Intracranial haemorrhage among Chinese children with immune thrombocytopenia in a Hong Kong regional hospital

Objective To evaluate potential risk factors, presenting symptoms, management, and outcomes of intracranial haemorrhage in Chinese children with immune thrombocytopenia managed in a regional hospital.

Design Retrospective case series.

Setting A regional hospital in Hong Kong.

Patients All paediatric patients with immune thrombocytopenia complicated by intracranial haemorrhage in the period January 1996 to December 2009.

Results Nine episodes of intracranial haemorrhage were reported in eight patients (aged 0.9 to 19 years) with immune thrombocytopenia; three of the patients had acute immune thrombocytopenia and the other five had chronic immune thrombocytopenia. Intracranial haemorrhage occurred as early as the initial presentation with immune thrombocytopenia (n=2) and as late as up to 5 years after the diagnosis. The median platelet count at the time of intracranial haemorrhage was 12 x 10^9/L (<10 x 10^9/L [n=4]; 10-20 x 10^9/L [n=2]; >20 x 10^9/L [n=3]). The bleeding was considered spontaneous in six episodes, while head trauma (n=2) and vascular malformation (n=1) were identified in three patients with mild-to-moderate thrombocytopenia (42-82 x 10^9/L) at the time of the bleed. Headache and mucosal bleeding were the commonest presenting symptoms (n=5). All patients received multimodal treatment after diagnosis of intracranial haemorrhage, and included platelet transfusion (n=8), intravenous immunoglobulin (n=6), methylprednisolone (n=4), and splenectomy (n=4); three individuals underwent neurosurgical interventions. One (11%) patient died of posterior fossa bleeding and one (11%) had neurological sequelae. All survivors achieved remission of their immune thrombocytopenia with a median follow-up of 5.3 years.

Conclusion Intracranial haemorrhage can occur anytime during the course of immune thrombocytopenia. A high index of suspicion for intracranial haemorrhage should be maintained during follow-up, as favourable outcomes can be achieved after early and vigorous interventions.

New knowledge added by this study
• Intracranial haemorrhage (ICH) can occur anytime during the course of immune thrombocytopenia as long as severe thrombocytopenia persists, but in children it also occurs with relatively safe platelet count when there are other predisposing factors like head trauma or cerebrovascular malformation.

Implications for clinical practice or policy
• A high index of suspicion for underlying ICH should be retained in patients with immune thrombocytopenia presenting with headache or mucosal bleeding.
• To minimise mortality and morbidity, early aggressive treatment, including neurosurgical intervention, is needed in the management of ICH in patients with immune thrombocytopenia.
香港一所分區醫院內患有免疫性血小板減少症的華籍兒童的顱內出血情況

### 目的
評估香港一所分區醫院內，患有免疫性血小板減少症的華籍兒童出現顱內出血的潛在危險因素、症狀、治療及結果。

### 設計
回顧性病例系列。

### 安排
香港一所分區醫院。

### 患者
1996年1月至2009年12月期間所有診斷為患有免疫性血小板減少症並出現顱內出血的華籍兒童。

### 結果
共有8名(9例)患有免疫性血小板減少症並出現顱內出血的患者，他們年齡介乎0.9至19歳。3名患者屬急性免疫性血小板減少症，另5名為慢性免疫性血小板減少症。有兩名患者在病發時已出現顱內出血的情況，其餘的分別在不同時段，最長者可在確診後5年才出現顱內出血。患者出現顱內出血的情況是時其血小板數量中位數為12x10^9/L；數量分佈為：<10x10^9/L(4例)、10-20x10^9/L(2例)、>20x10^9/L(3例)。6例屬自發性出血，另3例有輕度至中等(4.2-82x10^9/L)血小板減少症的患者中，2例和頭部創傷有關，另1例是患者患有腦部血管畸形。最常見的症狀為頭痛及粘膜出血(5例)。所有患者在顱內出血確診後均接受綜合治療，包括血小板濾過(6例)、靜脈注射免疫球蛋白(6例)、甲基強的松龍(4例)和脾切除(4例)。3名患者接受神經外科手術。1名患者(11%)因後顱窩出血而死亡，另1名患者(11%)有神經系統後遺症。在中位數5-3.6年的追蹤期內，所有生存患者的血小板減少症都有緩解。

