Secondary thrombocytosis

A J Vora, J S Lilleyman

Abstract
To estimate the incidence and causes of secondary thrombocytosis in children, a 12 month study of all patients attending a children's hospital and discovered to have a platelet count over two times the upper normal limit (>800x10⁹/l) was undertaken. Data so obtained were analysed both separately and together with those from two previous studies to gain as broad a perspective as possible.

Of 7916 children who had platelet counts during the study period, 36 (0.5%) produced a value >800x10⁹/l; there were 19 boys and 17 girls. There was a preponderance of young infants (median age 13 months). Twenty seven of the 36 had some sort of associated infection, bacterial in 18 and viral in nine. The other nine were either recovering from antineoplastic chemotherapy (n=6), were post-operative (n=2), or simply iron deficient (n=1). Combining these patients with those described in previous studies allowed a review of 139 unselected children with very high platelet counts. Fifty three (38%) had infections, 29 (20%) had traumatic or surgical tissue damage, 16 (11%) had malignant disease undergoing chemotherapy or surgery, and 13 (9%) had connective tissue or autoimmune disorders.

Secondary thrombocytosis is not rare and is most frequently seen in very young infants after infection. It can arise in a wide variety of other circumstances including re-bound of myelosuppression, iron lack, or as part of an acute phase response. It is clinically unimportant in terms of morbidity and requires no treatment other than that for the primary condition.

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Secondary thrombocytosis in children is usually symptomless but not uncommon. Its true incidence has only gradually become apparent over the last decade after the general introduction of machines that count platelets as part of a 'routine' blood count without any clinical indication to do so. Before that, unexpected high counts were only noticed if a laboratory scientist spotted an apparent excess number of platelets on a stained blood film.

While such technological trawling might provide useful physiological and pathological data, it also provokes concern among paediatricians who, being faced with platelet counts way outside the normal range, feel uncertain about their clinical importance.

There have been surprisingly few prospective studies of the clinical circumstances surrounding paediatric thrombocytosis. We have collected information over a 12 month period in a children's hospital and have analysed it alongside data from two previous reports in an attempt to compile for study as large an unselected group of children as possible with very high platelet counts.

Patients and methods
All patients who had a platelet count at the Sheffield Children’s Hospital over a 12 month period were prospectively collected. Those where the count was over twice the upper limit of normal (that is exceeded 800x10⁹/l) had their casenotes reviewed to find out the cause. Serial counts were logged in as many of them as possible.

Data were also extracted from the published reports of Addiego et al and Chan et al for comparison and to compile a composite analysis.

Results
During 1991 just over 16 000 platelet counts were performed on 7916 patients at the Sheffield Children’s Hospital. Of these individuals 458 (6%) produced one or more values >500x10⁹/l and 36 (0.5%) produced at least one count of >800x10⁹/l, two times the upper normal limit.

Of the 36, 19 were boys and 17 girls. Most were infants. Their ages ranged from 8 days to 13 years with a median of 13 months. Twenty seven (75%) had an identifiable infection of some sort as an associated feature: 18 were bacterial and nine viral. The other nine were recovering from chemotherapy for non-haematological malignant disease (n=6), were postoperative after a compound fracture (n=1) or splenectomy (n=1), and one patient had apparently uncomplicated iron deficiency. A breakdown of the 36 according to age and associated condition is given in table 1.

Seven children (0.1%) were ‘platelet millionaires’ with counts >1 000 000/mm³ (>1000x10⁹/l). All had an acute infection, though two were also recovering from antineoplastic chemotherapy and one was concurrently iron deficient.

The 27 patients with infection associated thrombocytosis did not produce their highest count until 5–18 days (median 7) after presentation, usually when symptoms were subsiding. Follow up data were available in only 21 of the 36. In all the platelet count had returned to normal within three months. Data on the exact time to recovery were incomplete, but the
Secondary thrombocytosis
did not fit clearly into any of the other categories. One had infantile spasms, one constipation,
and one had gastrochisis closed five weeks before.
Infections were the largest group (53/139;
38%) and the spectrum encountered was wide
(table 3). The commonest single disorder was
bacterial meningitis (8/53; 15%). In 51 cases
where the type of organism was recorded, it was
bacterial in 33 (64%).
The median age of children with thrombo-
cytosis ranged from 9 to 19 months and in all
studies there was a disproportionate number
of young infants.

