Temporary brittle bone disease

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Temporary brittle bone disease: association with intracranial bleeding

Abstract: We report 20 infants aged between 1 month and 6 months found to have subdural bleeding and also multiple unexplained fractures in a pattern similar to that described earlier as temporary brittle bone disease. Child abuse seemed unlikely as a cause of the fractures as in no case was there clinical evidence of injury commensurate with the fracturing, as some patients had fractures while in hospital and as metaphyseal lesions, when present, were often symmetrical in distribution. Abuse seemed unlikely to have been the cause of the subdural bleeding in several patients; three had clear histories of accidental injury and five had evidence that the initial bleeding was likely to have taken place at birth. Abuse also seemed unlikely as the cause of the syndrome; the nine patients who were returned to their parents had no subsequent allegations of abuse with a mean follow-up period of 15.8 years. The finding of hypermobile joints in the parents of eight of the children is an additional pointer to a natural cause for this condition. The cause of this combination of fractures and subdural bleeding is not yet clear but it is important to be aware that it can result from natural disease.

Keywords: bone disease; fractures; intracranial bleeding; non-accidental injury.

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Introduction

Over the last 20 years we and others have drawn attention to the likely existence of a syndrome characterised by fractures, and often very many fractures, in infants in the first year of life (1, 2). To this disorder we gave the provisional name temporary brittle bone disease as the cause was not yet clear. Other possible names such as 'temporary bone fragility' or 'metabolic bone disease of infancy' could well be appropriate. The subject has remained controversial as many of the clinical and radiological features of temporary brittle bone disease are also ascribed to child abuse (3, 4). There was, for example, in such patients a preponderance of rib fractures and metaphyseal lesions which were often regarded as characteristic of abuse.

However, the children thought to have temporary brittle bone disease had many clinical and radiological features in common, some of which could not be explained by child abuse. In particular, there was usually a gross discrepancy between the radiological and clinical evidence of injury (2). In addition a similar syndrome occurred in infants in hospital under circumstances in which abuse was very unlikely (5). Finally, when children with this syndrome have been returned to their supposedly abusive parents, none has suffered subsequent abuse (6).

Hitherto, we have reported only on 104 patients whose principal clinical findings were fractures (6, 7). We had excluded patients who not only had fractures but also had some other clinical problem such as intracranial bleeding. The purpose of the current paper is to report on 20 patients, the pattern of whose fractures was similar to that of other patients with temporary brittle bone disease but who also had evidence of subdural bleeding. We will explore the possible causes of this combination.

Patients and methods

Over the period 1985 to 2000 Colin R. Paterson investigated 20 children who appeared to have typical features of temporary brittle bone disease but also evidence of subdural bleeding. One was referred by a consultant paediatrician, two were referred by social workers and the remaining 17 were referred by lawyers acting for parents. The patients lived in the UK (18 cases), the USA (one case) and Denmark (one case). Thirteen were boys and seven were girls. Fifteen patients were examined personally.

The parents and any available grandparents were interviewed either in person or by telephone. A detailed history of the presentation and of earlier events was obtained; this included enquiries about any external evidence of injury such as bruising. A detailed family history was obtained in each case. Where possible parents were examined for joint laxity, expressing the findings as a Beighton score (8). Medical records and X-rays were reviewed in each case with the exception of case 17 for whom only the reports were available.

A database was prepared using Microsoft Access including, for each patient, birth weight, gestation, siblings, feeding, parental history, consanguinity, details of each fracture, history of vomiting,

diarrhoea, weight gain, subconjunctival bleeding, apnoeic spells, infections and evidence of trauma other than fractures. Physical features noted included the weight and length, the colour of the sclerae and the size of the anterior fontanelle. The laboratory findings were recorded where available; these included haemoglobin, neutrophil count, serum calcium, copper and alkaline phosphatase. Radiological investigations in this group of patients usually included ultrasound and computed tomography (CT) scans which were reviewed.

Results

Table 1 shows the details of the 20 patients together with relevant findings in the family history of each. We also noted the method of delivery in each case. Seventeen infants were born by vaginal delivery; in case 15 the delivery was difficult because of a large head. In case 18 vacuum extraction was required due to maternal exhaustion. In three cases birth was by caesarean section (in cases 10 and 12 because of previous sections and in case 7 because of severe pre-eclampsia). Joint laxity was noted if the Beighton score was 4 or more.

