

Intracranial haemorrhage in idiopathic thrombocytopenic purpura

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Abstract

A UK survey was carried out to discover the frequency, circumstances, and outcome of intracranial haemorrhage (ICH) complicating idiopathic thrombocytopenic purpura (ITP) of childhood. A questionnaire was circulated through the membership of the UK Paediatric Haematology Forum, and thence to local paediatricians and haematologists. It sought information on any child with ITP who had had an ICH during the 20 year period to January 1994.

Fourteen instances were discovered, seven before 1984 and seven after. Six children survived the event with minimal or no sequelae, four without craniotomy. An immediately precipitating cause was noted in four; two had arteriovenous malformations and two suffered head injuries. The event occurred over two weeks from diagnosis in seven cases and over two months in five. All children were profoundly thrombocytopenic at the time of their intracranial bleed. By calculation the 14 children would have represented some 0.1% of the total with ITP during the period under review.

ICH in childhood ITP may have a precipitating cause and is not necessarily fatal. There is no period of maximum risk, and it can occur at any time during the course of the illness when the platelet count is less than $10-15 \times 10^9/l$. It is an extremely rare event and previous estimates of its incidence may have been too high.

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Idiopathic (immune) thrombocytopenic purpura (ITP) in children is a frightening but usually trivial disease. Over 80% of sufferers will recover spontaneously well within six months,¹ and most of the rest, traditionally classified as 'chronic', will still remit long after that time.² It is also a rare disease with an incidence estimated at 4/100 000 per year,² and as its treatment is not based on specialist centres, few clinicians have much experience in its management.

Mortality has always been recognised to be low, even though early estimates may have been inflated by the inclusion of more serious disorders that would not now be confused with ITP.³ It is, however, the fear of fatal intracranial haemorrhage (ICH) that drives paediatricians to keep children with ITP in hospital,

to restrict their activities, and to subject them to sometimes hazardous therapeutic regimens.

Relatively little is known about which children suffer an ICH and what happens to them. There is a widely held but unsubstantiated belief that the problem is more likely to arise in the first few days after the onset of ITP, and that the risk dwindles thereafter irrespective of the platelet count.⁴ As far as outcome is concerned, aggressive surgical intervention has been successful in salvaging some patients,⁵ but whether it is always necessary is unclear.

A nationwide survey was carried out in an attempt to shed more light on the true risk of ICH, the circumstances under which it might arise, and the outlook for the unlucky children who have one. The results are presented here and analysed alongside similar patients described in the recent literature.

Patients and methods

Based on the assumption that ICH or other life threatening or fatal haemorrhage in ITP is such a catastrophic event that any clinician having seen or heard of one in the last 20 years would be likely to recall it, a simple questionnaire was circulated in chain letter fashion to paediatricians and haematologists in the UK asking them to respond if they remembered such a case between 1974 and 1994 and to forward the form to colleagues as appropriate, including those recently retired. The initial mailing was done to members of the Paediatric Haematology Forum of the British Society for Haematology, with a second mailing to the full membership of the British Society for Haematology six weeks later.

Simple data were required including the age of the child at the time of diagnosis, whether there was any doubt about the diagnosis, how long after diagnosis the ICH occurred, what treatment had been given beforehand, what was done at the time, and what the outcome was. Details of any precipitating or associated cause were also asked for and details concerning any other life threatening or fatal haemorrhage in a child with ITP.

Questionnaire recipients not having ever seen a case of ICH or other life threatening bleed were asked not to respond.

To estimate the incidence of ITP in the UK population, a prospective cohort of children from the Sheffield Health Authority catchment area (population 480 000) was collected over 15 years to January 1994.

