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ORIGINAL ARTICLE

A Novel Mutation Leading to Wiskott-Aldrich Syndrome in an Ethiopian Boy: a Case Report and a Review of Literature

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Abstract
Wiskott–Aldrich syndrome is an X-linked recessive primary immune-deficiency disorder very rarely reported from black African children. A 12-year old boy with recurrent sinopulmonary and diarrheal infections, eczema, thrombocytopenia, and low platelet volume was found by whole genome sequencing to harbor a predicted pathogenic c.1205dupC (p.Pro403Alafs*92) variant of a mutation in the *WAS* gene — confirming the diagnosis. This case report summarizes his presentation and management and provides a useful summary of the diagnosis and the responsible novel genetic mutation.

Keywords Wiskott-aldrich syndrome · inborn errors of immunity · child · African

Background

Wiskott–Aldrich syndrome (WAS) is a rare primary immune-deficiency disorder (PID), or inborn error of immunity (IEI), with an incidence of 1–4 cases per a million people [1, 2]. According to the International Union of Immunological Societies committee on IEI, it is classified as a syndromic IEI with combined T and B cell defects [3]. Individuals present with varying degrees of severity of recurrent infections (predominantly sino-pulmonary), thrombocytopenia with low platelet volume and eczema [4]. Based on its X-linked recessive nature, males are predominantly affected: two-thirds of cases are inherited, while a third may be due to sporadic mutations [5]. Mutations in the *WAS* gene compromises the actin cytoskeleton of hematopoietic cells, impairs cell migration and immune cell signaling, causing defects in platelets, T, NK and B cells associated with the disorder [6]. Diagnosis typically requires identification of a rare genetic variant complemented by molecular and cellular investigations confirming the deleterious impact of the variant [7]. Unfortunately, the rarity of genetic variants is often dependent on ethnicity/ancestry, which may not be well represented in public genomic databases. As well, in-depth investigations are not routinely available in some countries or in settings with low resources for rare diseases [8]. These limitations hamper the optimal clinical diagnosis and management of affected patients, and stunt the knowledge contributions of such settings/countries to the global IEI community, although efforts are being made to overcome some of these obstacles [8]. Few cases of WAS have been reported from Africa. In Ethiopia, a patient based on clinical diagnosis alone has previously been described [9]. Here, we report an Ethiopian child with WAS and genetically-probable mutation, highlight the issues with confirmatory testing, and provide a review of published African cases.

Case Report

A 12-year old Ethiopian boy of black African race presented to our center for evaluation of recurrent infections since infancy. He was born at 39 weeks of gestational age to non-consanguineous parents with a birth weight of 3200 g. His medical history up to the age of 1 year was unremarkable.

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He is the second child of the family, and his older and younger brothers are apparently healthy.

He first presented for medical attention at 1 year of age with cough of 3 days duration accompanied by low-grade fever. On physical examination, he maintained his saturation of oxygen at 92% in room air but was tachypneic. He had fine crepitations over his right lower-thirds lung. With a diagnosis of community-onset pneumonia, he was prescribed 7 days of oral antibiotics and his illness resolved. He had a similar acute onset of cough and fever at age 2 1/2 years and with physical examination showing hypoxia, tachypnea, flaring of ala nasae, intercostal, and subcostal retractions; he received in-patient treatment with parenteral antibiotics for severe pneumonia. At age 3 years, he presented with weight loss and low grade fever of 1 month duration along with sweating (worse at night) and intermittent cough. He also had profuse epistaxis. His lab work-up showed an erythrocyte sedimentation rate (ESR) of 110 mm/h and chest x-ray showing hilar lymphadenopathy and collapse consolidation. He was started on anti-tubercular treatment despite his sputum Genexpert for *M. tuberculosis* being negative based on clinical and imaging findings. During follow-up visits, his symptoms had resolved. He had three further hospitalizations for severe pneumonia from age 5 to 8 years (details of which could not be extracted). At age 10 years, he presented with cough, grunting and fast breathing of 1 month duration. His saturation of oxygen in room air was 80%, with respiratory rate of 45 per minute and temperature of 39 °C. His complete blood count showed white blood cells of 20,000/mm^3, with 68% neutrophils and platelets 32,000/mm^3. His chest x-ray showed multifocal pneumonia. After 3 days of intravenous ceftriaxone and oral azithromycin, he showed minimal improvement and a chest CT was ordered which showed multifocal pneumonia and a right upper lobe focal bronchiectasis. His antibiotics were revised to vancomycin and cefepime, and he was discharged after 7 days of treatment. His past medical history was also notable for recurrent diarrheal infections (no microbe identified). He was also under follow-up at various dermatology clinics for eczema starting at 18 months of age and takes intermittent topical mometasone furoate ointment and daily application of topical emollients. On each of his medical check-points throughout his childhood, varying degrees of bleeding diathesis with consistent thrombocytopenia were noted but hematologic/oncologic work-ups failed to identify an underlying diagnosis. His parents could not recall any family member with a history of seeking medical care for recurrent illnesses since childhood. The patient did not show vaccine-related adverse reaction after receiving his age-appropriate vaccines.