### 結論
血小板減少症的病情中隨時會出現顱內出血。由於診後血的情況，其餘的分別在不同時段，最長者可在確診後5年才出現顱內出血。患者出現顱內出血的情況是時其血小板數量中位數為12x10^9/L；數量分佈為：<10x10^9/L(4例)、10-20x10^9/L(2例)、>20x10^9/L(3例)。6例屬自發性出血，另3例有輕度至中等(4.2-82x10^9/L)血小板減少症的患者中，2例和頭部創傷有關，另1例是患者患有腦部血管畸形。最常見的症狀為頭痛及粘膜出血(5例)。所有患者在顱內出血確診後均接受綜合治療，包括血小板濾過(6例)、靜脈注射免疫球蛋白(6例)、甲基強的松龍(4例)和脾切除(4例)。3名患者接受神經外科手術。1名患者(11%)因後顱窩出血而死亡，另1名患者(11%)有神經系統後遺症。在中位數5-3.6年的追蹤期內，所有生存患者的血小板減少症都有緩解。

### Introduction
Immune or idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterised by isolated thrombocytopenia in the absence of other causes or disorders associated with thrombocytopenia. 1 It is due to antiplatelet antibodies, usually directed to epitopes on GPIb/IIa, GPIb/IX or both, which result in platelet destruction by the reticuloendothelial system. In children, it is usually a self-limiting disorder with a 6-month remission rate of about 70 to 85%. 2-4 Nonetheless, intracranial haemorrhage (ICH) is its most devastating complication, which confers significant morbidity and mortality. 5 As indicated in the majority of recent reports, in children with ITP, its incidence varied from 0.1 to 1.0%. 5-10 Causative factors, predictors, and outcomes of ICH in ITP have been difficult to ascertain due to its rarity.

Proper case series of acute and chronic ITP in Chinese children are lacking. In particular, only two cases of ICH have been described out of 506 children with chronic ITP from Tianjin and Hong Kong, and details about their circumstances were not available. 11,12 Our study was performed to better understand ICH in Chinese children with ITP.

### Methods
This was a retrospective case series. All patients with primary ITP complicated with ICH, who were managed in the paediatric unit of our regional hospital from January 1996 to December 2009, were identified. Their records were retrieved by reference to the Clinical Data Analysis and Reporting System, using diagnosis codes for ITP (ICD-9: 287.3 Idiopathic Thrombocytopenic Purpura; 287.3 Immune Thrombocytopenia Primary; 287.5 Immune Thrombocytopenia) and ICH (ICD-9: 432.1 Subdural Hemorrhage; 432.0 Epidural Hemorrhage; 432.9 Intracranial Hemorrhage; 431 Stroke/Acute CVA, intracranial hemorrhage; 801.22 Head injury, intracranial haemorrhage). All patients fulfilled the diagnostic criteria of the American Society of Hematology for ITP and had onset of their disease before the age of 18 years. 2 Patients with thrombocytopenia secondary to known causes were excluded. These included systemic lupus erythematosus (SLE), drugs, malignancies, specific congenital syndromes. Patients with co-morbid conditions associated with bleeding diathesis, at or before the occurrence of bleeding, were also excluded. Children with thrombocytopenia for <6 months were defined as having acute ITP and those with ≥6 months of thrombocytopenia were regarded as having chronic ITP. Confirmation of ICH was based on neuroimaging.

The data collected included age, gender, type of ITP, platelet count at the time of ICH, the interval from diagnosis to development of ICH, associated factors (head trauma, cerebral arteriovenous malformation [AVM], and concurrent medications having antiplatelet effects), presenting symptoms, site of ICH, therapy received at the time of ICH, as well as outcome (mortality or any neurological sequelae).

### Results
In all, there were 276 patients with childhood ITP during the study period. Eight of these patients (2 boys and 6 girls) endured nine episodes of ICH; one patient with chronic refractory ITP had two episodes of ICH. At the time of their ICH, the median age of the affected children was 10 (range, 0.9-19) years. There were three patients with acute ITP, and five with chronic ITP. The clinical profiles of these eight patients with ICH are shown in the Table.
Platelet count and latency between onset of immune thrombocytopenia and intracranial haemorrhage

The median platelet count of the eight patients at the time of their nine episodes of ICH was 12 x 10^9/L (range, 3-82 x 10^9/L); four (44%) of the episodes occurred with a platelet count of <10 x 10^9/L, two (22%) ensued with counts of 10-20 x 10^9/L, and three (33%) had a platelet count of >20 x 10^9/L (range, 42-82 x 10^9/L) at the time of ICH. Moreover, in each case an additional risk factor could be identified; two had preceding head trauma and one had a cerebrovascular malformation (cavernoma).