Published details of children with ICH complicating ITP were drawn from articles

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Table 1 ICH in ITP in the UK: January 1974–January 1994

Patient No	Sex	Age (years)	Weeks to ICH	Prior therapy	Platelet count ($\times 10^9/l$)	Other features	Craniotomy	Splenectomy	?Survived	Year
1	F	2	54	Steroids	<10	?AVM	Yes	Yes	Yes	1986
2	M	14	37	Steroids/IFN	<10	HI	No	No	No	1988
3	M	9	<1	?	'Very low'	No	Yes	Yes	No	1978
4	F	6	<1	Steroids	<10	AVM	Yes	No	No	1987
5	M	0.3	8	Steroids/IG	<10	No	No	No	Yes	1993
6	F	2	<1	Steroids	<10	No	No	No	No	1987
7	F	3	3	None	15	No	No	No	Yes	1986
8	M	10	1	Steroids	<10	No	Yes	Yes	No	1986
9	F	3	<1	?	'Very low'	No	No	No	Yes	1983
10	M	8	<1	?	<10	Varicella	No	No	No	1980
11	F	8	1	?	'Very low'	No	No	No	No	1980
12	M	12	26	?	<10	HI	No	No	No	c1978
13	M	14	2	Steroids	<10	AVM	Yes	Yes	Yes	1982
14	F	0.2	364	Steroids	<10	No	No	Yes	Yes	1981

HI=head injury; AVM=arteriovenous malformation; IFN=interferon; IG=intravenous gammaglobulin.

appearing after 1970. Earlier studies were excluded due to the increased likelihood of conditions other than ITP being inadvertently included.

Results

Fourteen children with ITP who had had an ICH during the period in question were identified by the survey. Their details are shown in table 1. Half arose during the first decade of the study, and half in the second. Ten were from England, two from Scotland (one already reported⁶), and one each from Wales and Northern Ireland. No other type of life threatening or fatal haemorrhage was reported.

ICH occurred within a week of the onset of ITP in seven children and over two months later in five. All patients had a 'very low' or $<15 \times 10^9/l$ platelet count at the time.

Four had an obvious precipitating or complicating factor. Two (patients 2 and 12) had a head injury, and two (patients 4 and 13) were discovered at craniotomy to have arteriovenous malformations. A third child (patient 1) also had a 'possible' arteriovenous malformation, but this could not be confirmed histologically due to material being necrotic.

Six children survived; five had minimal or no sequelae and one (patient 5) had not been followed up long enough at the time of writing for any late effects to be determined. Five had emergency splenectomies and five craniotomies; four had both and two survivors had

neither. Data on other treatments were incomplete, though most if not all had platelet transfusions, steroids, and high dose intravenous immunoglobulin.

The question whether patients had 'simple' ITP arose in four cases. One child (patient 10) had haemorrhagic disseminated varicella at the time of the ICH, though no evidence of encephalopathy or disseminated intravascular coagulation was found. Another four month old (patient 5) had a positive direct antiglobulin test on his red cells without overt haemolysis, and was excreting cytomegalovirus. A third (patient 2) developed ITP 12 months after completing chemotherapy for Hodgkin's disease, and the youngest child at diagnosis (patient 14) had chronic relapsing steroid responsive thrombocytopenia for seven years before the ICH and was also described as having common variable immunodeficiency.

FREQUENCY OF ICH

During the 15 year period to January 1994, 70 Sheffield children developed ITP, giving an annual incidence of 4.8/100 000 in the population under 15 years old. Extrapolating to the UK population overall (based on the 1981 national census) this would suggest that some 533 new cases occur in the UK per year. The prevalence would be slightly higher due to the small number of children with chronic ITP. The 14 instances of ICH would thus arise from a group of at least 11 000 children with ITP, suggesting that the problem occurs in roughly one child in 1000. Even assuming the survey failed to capture 50% of the cases of ICH occurring during the study period, the proportion would rise to only one child in 500, though this figure should be interpreted with caution (see discussion).