On physical examination, he appeared chronically sick, but his vital signs were within normal limits for age. He had excoriated lips and geographic tongue without tonsillar atrophy. He had right anterior and posterior cervical lymphadenopathy and splenomegaly of 3 cm below left costal margin. His integumentary examination showed pale palms, scales over his scalp with thinned-out silky hair and healed macules over whole body while he also had grade IV clubbing.

His complete blood count revealed a white blood cell count of 7400/mm^3, neutrophil count of 4900/mm^3, a mild lymphopenia of 1300/mm^3 (normal limits for age: 1900–7000/mm^3), eosinophil count of 85/mm^3, hemoglobin of 9 g/dl, platelets of 23,000/mm^3 (normal limits for age: 150,000–400,000/mm^3) and mean platelet volume of 5.9 fl (normal limits for age: 8.9–11.8 fl). His HIV serologic test was negative. His peripheral smear and bone marrow aspirate showed low platelet counts with no further abnormalities. He had a normal thymic shadow on his chest x-ray and his serum ferritin levels and electrolyte measurements, specifically calcium levels, were normal for age. His immune work-up showed borderline low serum immunoglobulin IgG of 4.87 g/L (normal limits for age: 4.8–22.9 g/L), normal IgM and IgE while he had elevated serum IgA of 4.97 g/L (normal limits for age: 0.33–2.76 g/L) (Fig. 1).

Whole genome sequencing in a regional, clinically-certified diagnostic laboratory and analyzed based on the recommendations of American College of Medical Genetics revealed a variant — c.1205dupC (p.Pro403Alafs*92) — in the *WAS* gene. On further analysis, this variant is not reported in the literature nor in gnomAD, ClinVar, Human Gene Mutation Database (HGMD), or e!Ensembl databases. The c.1205dupC variant occurs in exon 10 of the *WAS* gene, which has a pLi of 1.00 and p.LoF observed/expected (o/e) of 0.00 (CI: 0.00–0.15), indicating that it is intolerant of variants that cause loss of function. The duplication is predicted to be frameshift in the proline-rich region of the molecule (Fig. 2) and disease causing by SIFT and MutationTaster (probability of 1), with the latter predicting potentially causing a slightly truncated protein (due to a mutant stop codon at cDNA position 1482, rather than the wild-type position 1509, with the theoretical nonsense mediated decay boundary at position 1403), resulting in loss of protein function.

Due to resource limitations, further testing of family members, as well as molecular confirmation, including Sanger sequencing, protein expression levels, and F-actin polymerization, were not possible. Nonetheless, give the deleterious nature of the insertion and resulting frameshift in WAS and the compatible clinical picture, this finding most likely confirms his diagnosis of Wiskott–Aldrich syndrome.

Following his diagnosis, he is on thrice weekly Azithromycin prophylaxis. His parents have been counseled on the need for familial screening (not yet done) while options for hematopoietic stem cell transplantation (not available in Ethiopia) are being explored abroad.