Three patients (33%) developed ICH within 1 month of the diagnosis of ITP, two of whom had ICH as the initial presentation. Four (44%) of the ICH episodes developed more than 6 months after the onset of ITP, the longest latency being 5 years.

Predisposing factors, presenting symptoms, and site of intracranial haemorrhage

No specific predisposing factor except low platelet count was found in six (66%) of the episodes of ICH, two episodes were precipitated by head trauma, and one (an intraventricular bleeding) ensued in a patient with a right thalamic cavernoma. No patient reported the concurrent use of antiplatelet agents such as aspirin or any other non-steroidal anti-inflammatory drug.

Headache (n=5) and bleeding other than in the skin (mucosal bleeding [n=4]; genitourinary bleeding [n=1]) were the most common presenting symptoms and occurred during five (56%) out of the nine episodes. Other presenting symptoms included sudden collapse (n=1), scalp haematoma (n=2), and hemiparesis (n=1).

Four patients developed intracerebral haemorrhage and two had epidural haematoma resulting from head injuries. One had an intraventricular haemorrhage from a thalamic cavernoma. The only patient in our series who died was a female with cerebellar bleeding.

**Treatment and outcome**

Immediately after the diagnosis of ICH, all of the patients were kept under close observation or in intensive care and received treatment aimed to maintain platelet counts greater than 100 x 10^9/L. The neurosurgical team was consulted in all cases and surgical intervention was carried out if there was clinical deterioration. Multi-agent medical treatment was commenced in all patients, and included...
intravenous methylprednisolone (n=4), intravenous immunoglobulin (IVIG) [n=6], and platelet transfusions (n=8). One patient was also treated with rituximab (anti-CD20 monoclonal antibody) for her chronic refractory ITP.

Three patients underwent neurosurgical intervention—one had extraventricular drainage and the other two underwent emergency clot evacuation. After having the ICH, splenectomy was performed in four patients who had a poor response to medical treatment.

There was one (11%) death in our series. Patient 2 presented with recurrent epistaxis and sudden onset of headache and had a platelet count of 8 x 10^9/L. Initially, there were no focal neurological signs and computed tomography (CT) of the brain was unrevealing. A platelet transfusion was given to correct the thrombocytopenia, as previously her response to IVIG had been suboptimal. Nevertheless, she suffered a cardiopulmonary arrest shortly thereafter and repeat CT of the brain showed cerebellar haemorrhage and hydrocephalus (Fig 1), and the patient died soon after. Neurosurgical intervention was not undertaken as her neurological condition was deemed unsalvageable.

Patient 8 endured a residual neurological deficit, after developing a left frontal haematoma with a subarachnoid haemorrhage, despite undergoing clot evacuation (Fig 2). She recovered from her right hemiparesis and facial nerve palsy 4 months after her ICH. However, she had a residual right homonymous hemianopia that persisted up to the last follow-up. All other patients enjoyed a full neurological recovery.

Complete remission of ITP ensued in all the surviving patients, with their median follow-up of 5.3 years. Three patients went into remission after medical treatment alone, and four proceeded to splenectomy, three of whom attained normal platelet counts. One patient with chronic refractory ITP (patient 3) had two episodes of ICH. After the first episode of right frontal subdural haemorrhage, she received steroid, vincristine, azathioprine, and mycophenolate mofetil, and also underwent splenectomy. However, her response to treatment was transient. She experienced a second ICH 4 years after the first one. Finally, her ITP went into remission following treatment with rituximab.

Two (25%) of the patients went on to develop frank SLE more than 1 year after their ICHs, despite their thrombocytopenia being in remission post-splenectomy. Both women had high titres of antinuclear antibody around the time of their ICH (1:2560 in patient 1 and 1:640 in patient 4) but no other SLE-qualifying features (based on the American College of Rheumatology).

Discussion

Whilst ICH is a rare complication of ITP, it is devastating. The majority of recent reports indicate that in children with ITP, its incidence is between 0.1 and 1.0% per year.5-10 Bansal et al15 reported ICH in 11 (4%) cases out of 270 children after a follow-
up of up to 14 years; seven of whom died from this complication. Most of these studies involved surveys in a number of institutions, which probably explains the wide variations in reported incidence. Our series shows a relatively high frequency of ICH (2.9%) over the 14-year period of the study. However, such estimation may not be valid or comparable with previous studies, as ours was only a single-centre study conducted in a regional hospital and the sample size was relatively small. Moreover, its main objective was to investigate the risk factors, management, and outcome of ICH in Chinese patients with ITP.

