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Secondary thrombocytosis

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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 (>800×10⁹//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 >800×10⁹/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 postoperative (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 rebound from 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 800×10⁹/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*[1] and Chan *et al*[2] 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 >500×10⁹/l and 36 (0·5%) produced at least one count of >800×10⁹/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 (>1000×10⁹/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

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median appeared to be around four weeks. Two infants took three months to return to normal.

Data taken from the studies of Addiego *et al*[1] and Chan *et al*[2] allowed a compilation of 139 children with secondary thrombocytosis and a platelet count two or more times the upper limit of normal. (Addiego *et al* used a threshold of 800×10^9/l and Chan *et al* 900×10^9/l.) These were grouped by their associated conditions as indicated in table 2. Where more than one group might have been appropriate for a patient (postoperative for malignant disease with or without chemotherapy, for example), the categorisation is unreliable. Four children could thus have been misallocated but this would not alter the overall pattern. 'No obvious cause' was used to describe three patients of Chan *et al* who did not fit clearly into any of the other categories. One had infantile spasms, one constipation, and one had gastroschisis closed five week 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 thrombocytosis ranged from 9 to 19 months and in all studies there was a disproportionate number of young infants.

*Table 1 Age and causes of secondary thrombocytosis**

Age	*No of patients*	*Associated condition (No of patients)*
0–6 months	14	Infection (13) After chemotherapy (1)
6 months–2 years	6	Infection (5) Iron deficiency (1)
2–3 years	5	Infection (4) After chemotherapy (1)
3–4 years	3	Infection (2) After chemotherapy (1)
6–13 years	8	Infection (3) After chemotherapy (3) Compound fracture (1) After splenectomy (1)
Total	36	

*Data from present study.

*Table 2 Conditions associated with thrombocytosis (platelet count $>800\times10^9$/l) in 139 patients**

	No (%) of patients
Infection	53 (38)
Surgery/trauma/tissue damage	29 (21)
Malignant disease/chemotherapy	16 (12)
Connective tissue disorders	13 (9)
Respiratory distress	11 (8)
Iron deficiency	8 (6)
Metabolic disorders	6 (4)
No obvious cause	3 (2)

*Data from present study, Addiego *et al*,[1] and Chan *et al*.[2] See text for further description.

*Table 3 Infections associated with platelet counts $>800\times10^9$/l in 53 patients**

	No of patients
Respiratory:	
Pneumonia	9
Bronchiolitis	3
Tonsillitis	1
Croup	3
Gastrointestinal:	
Viral enteritis	4
Bacterial enteritis	1
Peritonitis (postoperative)	7
Appendicitis (postoperative)	2
Hepatitis	1
Neurological:	
Bacterial meningitis	8
Meningoencephalitis	3
Infected cerebrospinal fluid shunt	1
Others:	
Urinary tract	3
Viral fever	2
Septic arthritis	2
Osteomyelitis	1
Soft tissue abscess	1
Pericarditis	1

*Data from present study, Addiego *et al*,[1] and Chan *et al*.[2]

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 relatively 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 500×10^9/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*[2]) and 2% (Heath and Pearson[3]). 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 thrombocythaemia or those associated with myeloid leukaemias) all are secondary. The majority are associated with infection, though they usually follow rather than accompany it. Bacterial infections predominate, and meningitis is a particular culprit.[4] 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 coagulopathy, a hypothesis also supported by Weissbach *et al*.[5] The preponderance of very young infants behaving in such a fashion could reflect their more labile platelet homoeostasis.

Other commonly associated conditions are varied but many are inflammatory including surgery, trauma, and connective tissue disorders. 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 arthritis.[6] 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.[7]

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

part of the disease itself. This contrasts with adults where cryptic malignant disease is a relatively frequent cause of unexplained thrombocytosis.[8]

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.[9] 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.[7] 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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