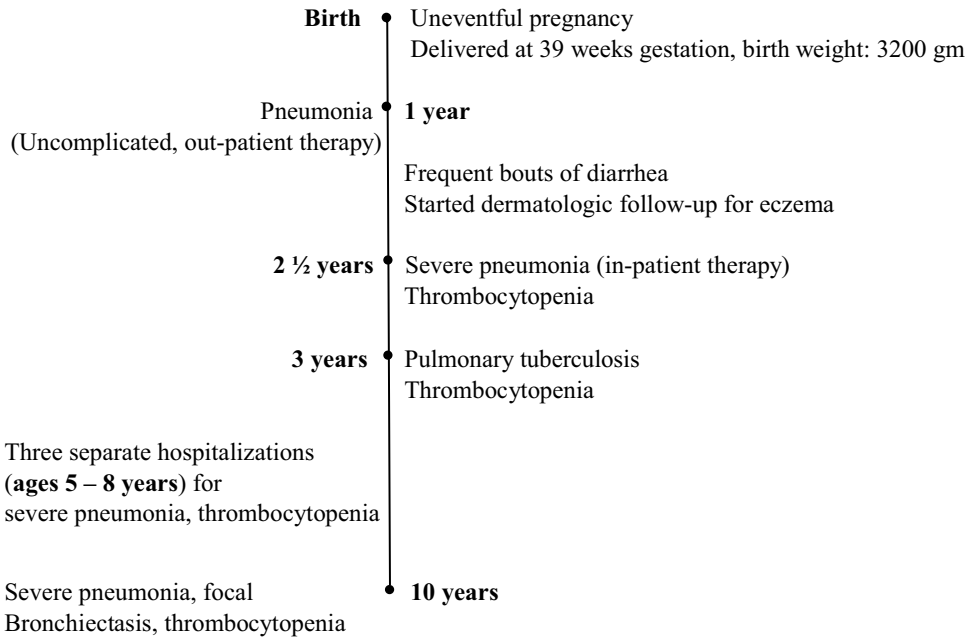

Fig. 1 Timeline of clinical course

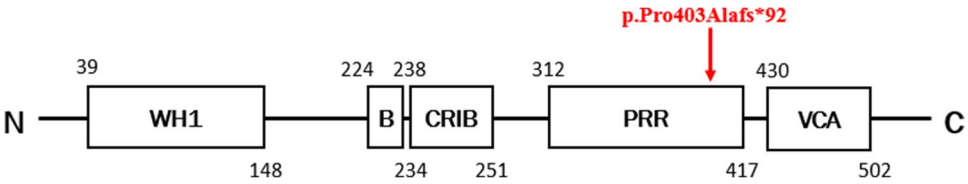

Fig. 2 Mutation detected in the WAS gene of the patient

Discussion

Though the average age at diagnosis of children with WAS is close to 2 years of age, resource constraints in diagnostics have meant that very few of affected black African children have had their diagnosis confirmed [2, 9]. The fact that our patient survived up to 12 years of age indicates he may have had a milder form of WAS which later on progressed to have severe clinical features, as backed by his high WAS-clinical scoring (he has the classic triad of micro-thrombocytopenia, eczema, recurrent infections and immunodeficiency) [10]. The leaky aspect of the WAS phenotype may also reflect the hypomorphic nature of the bioinformatics prediction, that is, that a slightly truncated protein is produced due to this mutation, providing some residual function.

While clinical diagnosis based on classic presentations have been reported from South Africa and Ethiopia, a literature search reveals only three other cases — two boys from Tanzania and one from South Africa — whose diagnoses were confirmed with identification of the culprit mutation [7, 11–14] (Table 1). The description of our patient with in this context is important to highlight the presentation of WAS in countries where training programs and specialized clinical immunology practice are lacking. In addition, the inability to characterize the molecular consequences of the identified genetic variant due to global inequities in diagnostics provides not only clinical uncertainty in low-resource settings, but also creates a knowledge gap for the global community of inborn errors of immunity.