Severe bleeding is more likely in children with severe thrombocytopenia.14 Most studies about ICH in children with ITP reported a median platelet count at the time of the bleed to be below 20 × 10^9/L.5,6,9,10,15 Our study yielded similar findings; the median platelet count when the ICH ensued was 12 × 10^9/L, and in six (66%) of the episodes it was <20 × 10^9/L. Though most episodes of ICH occur in children with severe thrombocytopenia, such bleeds can occur in the presence of modest thrombocytopenia whenever there are other predisposing factors (head trauma, cerebral AVM, concurrent medications with antiplatelet agents).3,4,6,15 In our series, three (33%) of the episodes occurred at platelet counts of >40 × 10^9/L (range, 42.82-82 × 10^9/L); two of the affected patients had antecedent head trauma. It is therefore crucial to avoid head trauma at any time during the course of ITP.

A few instances of ICH in childhood ITP have been reported with cerebral AVMs over the past few decades.2,16 and was found in one of our patients who had a right thalamic cavernoma that resulted in an intraventricular haemorrhage. Cavernomas of the cerebral nervous system have no arteriovenous shunt and are associated with a higher risk of bleeding in children than in adults.17,18 The relationship between cerebral AVMs and ICH in childhood ITP is poorly understood and deserves further study.

There is considerable variation in the latency of ICH following the onset/diagnosis of ITP. Most studies reported that ICH commonly ensued within the first 4 weeks of the diagnosis.3,4,15 Nevertheless, a substantial proportion of chronic ITP patients develop ICH after many years.3,5,8-10 Our results also revealed such variation in latency, as ICHs were encountered at the initial presentation of ITP and up to 5 years later. This indicates that ICH can occur at anytime during the course of ITP, possibly whenever the thrombocytopenia is severe, or following head trauma.

Identification of presenting symptoms can help early recognition of ICH and, in turn, facilitate early interventions to minimise morbidity and mortality. Both headache and bleeding (other than cutaneous bleeding) are common presenting features in patients with ITP with underlying ICHs.6,10,15 Our findings also concurred with such observations.

The site of an ICH has been known to be crucial, and posterior fossa haemorrhage is particularly dangerous and liable to cause death. Oedema around the haematoma may lead to acute hydrocephalus, followed by tonsillar herniation and brainstem compression. The only death in our series was in a female who deteriorated rapidly on developing a cerebellar haemorrhage. This occurred despite appearing to be stable initially, and emphasised the danger of bleeding in the posterior fossa. A similar case of posterior fossa haemorrhage and death was reported by Woerner et al.19

As suggested in the international consensus report on the investigation and management of primary immune thrombocytopenia, in organ- or life-threatening situations such as the development of ICH, early and aggressive medical therapy should include platelet transfusions together with intravenous high-dose corticosteroids, IVIG, or intravenous anti-D immunoglobulin. The goal of treatment is to raise the platelet count to a level at which the risk of further bleeding is minimised.20 The role of multi-agent combination therapy was emphasised by Boruchov et al.20 In their series, 71% of patients who were completely unresponsive to oral steroids or IVIG responded to various combinations of intravenous therapies, including IVIG, methylprednisolone, anti-D immunoglobulin and/or vincristine. Using this strategy they achieved peak platelet counts of ≥30 × 10^9/L. In our series, 88% patients also responded well to the aggressive medical therapy with platelet count exceeding 30 × 10^9/L within 1 day.

Despite the relatively high frequency of ICH among our ITP patients, mortality and residual neurological sequelae rates (both 11%) were surprisingly low, which seems to demonstrate the importance of early aggressive treatment, including timely neurosurgical intervention.

Conclusion

In childhood ITP, ICH remains an important, though rare complication. The duration of the illness does not predict the timing of the bleeder. Persistent severe thrombocytopenia (<20 × 10^9/L) portends a higher risk of ICH but no simple threshold of platelet count can be considered sufficiently protective against the complication. Early diagnosis, vigorous restoration of haemostasis, and timely neurosurgical interventions can confer favourable outcomes.