Discussion
The incidence of thrombocytosis in children
depends on what threshold of platelet count is
taken as the cut off point. It also depends on the
population being studied because of the rela-
tively higher frequency in neonates. Taking
these factors into account, however, it seems
that as many as 5–10% of unselected hospital
based children will have a platelet count over
500×10⁹/l. The proportion having very high
counts (we chose to define this as twice the
upper limit of normal) is harder to estimate but
is somewhere between 0-04% (Chan et al) and
2% (Heath and Pearson). Our own study would
neatly fall in between at 0-5%.
So thrombocytosis is not uncommon, but the
questions that immediately arise are (a) what
causes it, (b) is it diagnostically useful in terms of
indicating any particular pathology, and
(c) does it have any clinical importance in its
own right?
The causes of thrombocytosis in childhood
are legion, but apart from the extraordinarily
rare primary varieties (essential thrombo-
cythaemia or those associated with myeloid
leukaemias) all are secondary. The majority are
associated with infection, though they usually
follow rather than accompany it. Bacterial infec-
tions predominate, and meningitis is a particu-
lar culprit. The time scale and pattern seen in
the Sheffield cohort exemplifies this and
suggests that the high platelet count may be a
'rebound' phenomenon after a period of short
platelet survival due to consumptive coagulo-
pathy, a hypothesis also supported by
Weissbach et al. The preponderance of very
young infants behaving in such a fashion could
reflect their more labile platelet homeostasis.
Other commonly associated conditions are
varied but many are inflammatory including
surgery, trauma, and connective tissue dis-
orders. Kawasaki disease is often associated
with high counts during the acute phase of the
illness, and thrombocytosis is also seen in most
children with active juvenile rheumatoid arth-
ritis. The genesis of the high platelet count in
such circumstances is not entirely clear. Platelet
production is altered and may be regulated by a
variety of cytokines, notably interleukin-6 (IL-
6), and this, together with other agents, is
produced as part of the acute phase response.

Another common circumstance where high
platelet counts are found is in children with
malignant disease, but usually after surgery or
myelosuppressive chemotherapy rather than as

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age and causes of secondary thrombocytosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>No of patients</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>0-6 months</td>
<td>14</td>
</tr>
<tr>
<td>6 months–2 years</td>
<td>6</td>
</tr>
<tr>
<td>2–3 years</td>
<td>5</td>
</tr>
<tr>
<td>3–4 years</td>
<td>3</td>
</tr>
<tr>
<td>6–13 years</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
</tr>
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</table>

*Data from present study.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Conditions associated with thrombocytosis (platelet count &gt;800×10⁹/l) in 139 patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>No (%) of patients</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Infection</td>
<td>53 (38)</td>
</tr>
<tr>
<td>Surgery/trauma/tissue damage</td>
<td>29 (21)</td>
</tr>
<tr>
<td>Malignant disease/chemotherapy</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>6 (4)</td>
</tr>
<tr>
<td>No obvious cause</td>
<td>3 (2)</td>
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</table>

*Data from present study, Addiego et al, and Chan et al. See text for further description.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Infections associated with platelet counts &gt;800×10⁹/l in 53 patients*</th>
</tr>
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<tbody>
<tr>
<td>Infection</td>
<td>No of patients</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Respiratory:</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
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<tr>
<td>Bronchiolitis</td>
<td>3</td>
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<tr>
<td>Tonsillitis</td>
<td>1</td>
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<tr>
<td>Croup</td>
<td>3</td>
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<tr>
<td>Gastrointestinal:</td>
<td></td>
</tr>
<tr>
<td>Viral enteritis</td>
<td>4</td>
</tr>
<tr>
<td>Bacterial enteritis</td>
<td>1</td>
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<tr>
<td>Peritonitis (postoperative)</td>
<td>1</td>
</tr>
<tr>
<td>Appendicitis (postoperative)</td>
<td>2</td>
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<tr>
<td>Hepatitis</td>
<td>1</td>
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<tr>
<td>Neurological:</td>
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<tr>
<td>Bacterial meningitis</td>
<td>8</td>
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<tr>
<td>Meningoencephalitis</td>
<td>3</td>
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<tr>
<td>Infected cerebrospinal fluid shunt</td>
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<tr>
<td>Others:</td>
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<tr>
<td>Urinary tract</td>
<td>3</td>
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<tr>
<td>Viral fever</td>
<td>2</td>
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<td>Septic arthritis</td>
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<tr>
<td>Osteomyelitis</td>
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<td>Soft tissue abscess</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data from present study, Addiego et al, and Chan et al.
part of the disease itself. This contrasts with adults where cryptic malignant disease is a relatively frequent cause of unexplained thrombocytosis. The association between iron deficiency and excess platelets is more puzzling but undoubtedly exists, even in the absence of bleeding when the deficiency is dietary. Usually the increase in platelet count is modest, and the eight patients documented here may represent the tail of a distribution curve. We are presently investigating this point further in another study comparing iron deficient children with normal controls.

Because of the wide variety of associated conditions, thrombocytosis is seldom helpful in deciding what might be wrong with a patient where this is not obvious, though there are occasional exceptions. We recently were alerted to a case of Kawasaki disease by a high platelet count, where the child had run the acute course of the disease at home and had had a blood count done because of pallor. Secondary thrombocytosis seldom, if ever, requires intervention and can be safely left to run its course in children. Paediatricians should concentrate on the underlying problem. Primary thrombocytosis, though extremely rare in childhood, may be different, and myelosuppressive or antiaggregating treatment may be appropriate. For that reason very high platelet counts that are not associated with any of the conditions described above should be further investigated, but not immediately. Based on our findings it would seem reasonable to wait for at least three months before considering a search for myeloproliferative disease.

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