Bleeding and splenectomy in Wiskott Aldrich syndrome: a single centre experience

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Clinical implication

This single centre retrospective review shows that splenectomy is an effective option for management of thrombocytopenia in X-linked thrombocytopenia (XLT). In contrast, more than half of patients with classical Wiskott Aldrich syndrome (WAS) experienced post-splenectomy thrombocytopenia relapse.

To the Editor

Wiskott Aldrich syndrome (WAS), caused by loss of function mutations in the *WAS* gene, results in a classical triad of combined immunodeficiency, eczema and microthrombocytopenia, associated with an increased risk of autoimmunity and malignancy[1]. Attenuated WAS, also known as X-linked thrombocytopenia (XLT), represents a milder form of the disease mainly limited to thrombocytopenia[2, 3] (Table E1). Despite differences in other disease features, patients with XLT and WAS demonstrate similarly low levels of platelets[4,5]. In both groups, severity of thrombocytopenia is categorised by platelet count as mild (50-150 $x10^9$/L), moderate (20-50 $x10^9$/L) or severe (<20 $x10^9$/L). Serious bleeding has been reported to occur in up to 30% of patients, including a 10-20% risk of intracranial haemorrhage (ICH)[1,4,6]. Surprisingly, no clear correlation between degree of thrombocytopenia and serious bleeding episodes has been identified[6].

While there is broad consensus that thrombocytopenia in classical WAS should be treated by early allogeneic haematopoietic stem cell transplantation (HSCT) or experimental gene therapy, management in XLT continues to be the subject of debate, as the risks and complications of definitive treatments are still widely considered to be unacceptable in this milder disease. The role of splenectomy in WAS and XLT is contentious mainly due to concerns about severe infection and reliability to reduce serious episodes of bleeding[6]. In the absence of other effective therapies, our centre offers splenectomy to patients with XLT where severe thrombocytopenia significantly limits normal activity and quality of life. To assess the efficacy and safety of this practice, we reviewed our outcomes for splenectomy in patients with XLT and classical WAS.

A retrospective study was conducted of patients with a confirmed molecular diagnosis of WAS from 1992 – 2017 (all clinical severities). Information on platelet counts, serious

bleeding and treatment was recorded. For patients who underwent splenectomy, vaccine responses, infections and prophylactic antibiotics were documented.

Of 102 patients, 68 had a diagnosis of classical WAS and 34 of XLT. Nineteen children have undergone splenectomy (19%), 10 of whom had XLT (Table 1). Median follow up is eight years (range 1 - 24.6 years), with 187 total years of patient follow-up. Shorter follow-up for XLT patients compared with classical WAS (4.93 and 16.45 years respectively) reflects our recent trends in favour of splenectomy for XLT to allow engagement in normal physical activity.

We observed only six episodes of serious bleeding (defined as requiring medical intervention) in our whole WAS cohort of 102 patients (overall incidence 6%), none of whom had at the time undergone splenectomy. Of these, five occurred in patients with classical WAS; three of whom had an ICH (one fatal) and two had serious GI bleeds. Serious bleeding episodes in classical WAS were associated with documented immune-mediated thrombocytopenia (ITP) in two out of five patients and suspected, based on worsening thrombocytopenia and presence of other autoimmune cytopenias, in another two. One patient with XLT required surgery for an ICH following significant blunt trauma and fully recovered.

Six patients with classical WAS underwent splenectomy prior to definitive stem cell therapy; two following episodes of serious bleeding, one to prevent serious bleeding in a patient with gastrointestinal angiodysplasia and three to manage thrombocytopenia in patients where corrective stem cell therapy was delayed. Three patients with classical WAS underwent splenectomy after corrective stem cell therapy (two HSCT, one gene therapy) for persistent thrombocytopenia. All ten patients with XLT underwent elective splenectomyfor quality of life reasons to allow engagement in normal physical activities including contact sports.

