Clinical Features and Outcome of 23 Patients with Wiskott-Aldrich Syndrome (WAS): A Single-Center Experience

Haskologlu et al. Clinical features and Outcome of WAS patients

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Abstract

Objective: Wiskott-Aldrich syndrome (WAS) is an X-linked primary immune deficiency characterized by micro thrombocytopenia, eczema and recurrent infections.

Material-Method: We retrospectively evaluated the clinical course, immunological features, treatment and outcome in a total of 23 WAS patients together with the data related to 11 transplanted cases among them between 1982-2019.

Results: Before admission, 11 patients (48%) were misdiagnosed as immune thrombocytopenia (ITP). WAS score was mostly 4 or 5. Eleven patients were transplanted and they had an overall survival (OS) rate of 100% during a median follow-up period of 8.5 years (8months-20years). Five patients who were not transplanted died at median 7 years (2-26 years). Untransplanted patients had high morbidity due to organ damages mostly caused by autoimmunity, bleeding and infections. Two novel mutations were also defined.

Conclusion: All male babies with microthrombocytopenia should be evaluated for WAS. Hematopoietic Stem Cell Transplantation (HSCT) should be performed at the earliest age with the best possible donors.

Key words: Wiskott-Aldrich syndrome, microthrombocytopenia, hematopoietic stem cell transplantation

Öz

Amaç: Wiskott-Aldrich Sendromu (WAS) X-e bağlı geçen mikrotrombositopeni, egzema ve tekrarlayan enfeksiyonlarla karakterize bir primer immune yetmezlidir.


Bulgular: Başvurudan önce 11 hasta yanlışlıkla immun trombositopeni (ITP) tanıısı almıştı. WAS skoru çoğunlukla 4 ve 5 puandı. On bir hastaya nakil yapıldı ve median 8.5 yıl (8ay-20yıl) izlem süresinde hayatta kalma oranı %100 oldu. Nakil yapılamayan 5 hasta medyan 7 yılda (2-26 yıl) kaybedildi. Nakil yapılayan hastalar çoğunlukla otoimmünite, kanama ve enfeksiyonların neden olduğu organ hasarları nedeniyle yüksek morbiditeye sahipti. Ayrıca, iki yeni mutasyon tanımlandı.

Sonuç: Mikrotrombositopenisi olan tüm erkek beşekler WAS açısından değerlendirilmelidir. Hematopoietik kök hücre nakli (HKHN) mümkün olan en iyiдонörlerle en erken yaşta yapılmalıdır.

Anahtar kelimeler: Wiskott-Aldrich sendromu, mikrotrombositopeni, hematopoietik kök hücre nakli

Introduction

Wiskott-Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by immunodeficiency, thrombocytopenia, and eczema [1,2]. WAS gene encodes WAS protein (WASp) [3]. WASp is an important regulator of the actin cytoskeleton required
for many hematopoietic and immune cell functions [4,5]. Estimated incidence of WAS is one in 100,000 live male births [6]. The presence and the severity of the clinical findings are variable [7]. The severity of the clinical presentation is measured by WAS score that was described by Zhu Q et al. [8]. Patients with a WAS score of ≥3 points are regarded as severe phenotype [8, 9].

The first patient with WAS in Turkey (P1 in this cohort) was diagnosed by Emel Babacan in 1982 [10]. Currently, HSCT is the most important curative treatment for WAS [11-17]. We aimed to evaluate the clinical features and outcome of our Wiskott-Aldrich Syndrome cohort: synopsis of a single-center experience with long term-follow-up.

**Material-Method**

From 1982 to 2019 23 WAS patients from 15 families were diagnosed and followed up at Ankara University Medical School, Department of Pediatric Immunology and Allergy. WAS diagnosis was confirmed according to European Society of Immune Deficiency (ESID) criteria [18]. Parental consents were obtained in all. WAS score, where each clinical feature was given a point, was used to evaluate clinical severity of the patients. The patients with microthrombocytopenia received a score of 1 without any other clinical or laboratory signs. Patients with platelet abnormalities and moderate eczema scored 2 with or without minor infections. patients with chronic but manageable eczema or recurrent infections, or both have scored 3. Score 4 for patients with severe eczema and recurrent life-threatening infections. A score of 5 was assigned when patients with eczema and/or frequent infections developed autoimmune diseases or malignancies.

**Statistical Analysis**

Qualitative variables calculated as median (minimum-maximum) whereas categorical variables as frequency (percentage)

**Mutation Analysis**

Mutation analysis of exon 1 to 12 of the WAS gene was performed for 21 of the 23 patients according to described sequencing technique by Lutsiky MI et al. [19] Since the remaining two cases did not have enough DNA samples their mutation analysis could not be performed.