Presentations

Table 2 outlines the presenting problems in the 20 patients. It should be noted that in many of the patients there were symptoms in advance of presentation which, with hindsight, were clearly relevant. For example eight patients had apnoeic spells and six had unexplained vomiting. Seven patients had been noted to have increased head sizes. Some patients had been investigated earlier but appropriate action was not taken at the time. In case 12 heavily blood stained cerebrospinal fluid (CSF) with a xanthochromic supernatant was found 1 week before the respiratory arrest. In case 18 xanthochromia was found in the CSF at the age of 6 weeks. Table 2 also records the retinal findings at the time of admission. There was no record of a retinal examination in three cases.

Fractures

Table 2 also shows the fractures found at the time of presentation and later. There was seldom any uncertainty about the diaphyseal fractures or the number of rib fractures. Dispute between experts sometimes related to whether the metaphyseal lesions were fractures. For the skull fractures, it was impossible to eliminate fracture-like normal variants such as parietal fissures (9–11). All reported fractures were included. In only one case was a fracture found that was suspected clinically prior to radiology. In aggregate our 20 patients had 96 rib fractures,

Table 1 Details of the 20 patients.

Case	Sex	Gestation (weeks)	Multiple pregnancy	Family history
1	F	26	Triplet	One co-triplet had spontaneous intracranial bleed at 6 weeks of age while in hospital
2	M	28	Twin	Co-twin had multiple rib fractures at 3 months of age
3	M	29	No	
4	F	29	No	
5	M	30	No	Mother had marked joint laxity
6	M	31	No	
7	M	32	No	
8	F	32	No	
9	M	37	No	Mother had joint laxity
10	F	37	Twin	Co-twin died in utero. Father and grandmother had von Willebrand's disease
11	F	38	No	Mother had joint laxity
12	F	38	No	
13	M	39	No	
14	M	39	Twin	Co-twin had multiple severe apnoeic attacks
15	M	39	No	Mother and maternal grandfather had joint laxity
16	M	40	No	Brother had fractures found at 4 months of age
17	M	40	No	Mother, maternal grandfather and one uncle had joint laxity
18	M	40	No	Father had joint laxity
19	F	41	No	Mother had joint laxity
20	M	42	No	Half brother had fractures at 4 months. Father had joint laxity

Table 2 Presenting features of the 20 patients.

Case	Age[a]	Initial problems	Scan findings	Retinal haemorrhage	Skeletal findings
1	3 months (term)	Fall followed later by apnoea and resuscitation	Bilateral subdural collections old and recent	Bilateral	Skull fracture, probably recent. Old fractures left radius, ulna, tibia. Two new rib fractures after admission
2	3 months (term)	Recurrent apnoeic episodes. Increasing head circumference	Bilateral low and high density subdural collections	None	Thirteen rib fractures, fractures of left radius and ulna. Metaphyseal lesions both upper femora
3	4 months (6 weeks)	Recurrent apnoeic episodes. Sudden prolonged apnoea	Bilateral subdural collections, low density	Bilateral	Three rib fractures
4	3 months (2 weeks)	Sudden epileptic fit followed by apnoea	Bilateral thin subdural collections, progressive cerebral changes later	Bilateral	Five old rib fractures. Recent fractures of both radii, left tibia and right humerus. Bones notably demineralised
5	4 months (7 weeks)	Two apnoeic episodes	CT initially showed old subdural bleeding. New bleed 1 week after admission	None	Six healed rib fractures
6	3 months (4 weeks)	Apnoea at 6 weeks. Increasing head circumference (noted from age 2 weeks). Investigated at 3 months	Low density subdural collections	None	Five rib fractures. Two long bone fractures at age 9 months
7	6 months (4 months)	Enlarged head noted from soon after birth. Symptomatic transverse fracture of right femur	Low density subdural collections	None	Five healed rib fractures. Transverse fractures of right femur and right radius
8	4 months (2 months)	Head injury	Small left sided subdural bleed. Later larger and bilateral	None	Two old rib fractures
9	3 months	Recurrent apnoeic episodes. Frequent vomiting. Sudden death	Post mortem: fresh blood over both hemispheres	Not recorded	At least 18 old rib fractures. Fresh transverse fractures of right radius and ulna. Probable metaphyseal lesions both lower femora
10	1 month	Repeated vomiting	Bilateral old and recent subdural collections	Bilateral	Five healed rib fractures. One further rib fracture in hospital. Healing fracture of left radius found later. Two parietal fractures or fissures
11	1 month	Spiral fracture of right humerus. Previous projectile vomiting, high-pitched scream and enlargement of head	Bilateral subdural collections both high and low density	Bilateral	Right humerus fracture. Parietal fracture or fissure
12	1 month	Repeated apnoeic episodes. Respiratory arrest. (Blood found in CSF 1 week earlier)	Bilateral old and recent subdural collections	Bilateral	Twelve rib fractures of two different ages
13	3 months	Sudden vomiting followed by coma 7 h after diphtheria-pertussis-tetanus vaccination	Bilateral subdural collections both high density and low density	Bilateral	Three rib fractures
14	2 months	Recurrent apnoeic episodes from birth. Frequent vomiting	Bilateral subdural collections of different densities	Bilateral	Two old rib fractures. One new rib fracture 1 week later. Parietal fracture or fissure
15	1 month	Head circumference enlarged from birth. Severe screaming and vomiting	Operation: bilateral subdural bleeding	Not recorded	Metaphyseal lesions both lower femora, both upper tibiae and both lower tibiae
16	4 months	Recurrent projectile vomiting	Bilateral old symmetrical subdural collections.	None	Undisplaced oblique fractures of left femur and tibia. Parietal fracture or fissure