Lowest pre-splenectomy platelet counts in the two groups were comparable, but response to splenectomy differed (Figure 1). Five of the nine patients with classical WAS (56%) had recurrence of thrombocytopenia post-splenectomy (defined as two consecutive platelet counts of < 100 x 10^9/L), four of whom relapsed within a year. Three of these, two of whom had splenectomy for ITP, had recurrence of severe thrombocytopenia that corrected post-HSCT. One had recurrence of thrombocytopenia in the context of graft failure post-HSCT, which corrected after a second transplant and another had undergone splenectomy in the setting of suspected post-HSCT autoimmunity (autoimmune haemolysis and neutropenia with suspected ITP) and has ongoing mild thrombocytopenia. In contrast, all XLT patients responded well to splenectomy with an immediate and sustained platelet rise to > 100 x 10^9/L (> 150 x 10^9/L in all bar one patient), and no relapse.

There have been no major infectious complications post-splenectomy in either group. All XLT and post-HSCT WAS patients were vaccinated with Prevenar 13, Hib, Men B and C conjugate vaccines prior to splenectomy and vaccine responses are monitored. 12/12 patients who had specific antibody responses recorded post-splenectomy generated a protective antibody response (11 to tetanus +/- Hib and eight to at least 9/13 pneumococcal serotypes). Additionally, all patients are taking antibiotic prophylaxis, which together may account for the lower incidence of serious infection in our cohort compared with others. It is, however, important to note that median age of serious infection in splenectomised patients is reported elsewhere to occur in patients in their 20s[6], highlighting the need for longer term follow-up of our patients.

Here we present a single centre experience of bleeding and splenectomy in classical WAS and XLT. In contrast with previous literature, we observed a surprisingly low incidence of serious bleeding (6%); lower in XLT compared with classical WAS (3% and 7% respectively). These findings may relate to a number of factors including (i) tight criteria for assigning a diagnosis of XLT, (ii) prompt diagnosis and aggressive treatment of ITP, and (iii)

early definitive therapy for patients with classical WAS. In our experience, splenectomy in classical WAS has variable efficacy, with less than half of patients achieving a significant and sustained rise in platelet count, probably because of the contribution of early onset autoimmunity. In contrast, we found splenectomy to be universally successful in treating thrombocytopenia in patients with XLT, where autoimmune destruction has not been demonstrated in our cohort. This has allowed broad engagement in physical activities and participatory contact sports. We have not formally measured quality-of-life indices in this group, but anecdotally normalisation of platelet counts substantially reduces patient and family anxiety over bleeding risk and suspicion of physical abuse[7]. We have not observed any serious infections post-splenectomy. Limitations of this study include its small sample size and relatively short follow-up time, particularly for XLT patients, which mean that caution should be exercised when interpreting these results. Although a retrospective review is the only feasible study design for this rare disease, we now have an opportunity for prospective evaluation.

~~In conclusion, we believe that the option of elective splenectomy for XLT *requires careful discussion* on an individual family basis, taking into consideration medical factors and impact on quality of life, but should not be dismissed as an effective therapy even if considered entirely on the grounds of life quality.~~

In conclusion, we believe that splenectomy for classical WAS is not recommended unless there is likely to be significant delay in definitive therapy, or in emergency situations. In particular, caution should be exercised when considering splenectomy in the context of ITP, where our data suggest it is less likely to be successful. In contrast, we recommend splenectomy for XLT where the child's quality of life is significantly impaired by bleeding risk limiting engagement in physical activity or resulting in substantial anxiety.

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Figures

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157 **Figure 1: Platelet response to splenectomy.**

158 Platelet counts for patients with XLT (A) and classical WAS (B) are compared at their lowest,
159 immediately pre-, 2-3 days post-, 1 year post-splenectomy and most recently. Red dots
160 represent patients with relapse of thrombocytopenia (two consecutive counts < 100 x 10^9/L,
161 represented by dotted line) post-splenectomy.