WAS presents as a triad of bleeding tendencies, eczema and frequent severe infections including pneumonia, otitis media, sinusitis, skin and soft tissue infections, and dysentery [15]. But the actual presenting manifestations may vary depending on the severity of mutation and the corresponding levels of the mutated WAS protein [2]. The clinical course in affected children may be complicated by alveolar hemorrhage, bronchiectasis, vascular abnormalities, and increased tendencies for leukemias, lymphomas, and autoimmune disorders [16–19].

The low platelet counts and mean platelet volume, low serum immunoglobulins G and M and mildly elevated IgA and IgE should suggest a diagnosis of WAS in a child (especially a boy) presenting with recurrent infections in the absence of an acquired etiology. Various methods of genetic testing like single- and multi-gene sequencing, whole exome sequencing and whole genome sequencing (preferred test) provide confirmation of the diagnosis [20]. Prenatal

Table 1 A review of case reports of children with WAS from African countries

Authors	Journal and year of publication	Age at first presentation	Immune work-up (flow cytometry, immunoglobulins)	Mutation testing	Targeted preventive/curative treatment and outcome
Lanzkowsky and Levy (South Africa) [11]	*S Afr Med J*. 1965	1 month, male	None	No index or family testing	Not specified
Jebessa and Alemayehu (Ethiopia) [9]	*Eth J Hlth Sci* 2020	4.5 years, male	None	No index or family testing	Prophylactic trimethoprim-sulfamethoxazole and acyclovir, intermittent platelet transfusions (died)
Glanzmann et al. (South Africa) [14]	*BMC Med Genet* 21, 124 (2020)	3 years, male	Elevated IgE; normal IgA, IgG, IgM, expanded T cell subsets and T cell receptor excision circle (TREC) screening	c.826 A > T (K288X) mutation in exon 9 of the WAS gene (NM_000377.3), His mother is a heterozygous carrier of the variant while it is completely absent in his father	Not specified (died)
Mawalla et al. (Tanzania) [13]	*Ther Adv Rare Dis* 2021	10 months, male	High IgE and IgA; normal IgG and IgM	NM_000377.2:c.360 + 1G > A (family members not tested)	Prophylactic azithromycin and topical mupirocin (died)
Kiputa et al. (Tanzania) [12]	*J Med Case Reports* 2022	8 months, Male	Elevated IgG, IgA and IgE; Normal IgM	c.403C > T p.(Gln135*), NM_000377.2:c.403C > T	Prophylactic trimethoprim-sulfamethoxazole, topical mupirocin, weekly topical mix of clotrimazole + gentamycin + beta-methasone over ears (died)
Alemayehu and Vinh (Ethiopia)	Under discussion here	12 years, male	Elevated IgA, borderline low IgG, normal IgM and IgE	c.1205dupC (p.Pro403Alafs*92) mutation of WAS (family members not tested)	Prophylactic azithromycin (under evaluation for HSCT)

screening (amniocentesis, chorionic villous sampling) for future siblings in cases like this where the mutation has already been identified is important for family planning as relatives may be carriers [20].

The management of WAS revolves around hematopoietic stem cell transplantation (HSCT) and/or gene therapy in accordance with the patient's specific inborn genetic immune error [21]. Survival is marked when affected children receive HSCT from a non-carrier sibling donor [22]. Prevention centers on immunoglobulin replacement therapy, maintaining adequate hand hygiene and prophylactic antibiotics [23, 24]. Follow-up and treatment of eczema and thrombocytopenia are other aspects of management of affected children [2]. Platelet transfusions are only recommended when platelet counts are less than or equal to 5000/mm^3 for an otherwise stable child or if greater than 10,000/mm^3 in cases of bleeding or infections [25].

Our case report reports a novel, probable mutation causing Wiskott–Aldrich syndrome in an Ethiopian. Further immunologic testing (flow cytometry and post-vaccine titers) and molecular biologic evaluations could not be made because of diagnostic limitations, highlighting the obstacles in global equity that affects the world of inborn errors of immunity.

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Author Contributions TA: conception and design of the study, data collection, data analysis, manuscript preparation, and revision. DCV: data analysis, manuscript preparation, and revision.

Data Availability All data pertaining to the report are included within the manuscript.

Materials Availability All data pertaining to the report are included within the manuscript.

Declarations

Ethics Approval Approval was not required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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