(Table 2 Continued)

Case	Age[a]	Initial problems	Scan findings	Retinal haemorrhage	Skeletal findings
17	5 months	Unexplained illness, eventually investigated for meningitis	Bilateral subdural collections mainly low density	Bilateral	Right ulna fracture
18	4 months	Increasing head circumference from birth. (CSF at 6 weeks showed xanthochromia)	Bilateral subdural collections old and recent	Not recorded	Three healing rib fractures. Two undepressed skull fractures. Three old undisplaced diaphyseal fractures
19	2 months	Recurrent brief apnoeic spells. Increasing head size. Fits and vomiting.	Bilateral low density subdural collections	Bilateral	Three rib fractures, fractures of right humerus, right femur, left tibia and right clavicle
20	2 months	Head injury followed by apnoea	Fresh blood in left subdural space, interhemispheric fissure and both ventricles	Bilateral	Eighteen old rib fractures. Parietal fracture

[a]Age when fracture(s) first found. The corrected age is shown in brackets for cases 1–8. In 17 cases this was also the age when the subdural bleed was identified. In case 19 the fractures were found at 2 months and the bleed at 3 months. In case 2 the fractures were found at 3 months and the bleed at 6 months. In case 11 a fracture was found at 1 month and the bleed at 2 months.

25 diaphyseal fractures (almost all undisplaced), 32 metaphyseal lesions (symmetrical in five patients), nine skull fractures or fissures and one clavicular fracture. Figure 1 shows the age at which the fractures were first found.

External evidence of injury

All the children had been seen regularly prior to admission by physicians or nurses. In 18 cases there was no evidence of bruising prior to or at admission. In case 15 the parents reported one bruise on the left shin 2 weeks before presentation. In case 19 the parents noted frequent unexplained bruising which was later also reported by the foster mother. One patient (case 2) bruised often in foster care. Episodes of petechiae were reported in five patients while in hospital or foster care. In no case was there bruising at or near the sites of the fractures.

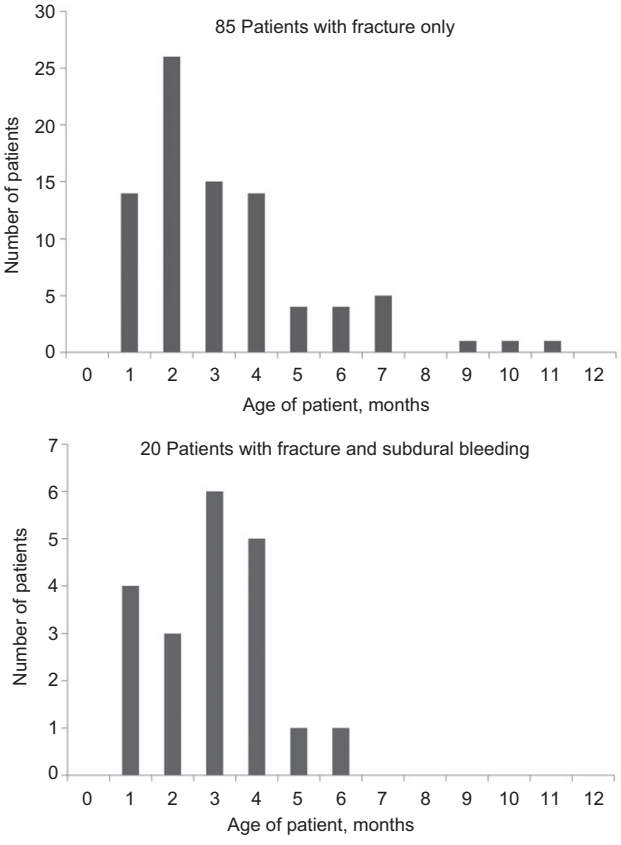

Figure 1 Age when first fracture found in 20 patients with fractures and subdural bleeding compared with 85 patients with temporary brittle bone disease who only had fractures (6, 7).

