Paediatric Cardiology

Bleeding problems in a patient with Williams syndrome

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Summary

Williams syndrome is a multisystem disorder caused by a quantitative reduction in elastin. The cardiovascular anomalies often require extensive surgery. We describe a bleeding tendency in a child with Williams syndrome. Health care workers managing such patients should be aware of possible bleeding tendencies in children with Williams syndrome and be prepared for prolonged bleeding during investigative and surgical procedures.

Case report

A 9-year-old girl with Williams syndrome, supravalvular aortic and pulmonary stenosis with extensive hypoplasia of the aortic arch and main branches (Fig. 1) presented with large spontaneous mucosal bleeds. Her mother described how 2 days before she had been woken up by choking sounds coming from her child. Large amounts of fresh clotted blood were found in the child's mouth with no evidence of epistaxis. One month previously the child had had a spontaneous vaginal bleed. She was otherwise completely well and on no medication. Mother and child lived alone, and the child attended a school for children with learning disabilities. There was no family history of a bleeding tendency.

On clinical examination she had the typical Williams facies (Fig. 2) and personality. She tended to keep her mouth open. Oronasopharyngeal examination was normal. She was not pale and there was no evidence of subcutaneous or submucosal bleeds or haemarthroses. Anthropometric examination showed weight, length and head circumference on the 50th, 10th, and 50th percentiles for age, respectively.

Cardiovascular examination revealed all pulses to be palpable, and blood pressure recordings were 151/112 mmHg and 168/116 mmHg in the right and left leg, respectively. Lower readings were recorded in the right arm (128/73 mmHg) and left arm (80/69 mmHg) (Fig. 1). The heart showed signs of biventricular hypertrophy with aortic and pulmonary stenosis murmurs. There was no clinical pulmonary hypertension or cardiac failure. There were no abdominal bruits and the genitalia were normal for a prepubertal female. The central nervous system was normal with signs of mild global mental retardation.

Systematic investigation of the bleeding diathesis was initiated (Table I). Bone marrow aspiration and trephine
biopsy findings were unremarkable except for a moderate megakaryocyte hypoplasia with normal megakaryocyte morphology. Bleeding time, assessed by the template method (Simplate), was repeatedly prolonged by more than 11 minutes, i.e. excessively relative to the moderately decreased platelet count.

Platelet aggregation studies showed normal aggregation with standard agonists such as adenosine diphosphate (ADP) (2.5 μM, 5 μM, 10 μM), adrenaline (10 μM), collagen (1 μg, 4 μg), ristocetin (0.325 mg/ml, 0.75 mg/ml, 1.5 mg/ml), arachidonic acid (15 mM). Figures in brackets denote final concentrations. Platelet adenosine triphosphate (ATP) release was decreased with ADP and collagen stimulants. The calcium-independent release reaction with thrombin as stimulant could not be measured accurately due to the low platelet count of the sample after preparatory washing steps. Flow cytometry showed a moderately decreased mepacrine binding of platelets compared with controls. No ultrastructural differences could be detected in the number and structure of the storage granules. A ristocetin co-factor activity of 114% (normal range 50 - 150%) excluded von Willebrand's disease.

All common infective parameters were normal and an extensive collagen disease screening was negative. Random serum calcium level was normal.

Clinical course

After the girl's mother was informed about the risks of surgery to correct the extensive cardiovascular defects she decided not to subject her child to any further surgical or medical intervention. The girl died 4 months later following a sudden massive pulmonary bleed after admission for a mild upper respiratory infection. The platelet count and clotting profile were similar to those in Table I.

Discussion

The main and associated features of Williams syndrome are listed in Tables II and III, and our knowledge of the associated findings continues to increase. Despite this, our understanding of the cause and pathogenesis has advanced little. Recently a submicroscopic deletion on the elastin gene locus on chromosome 7q11.23 was described in more than 90% of cases of classic Williams syndrome.16,17 The breakpoint is located in the same region in which a translocation had disrupted the gene in a family with supravalvar stenosis.13 This results in a quantitative reduction in elastin during vascular development. Hemizygosity is the probable cause of the vascular abnormalities. The relationship between elastin gene disruption and the phenotype still does not help to explain the pathophysiology of the progressive cardiovascular changes.