**Results**

**Clinical Features of the Patients**

The median age at the onset of symptoms was 15 days (1 day-7 months). Before admission to our department, 48% (n:11) of the patients were diagnosed as ITP, 13% (n:3) as cow milk protein allergy (CMPA) and 9% (n:2) as juvenile myelomonocytic leukemia (JMML). The median age at WAS diagnosis was 24 months (1 month-132 months). 69% had a positive family history. The most common complaint was petechia (91%). IVIG (400 mg/kg/3 weekly) and antimicrobial prophylaxis were given to all. Chronic renal failure (CRF) developed in 3 patients two of them with IgA nephropathy and leukocytoclastic vasculitis (LCV) and one of them with only LCV. In five patients EBV associated lymphoproliferation detected. One patient developed EBV associated non-Hodgkin’s lymphoma (NHL). 5 patients died between 2-26 years (median 7 years) due to severe infections (n=2), life threatening bleeding (n=2), NHL (n=1). Survival rate without transplantation is 58%, the oldest patient is 38-year-old now. The demographical, clinical, genetic characteristics and follow-up of patients are given in Table-1. WAS score was mostly 4 or 5 in our patients. The laboratory characteristics and immune work-up is presented in Table 2.

**Genetic Studies**

Two novel mutations were defined in 3 patients (P10, P11 and, P21) from 2 different families. A novel Single Nucleotide Variation (SNV) mutation in exon 2 (c.273G>C p.Q91H) resulting in a premature stop codon, leading to a shortened transcriptstop gained detected in P10 and P11. In P21 a novel missense mutation defined in exon 2 c.209G>A that resulting in amino acid changes glycine to glutamic acid.p.G70E. Three novel mutations in 4 patients (P12, P17,
P18 and P20) were previously reported by the authors [20-22]. Known mutations were detected in the remaining 14 patients [19,23-27].

Data Related to HSCT
Survival was 100% in transplanted patients. HSCT related data were given in Table 3. 11 patients had received HSCT at median 3.5 years (10 months-9 years). 6.7x10⁶/kg (3.1-13x10⁶/kg) CD34+ stem cells were transfused. Either a myeloablative conditioning regimen (MAC) [consisted of a total dose of 16mg/kg busulfan and 200mg/kg cyclophosphamide or 16mg/kg busulfan and 160mg/m² fludarabine] or reduced intensity conditioning regimens (RIC) [consisted of treosulfan (>1y 42g/m², <1y 36g/m²) and 150mg/m² fludarabine or 140mg/m² melphalan and 150mg/m² fludarabine] were used. The decision of the regimen to be used was determined by evaluating the patient's clinical status, donor and availability of conditioning agents especially treosulfan. For the prophylaxis of graft versus host disease (GvHD) 5 patients received CsA, 5 received CsA and MTX, 1 patient received tacrolimus and MMF. ATG was added to unrelated donor transplants. The neutrophil and platelet engraftments were achieved on day 14 (10-20) and 27 (17-37) respectively. Acute GvHD (grade I-IV) observed in 36% of patients. A full donor chimerism was achieved in all except P11. Neither an autoimmune nor a malignant disease developed in any patient during the post-transplant follow up of median 8.5 years (1-20).

Discussion
Here, we evaluated the clinical features and treatment outcome of the largest series of WAS patients reported from Turkey. Since mucosal bleeding is the most prominent complaint in WAS, misdiagnosis like ITP, JMML and even CMPA were found to be common among our patients. ITP is rarely seen in early years of life [28]. However, according to our experience, and literature WAS patients have often diagnosed as acute ITP in infancy and chronic ITP in childhood at first [29,30]. Moreover, since hepatosplenomegaly, leukocytosis and thrombocytopenia or bloody diarrhea and eczema could be seen in WAS, those presentations can also be misinterpreted as JMML or CMPA [31, 32]. In our cohort, almost half of the patients (n:11, 48%). were misdiagnosed as ITP before admitting to our department. Likewise, three patients diagnosed as CMPA and two had a similar phenotype to JMML. One had splenectomy before WAS diagnosis. He had severe infections and died with intracranial bleeding (P11.) So, misdiagnosis, may cause diagnostic delay and, even fatal consequences especially in critically ill patients.

Severe thrombocytopenia with low MPV values (<7fL), is the most striking finding for the diagnosis of WAS [13-16]. Normal or high MPV have been reported in patients with autoimmunity, splenectomy, and repeated thrombocyte transfusions [33-36]. In our series, MPV was low in all, but normal in 2 patients who had repeated platelet transfusions. Patients with autoimmunity who were unresponsive to corticosteroid treatment and/or not received hematopoietic stem cell transplantation have the poorest prognosis [37]. Malignancies, especially EBV associated NHL reported as the most frequent in WAS [7,9,15,38]. In our cohort three patients with AIHA who received HSCT did not experience relapses and cured. One of our patients developed NHL, relapsed and died while two with EBV associated lymphoproliferation cured following HSCT.

Even in relatives with the same mutation, the severity of clinical findings and survival varied. It was also noteworthy that two patients with an intronic mutation had a JMML-like phenotype. The most striking features of the patients who had novel mutations were the very early onset of disease with severe phenotype (P10, P11 and, P21).