Laboratory findings

Many of our patients had haemoglobin levels lower than reference ranges appropriate for their age and maturity at birth. For each patient the value found was compared with the reference ranges of Saarinen and Siimes (12). The mean value was 82 g/L at a mean age of 10.5 weeks. In relation to the reference ranges the mean z-score was -3.50 standard deviation units. One patient (case 2) was excluded because on the day of birth his haemoglobin level fell from 180 to 136 g/L and he was transfused. Neutrophil counts were available for 15 patients; six had $<2\times10^9$/L.

We recorded any investigations relevant to the exclusion of coagulopathy. Of the 18 surviving patients 10 had no relevant tests apart from platelet counts. Six had basic investigations including prothrombin time, activated partial thromboplastin time (APPT) and fibrinogen. In four of these the results were normal, in one (case 6) a prolonged prothrombin time was found on three occasions but not pursued further and in one (case 8) a prolonged APPT was found but not investigated further. In one patient (case 2) fuller investigations were carried out including protein C, free protein S and anti-thrombin. In one patient (case 10) the basic tests were not done but factor VIII and von Willebrand antigen were measured in view of a history of von Willebrand's disease in the patient's father and grandmother.

Serum calcium figures were available in 14 patients. The results were normal in 11 and raised in three (at 2.86, 2.75 and 2.73 mmol/L). Serum alkaline phosphatase values were available for 12 patients; in eight the values were more than 2.5 times the upper reference value for adults. None of the infants in this series had serum 25-hydroxy-vitamin D assays. Serum copper assays were available for six patients (cases 2, 5, 8, 10, 16 and 17); the results were normal in each at an average age of 4.7 months.

One infant (case 7) was investigated with fibroblast culture and collagen biochemistry. No abnormality was found.

Judicial involvement

Table 3 shows the various ways in which the judiciary was concerned with these cases together with the outcome if known.

Table 3 Judicial involvement.

Case	Jurisdiction[a]	Judicial involvement
1	E&W	Criminal proceedings: father pled guilty to reduced charge on legal advice
2	SCO	Care proceedings: child returned to parents
3	E&W	Care proceedings: child initially fostered with grandparents. Returned to parents in 1 year
4	E&W	Care proceedings: finding of non-accidental injury and removed from parents
5	SCO	Care proceedings: outcome unknown
6	E&W	Criminal proceedings: parents acquitted by jury
7	USA	Care proceedings: child returned to parents
8	SCO	Care proceedings: returned to extended family including mother
9	E&W	Investigated by coroner after death in foster care. No criminal proceedings
10	E&W	Care proceedings: not contested to protect older siblings
11	E&W	Care proceedings: finding of non-accidental injury but returned to parents. Criminal proceedings: father acquitted by jury
12	E&W	Criminal proceedings discontinued
13	E&W	Investigated at request of social workers after previous finding of non-accidental injury. Returned to parents
14	SCO	Care proceedings: child returned to parents
15	E&W	Care proceedings: child initially returned to parents and later to father alone
16	E&W	Care proceedings: child removed from parents
17	E&W	Care proceedings: finding of non-accidental injury but returned to parents
18	DK	Care proceedings: child returned to mother after 3 years
19	E&W	Care proceedings: child returned to parents
20	E&W	Criminal proceedings: father convicted of murder

[a]E&W, England and Wales. SCO, Scotland. DK, Denmark.

Follow-up

Of the 17 infants who survived the acute illness, nine were returned to their parents, three were fostered long-term with other family members and three were removed permanently from their families. The outcome for two infants is not known. We have follow-up information on the nine patients returned to their parents (Table 4). None had subsequent allegations of non-accidental injury. Five had residual neurological problems. The relationship between

Table 4 Follow-up findings for nine patients returned to parents[a].

Case	Years	Outcome
2	12	Continuing disability. No fractures. Parents separated
7	11	No disability. No fractures
11	17	Continuing disability. No fractures. Parents separated
13	17	Continuing disability. No fractures. Parents separated
14	17	Some continuing disability. No fractures. Parents separated
15	17	Continuing disability. No fractures. Parents separated
17	17	No disability. No fractures. Parents separated
18	17	No disability. No fractures. Parents separated
19	17	No disability. Fractures at age 11[b]

[a]Follow-up information beyond the age of 18 was disregarded
[b]Fractures of right radius and ulna after tripping over badminton racket. Fractured two toes after stubbing foot.

the parents broke up in seven of the nine families in the aftermath of the illnesses in these children and the allegations of inflicted injury.

