia other than typical SCID [3].

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X-linked moesin-associated immune deficiency (X-MAID) is a newly described combined immunodeficiency that can present early in life with profound lymphopenia and hypogammaglobulinemia, fluctuating monocytopenia and neutropenia, poor immune response to vaccine antigens, and increased susceptibility to bacterial and varicella zoster virus (VZV) infections. This immunodeficiency is caused by genetic defects of the moesin (*MSN*) gene [4]. The seven patients currently reported in the literature did not undergo newborn screening. Here, we describe the first case of X-MAID identified by newborn screening.

A male born at 36 weeks to nonconsanguineous healthy parents after an uneventful pregnancy had out-of-range TREC copies (<252 copies/mL) on day 2 and 11, with a normal β-actin control. Confirmatory blood work in the third week of life revealed leukopenia and profound T, B, and NK cell lymphopenia (Table 1). However, normal in vitro proliferative response to phytohemagglutinin and normal thymic shadow on X-ray argued against SCID (Table 1). Nonetheless, because of the profound lymphopenia, amoxicillin prophylaxis was started and live vaccines withheld.

Severe neutropenia (absolute neutrophil count, 260 cells/μl) and monocytopenia (absolute monocyte count, 80 cells/μl) were still present on day 32, with no alloreactive autoantibodies against neutrophils or lymphocytes detected. Bone marrow aspirate and biopsy showed normal myeloid maturation and trilineage hematopoiesis with no myelodysplasia or hypersegmented neutrophils. Testing for *SBDS*, *HEX1*, *and ELANE* gene mutations was negative, as were a chromosomal microarray and search for mutations with a commercially available SCID gene panel. Telomere length studies on peripheral blood leukocytes were unremarkable. Aside from the persistent lymphopenia and fluctuating neutropenia and monocytopenia, the patient had low serum IgM and borderline low IgG. At 7 months of age, his antibody titers against tetanus and pneumococcus were protective, but when these titers declined by 20 months of age, immunoglobulin replacement was initiated (Table 1).

His infectious history was significant for fevers and cough at 1 and 2 months of life, with *Parainfluenzae virus* type 2 found on a nasal swab. Oral thrush partially refractory to nystatin treatment occurred up to 4 months of age, and a buccal swab was positive for *Candida lusitaniae*. At 15 months of age, he had 4 weeks of watery diarrhea. Stool PCR was positive for *Norovirus* 1. A nasal swab was positive for *Rhino/Entero virus* at 19 months of age. His growth has consistently fallen between the 5th and 25th percentile. His physical exam has been unremarkable, aside from oral thrush during infancy and persistent moderate atopic dermatitis. Normal lymph nodes are palpable. The patient is currently 27 months old and in good general condition.

Whole exome sequencing (WES) was performed when the patient was 25 months old, and showed a missense mutation within the *MSN* gene on the X chromosome (c.511C > T, p.R171W) that was confirmed by Sanger sequencing (Fig. S1a). The mother and the maternal grandmother are heterozygous for the same mutation, and both showed skewed X chromosome inactivation in all hematopoietic lineages (Fig. S1b). The p.R171W mutation has been previously reported in six patients with X-MAID and is associated with reduced

protein expression [4]. Interestingly, the patient's maternal grandmother had a brother who died at 19 years of age after a history of recurrent infections.

The *MSN* gene encodes for moesin (membrane-organizing extension spike protein or MSN), a member of the ezrinradixin-moesin (ERM) protein family. ERM proteins function as cross-linkers between plasma membranes and actin-based cytoskeleton [5]. Moesin is abundantly expressed in human hematopoietic cells and has an important function in regulating proliferation, migration, and adhesion of human lymphoid cells [6]. Subjects with X-MAID have a normal-sized thymus but few naïve T cells. This has led to hypothesize that the T cell lymphopenia could be due to impaired cellular egress from the thymus rather than a defect of T cell differentiation [4]. However, this hypothesis is challenged by the observation that the vast majority of $CD4^+$ cells from our patients had a naïve phenotype and an increase in the percentage of $CD8^+$ cells with an "exhaustion" phenotype ($CD45RA^+$ $CCR7^-$) was only observed during follow-up (Table 1).