During the last ten years, age at diagnosis decreased from 48.5 months to 6 months in our cohort. A substantial increase of awareness about WAS and advancements in its diagnosis
have contributed to this outcome. Recently, life expectancy was elevated to 20 years mostly with antimicrobial prophylaxis and IVIG [7,13]. Moreover, HSCT provides an excellent outcome and even cure [12,39]. In the multicenter study evaluating 96 transplanted WAS the OS was found to be 97% at 2 years [10]. The most important complication seen after HSCT was autoimmune disease independent of cGvHD associated with mixed chimerism. It was observed in 20% of the patients, at a median time of +1.5 years and mostly with unrelated donors [10]. Burroughs et al. recently reported the outcome of 129 transplanted WAS patients. Their OS for 5-years was 91% with a median follow-up of 4.5 years. It was shown that HSCT performed in the first 5 years were more successful. Also they found that the type of donor and conditioning intensity did not affect OS [40].

In our cohort, HSCT did not available for the patients diagnosed before 2000. They had poor quality of life with several morbidities and high mortality (42%, n:5) due to bleeding, infections and malignancy. In transplanted patients’ uneventful OS was 100% in median 8.5y (8months-20years).

In our study, we either used MAC (n:8) or RIC (n:3) regimens. None of the patients have graft failure. A stable mixed chimera developed only in one patient transplanted by MAC. He has a moderate but clinically nonsignificant thrombocytopenia for many years [41].

**Conclusion**

All male babies with thrombocytopenia should have their MPV measured and investigated for family history, the presence of infections and eczema for WAS diagnosis. Furthermore, the diagnoses of ITP, leukemia and CMPA can mask the diagnosis of WAS. Although the survival of WAS patients has increased with supportive treatment recently, patients can die at any time due to bleeding, infections and malignancy. As HSCT has a 100% success rate in these patients, it should be performed as early as possible after the diagnosis with the most appropriate donor. Gene therapy is a promising option that has the advantage of avoiding HSCT complications [42].

**Conflict of Interest:** The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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**Contributor's statements:**

SH: Concept, design, write manuscript

AO, GO, SKB, CI, KB: Data collection or processing

SC, LTS, FD: Analysis or Interpretation

AI: Analysis or Interpretation, write manuscript
References


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<th>Age at Diagnosis (month)</th>
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<td>9</td>
<td>3</td>
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<td>Freque nt URTI, bronch iolitis</td>
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<td>14</td>
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<td>Frequent tonsilitis, otitis, pneumonia, aphthous lesions, perianal abscesses, dental abscesses EBV infection</td>
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Imai K, Blood, 2004 + Alive

Kim MK, Bioc him Biophys Acta. 2004 + Alive

http://www.hg md.c f.ac.uk/ac/ge ne.php?gen=WA S - Died at the age of 4 due to intracranial hemorrhage
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<th>C.</th>
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<td>TNC (mm$^3$)</td>
<td>TEC (mm$^3$)</td>
<td>IgG (mg/dl)</td>
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<td>--------------</td>
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<td>-------------</td>
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<tr>
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<td>14000</td>
<td>4,6</td>
<td>11000</td>
<td>2500</td>
<td>8500</td>
<td>0</td>
<td>330</td>
</tr>
<tr>
<td>23 ASin cousins</td>
<td>14000</td>
<td>4,6</td>
<td>11000</td>
<td>2500</td>
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Table 2. Laboratory features and immune work-up
<table>
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<tr>
<th>Patient no</th>
<th>Transplant age (y)</th>
<th>Current age</th>
<th>Donor</th>
<th>Conditioning regimen</th>
<th>GvHD prophylaxis</th>
<th>Source of stem cells</th>
<th>Transferred CD34+stem cell (10^6/kg)</th>
<th>Platelet eng. (day)</th>
<th>Neutrophil eng. (day)</th>
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<tbody>
<tr>
<td>9</td>
<td>3</td>
<td>19</td>
<td>MSD</td>
<td>Bu, CY</td>
<td>CsA</td>
<td>BM</td>
<td>6.7</td>
<td>29</td>
<td>18</td>
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<td>10</td>
<td>9</td>
<td>19</td>
<td>MUD</td>
<td>Bu, CY, ATG</td>
<td>CsA + MTX</td>
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<tr>
<td>11</td>
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<td>Bu, CY</td>
<td>CsA</td>
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<td>11</td>
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<tr>
<td>12</td>
<td>10 mo</td>
<td>21</td>
<td>MRD</td>
<td>Bu, CY</td>
<td>CsA + MTX</td>
<td>BM</td>
<td>3.1</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

Plt: Platelet, MPV: mean platelet volume, TLC: total lymphocyte count, TNC: total neutrophil count, T cell: T cell
*Under IVIG
na: not available

Table 3. Data related to patients treated by HSCT
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<th></th>
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<th>CsA</th>
<th>BM</th>
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<td>Melfalan, Flu, ATG</td>
<td>CSA + MTX</td>
<td>BM</td>
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</tr>
<tr>
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<td>10 mo</td>
<td>2</td>
<td>MMUD (9/10)</td>
<td>Treo, Flu, ATG</td>
<td>Tacrolimus +MMF</td>
<td>BM</td>
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