LITERATURE REVIEW

Data on 20 children with ICH in ITP were extracted from published reports since 1970,^{1 2 4 5 7-13} and the patients' details are shown in table 2. They differ little from the UK children in terms of age and sex distribution. Their bleeds arose later after diagnosis (median 8 weeks *v* 2 weeks), and a slightly higher proportion survived (11/20 *v* 6/14). The highest platelet count recorded at the time of ICH was $17 \times 10^9/l$. Preceding head injuries were noted in

Table 2 ICH in ITP: published reports (since 1970)

Reference No	Patient No	Sex	Age (years)	Weeks to ICH	Platelet count ($\times 10^9/l$)	Other features	Craniotomy	?Survived
1	1	M	0.8	5	<10	HI	Yes	Yes
1	2	F	3	44	?	No	No	No
1	3	F	4	98	?	?	No	No
4	4	F	6	52	?	No	No	No
7	5	F	1	12	12	No	Yes	Yes
8	6	F	11	<1	?	No	No	No
5	7	F	10	48	12	No	Yes	Yes
5	8	M	8	<1	4	No	No	Yes
5	9	M	2	<1	1	Aspirin	Yes	No
9	10	F	13	1	0	No	Yes	No
10	11	M	10	6	6	No	No	Yes
11	12	M	8	12	5	HI	No	Yes
11	13	M	14	250	17	No	Yes	No
11	14	F	13	8	10	No	Yes	Yes
11	15	F	10	1	?	No	Yes	Yes
12	16	M	12	36	12	No	Yes	Yes
12	17	M	1	4	8	No	?	No
12	18	M	6	<1	0	HI	?	Yes
13	19	F	9	104	0	?	?	No
2	20	F	8	<1	?	No	No	Yes

HI=head injury.

three children. No mention of arteriovenous malformations was made in any report.

Discussion

Childhood ITP is an uncommon disease and ICH an extremely rare complication. Other types of life threatening or fatal haemorrhages are so infrequent that this survey failed to find a single one. Just how often ICH arises is hard to estimate precisely, though if the survey captured as many as half of the instances in the UK in the last 20 years, which is credible based on their distribution in time and space, the problem is likely to occur in less than one child with ITP in 500. This is a much lower figure than previously supposed.³

Glibly to estimate the risk at around 1:500, though, is to oversimplify the matter. Every reported case of ICH has arisen in a child with a very low platelet count ($<20 \times 10^9/l$ – effectively zero in most cases), and such patients form only a proportion of those with ITP at any given time from diagnosis. If, for example, a group of 100 newly diagnosed children were to be followed up, perhaps 90 would have very low platelets for a week, then, irrespective of treatment, the number would rapidly dwindle until by six months fewer than 10 would still be profoundly thrombocytopenic. From the tables in this report it can be seen that 17/34 (50%) intracranial bleeds arose over a month from the onset of ITP, and 11/34 (32%) after six months. If at six months the number of patients with very low platelet counts is 10% or less of the original total, then the risk of ICH must increase from around 1:850 in the first month to around 1:100 at six months.

It is important to be clear about this, as it dispels the myth that there is a maximum risk period immediately after diagnosis and also enables a better risk:benefit assessment of any contemplated treatment for the few unlucky children destined to have persisting profound thrombocytopenia for many months.

It should also be stressed that in half of the children in the UK survey, ICH was not a completely spontaneous event in otherwise ordinary ITP. That two had head injuries as a precipitating cause is perhaps not surprising. The clinical circumstances of four patients were atypical, though not in a way that might have indicated them to be at special risk, but it is of considerable interest that two (possibly three) children had a cerebral arteriovenous

malformation that raises the question about the frequency of the coincidence of ITP and arteriovenous malformation.

The survey gave no clear indication of the best way to treat ICH in ITP, though massive platelet transfusion with steroids and intravenous immunoglobulin seems to be an appropriate immediate first step while contemplating craniotomy and emergency splenectomy. The condition should not be regarded as fatal and a vigorous approach is entirely justified by the survival figures.

Whether the risk of ICH justifies potentially toxic treatment or splenectomy depends on the circumstances surrounding each individual patient. For the very few who remain symptomatic and stubbornly maintain a platelet count of zero for months or years one may be inclined to think so. For the others, and particularly for newly diagnosed children, the answer may be different.

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