This case illustrates the importance of newborn screening and WES for early recognition of X-MAID, and more in general of genetic causes of T cell lymphopenia. As compared to targeted sequencing of individual genes or of gene panels, WES has a superior capacity to identify disease-causing gene defects and may even be economically more convenient. Our case suggests that, in the presence of a male infant with a positive SCID newborn screening and fluctuating neutropenia and monocytopenia, diagnosis of X-MAID should be considered. Despite an immunological phenotype that matches our patients, the infectious history of the patients previously reported with the p.R171W mutation was more severe, even when adjusting for age, and included susceptibility to bacterial and VZV infections [4]. It is known that, in SCID patients, early diagnosis allows initiation of appropriate prophylactic measures that reduce the incidence and severity of infections, improving morbidity and outcome of hematopoietic stem cell transplantation (HSCT) [1]. Guided by newborn screening and WES, prompt diagnosis and immediate use of preventive measures (such as avoidance of live vaccines, use of antimicrobial prophylaxis and immunoglobulin replacement therapy) are also important in immunodeficiencies like X-MAID where, unlike typical SCID, HSCT may not be strictly required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Hematologic and immunologic characteristics

	Age DOL 18	Age 8 weeks	Age 11 months	Age 20 months	Normal for age
WBC (cells × 10^{-3} μL)	2.21	2.27	1.62	2.1	7.73–13.12
Hemoglobin (g/dL)	11.4	10.1	11.6	11.5	10.4–12.5
Hematocrit (%)	36.7	31.1	34.6	35.8	30.5–36.4
Platelets (Kcells/μL)	476	481	435	561	223–461
Lymphocytes (cells/μL)	-	950	930	1060	2320–5490
Neutrophils (cells/μL)	-	650	460	830	2470–6410
Eosinophils (cells/μL)	-	6	20	0	30–290
Monocytes (cells/μL)		90	175	60	250–1150
IgG (mg/dL)	525	227	372	410	400–1300
IgA (mg/dL)	<7	<7	29	-	20–230
IgM (mg/dL)	8	6	20	-	30–120
IgE (IU/ml)	4	13	5	-	0–30
$CD3^+$ (cells/ μL[%])	339 (77%)	374 (77%)	556 (80%)	927 (87%)	1900–6200 (49–84)
$CD4^+$ (cells/ μL[%])	299 (68%)	339 (70%)	447 (65%)	275 (26%)	1300–3400 (28–52)
$CD8^+$ (cells/μL[%])	21 (5%)	32 (7%)	98 (14%)	601 (57%)	620–2000 (14–30)
$CD16^+$ (cells/μL[%])	44 (10%)	33 (7%)	19 (3%)	24 (2%)	160–1100 (3–15)
$CD19^+$ (cells/μL[%])	42 (9%)	75 (15%)	103 (15%)	87 (8%)	610–2600 (13–37)
Naïve $CD3^+$ $CD4^+$ $CD45RA^+$ $CCR7^+$(% of $CD4^+$ cells)	86	83	79	70	66.3–89.4
Naïve $CD3^+$ $CD8^+$ $CD45RA^+$ $CCR7^+$ (% of $CD8^+$ cells)	44.8	25	17	62	57.8–82.9
$CD3^+$ $CD8^+$ $CD45RA^+$ $CCR7^-$ (% of $CD8^+$ cells)	8	23.4	42.9	54	6.4–20.8
Switched memory IgD-CD27 + B cells (% of $CD19^+$ cells)	-	-	8.5	-	3.9–13.6
Unswitched memory IgD^+CD27^+ B cells (% of $CD19^+$ cells)	-	-	2.1	-	4.1–13.9
PHA (cpm)	272,159	123,638	109,390	132,800	104,415–319,780
Anti-CD3 (cpm)	4266	13,927	52,345	51,506	74,586–194,337
T cell mitogen background (cpm)	1770	1874	543	459	321–2510
Tetanus toxoid (cpm)		51,310	-	54,123	14,938–96,819
T cell antigen background (cpm)	1120	1570	-	786	724–7752
TREC (copies/μL)	<252	-	-	-	>252
$CD31^+CD45^+$ (recent thymic emigrants)		-	70	-	57.8–76.6
Pneumococcus serotypes >1.13	-		12/23	4/23	-
Tetanus IgG	-		0.66	0.10	0.15–7.00

PHA phytohemagglutinin, *cpm* counts per minute, *TREC* T cell receptor excision circles, *DOL* day of life