Elastin forms the major component of elastic fibres in medium to large arteries, but is not present in capillaries, veins or supporting tissues. It is unlikely that the quantitative reduction of elastin in patients with Williams syndrome is responsible for a bleeding disorder.

Although the platelets were functionally morphologically normal, there were subtle differences in the storage pool capacity compared with normal controls.14 The slightly sub-normal ATP release and decreased mepacrine binding, with normal ultrastructural appearance in the absence of any drug ingestion or difficulty in venepuncture, could account for the spurious storage pool defect.15 A more plausible explanation is that during the pathological progression of medial hypertrophy, intimal and subintimal fibrosis with disruption of elastin fibres patterns and increased collagen deposition, platelet entrapment occurs.16 Conversely, platelet aggregation in areas of disrupted elastin fibre patterns might play an important role in

Fig. 1. Aortogram showing supravalvular aortic stenosis (large arrow) with hypoplasia of the arch and main branches (small arrows).

**TABLE I. INVESTIGATION OF BLEEDING TENDENCY**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>WCC = 4.9 x 10^11/1 (Normal range 5.1 - 13.9)</td>
</tr>
<tr>
<td></td>
<td>Hb = 11.9 g/dl (Normal range 11.1 - 15.4)</td>
</tr>
<tr>
<td></td>
<td>RCC = 3.8 x 10^11/1 (Normal range 4.01 - 5.39)</td>
</tr>
<tr>
<td></td>
<td>Platelet count = 104 x 10^11 (Normal range 150 - 400)</td>
</tr>
<tr>
<td>Blood smear</td>
<td>True thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Normal platelet size and morphology</td>
</tr>
<tr>
<td></td>
<td>Normal megakaryocyte count</td>
</tr>
<tr>
<td></td>
<td>No signs of peripheral platelet destruction</td>
</tr>
<tr>
<td>Coagulation profile</td>
<td>INR = 0.97 (Normal range 0.8 - 1.06)</td>
</tr>
<tr>
<td></td>
<td>PTT = 36.8 seconds (Normal range 25 - 42)</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>&gt; 11 minutes (Normal range 2 - 8)</td>
</tr>
<tr>
<td>Hess test</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>(No petechiae after 5 minutes at cuff pressure = 80 mmHg)</td>
</tr>
</tbody>
</table>

WCC = white cell count; Hb = haemoglobin; RCC = red cell count; INR = international normalised ratio; PTT = partial thromboplastin time.
the pathophysiological process described above. If more extensive cardiovascular pathology is present, as in our patient (Fig. 1), platelet aggregation and entrapment might be exaggerated. If platelet aggregation had in fact occurred in vivo, it could result in partial release of platelet content, explaining the decreased storage pool fluorescence of the platelets found by flow cytometry. It has been demonstrated with flow cytometry that ADP is capable of causing partial degranulation of platelets in vivo, independently of aggregation, fibrinogen binding or thrombin generation. ADP released by red cells undergoing shape changes at sites of changed bloodflow, e.g. arterial stenosis, can also activate platelets in vitro. However, these findings cannot explain the persistently prolonged bleeding time, as such platelets tend to cause a hypercoagulable state rather than a bleeding tendency."

No conclusion could be reached on the role of hypercalcaemia and platelet dysfunction in Williams-Beuren syndrome. High extracellular calcium concentrations can activate calcium-dependent platelet protease that in turn proteolyses the actin-binding protein in platelets. This could result in changes in the shape and release action of platelets. Hypercalcaemia, however, was not documented in our patient.

### Conclusion

Williams syndrome is a multisystem disorder. Defects in the elastin gene are responsible for the structural defects. This quantitative reduction in elastin may affect blood vessels but not capillaries. Low platelet counts may occur as a result of platelet adhesion (trapping) and aggregation at the sites of disrupted vascular structure and predispose to bleeding. The bleeding tendency could also be aggravated by partial platelet content release without aggregation, which results in partially dysfunctional platelets, as were found in this case study.

The possibility that the bleeding disorder in this patient...
may have been a chance or fortuitous occurrence cannot be excluded. Medical care workers caring for patients with Williams syndrome should be aware of this and be prepared for prolonged bleeding during investigative or surgical procedures.

References


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