Discussion

The combination of unexplained fractures with unexplained intracranial bleeding might be thought to be strong evidence for a diagnosis of child abuse. However, the combination of fractures with intracranial bleeding was recognised as early as 1946 by Caffey (13). He did not at that time postulate child abuse as the cause of the combination in all his cases. Indeed it is striking that one of the six cases reported by Caffey, a child of 10 months, developed a spontaneous fracture of the right radius while in hospital for treatment of a symptomatic subdural bleed.

Many infants currently identified as having subdural bleeding are thought to have the shaken baby syndrome, a triad of subdural bleeding, retinal haemorrhages and encephalopathy. Whether this view is accurate remains controversial. For example, there is biomechanical evidence to suggest that shaking without impact could not generate forces required to cause intracranial bleeding (14–16). Whatever the outcome of this debate, it is clear that six of the patients described here would not be regarded as examples of the shaken baby syndrome as retinal haemorrhages were not present. The retinal haemorrhages found in the other 11 patients presumably reflect increased intracranial pressure caused by the bleed (17–19).

The clinical and radiological features of the fractures in these patients closely resemble those of the patients without subdural bleeds (1, 2, 5). As with the latter there was a gross discrepancy between the radiological and clinical signs of fracture. For each of these patients there was reliable evidence that before the discovery of the fractures there were no clinical pointers to suggest that fractures might be present. Because of the other concerns about their health prior to the discovery of the fractures, most of these patients had been seen frequently at the times when fractures were taking place. This discrepancy is particularly significant in the case of the transverse fractures of long bones in which, had the bones been normal, inflicted injury would have been highly likely to leave other evidence. This discrepancy is also significant in relation to the many rib fractures. An infant's ribs are flexible and accidental injuries sufficient to cause more than about four rib fractures, such as those sustained in road traffic accidents, are usually fatal (20). In contrast seven of our patients had more than four rib fractures without overt evidence of injury. As with cases without subdural bleeding (1, 2) these discrepancies suggest bone abnormalities.

A similar conclusion can be drawn from the finding that in cases 1, 2, 4 and 10 there was good evidence that fractures had occurred while the children were in hospital. In case 8 all the fractures had occurred in foster care. As with patients without subdural bleeding this evidence makes a non-accidental cause for these fractures unlikely (5).

The age when the fractures were first found was similar to that of the patients without subdural bleeds. As with the latter there were patients whose metaphyseal lesions were symmetrical, further evidence against inflicted injury. As with the patients without subdural bleeds there were disproportionate numbers of infants born preterm or as a result of multiple pregnancies. Three of our patients were (unrelated) twins and one was a triplet. It seems likely that the syndrome seen here is, in relation to the fractures, identical to that described earlier as temporary brittle bone disease.

A review of the details of the intracranial problems in these patients also gives grounds for concern that child abuse was unlikely. In three cases (1, 8 and 20) there was a clear history of an accidental head injury including impact. In all the other cases there were, prior to the discovery of the subdural bleed, pointers which with hindsight were clearly relevant, such as apnoeic episodes, vomiting and increasing head circumference from an early age. In 15 of those the CT scans showed evidence of low density subdural collections, consistent with the history. In two cases (12 and 18) blood or xanthochromia was found in

cerebrospinal fluid prior to the disastrous presentation, but not acted upon. The rapid fall in haemoglobin in case 12 on the day of birth is also consistent with the original bleed having taken place about then. In five other cases (6, 7, 14, 15 and 18) there were symptoms or signs suggestive that the initial bleed might have occurred at the time of birth (Table 2). This possibility is well recognised even in infants born at term (21–23). Subdural haematomas can even be identified before birth (24) and there is evidence that some subdural bleeds identified in postnatal life have their origins in the fetus (25). Our study provides a strong reminder of the importance of routine measurements of head circumference for the early warning of intracranial bleeding.

In case 13 the fact that the sudden collapse into unconsciousness took place 7 h after a second diphtheria pertussis tetanus vaccination suggests that the immediate trigger for the collapse was an acute reaction to the immunisation (26).

Further evidence that these patients had not been the victims of child abuse can be obtained from the follow-up data. In the nine patients returned permanently to their parents there was no evidence of any subsequent allegations of abuse. In one survey the risk of additional abuse to children returned home after therapeutic intervention in the family was estimated to be between 20 and 37% (27). Had our patients been the victims of abuse it would have been severe and repeated; apart from the subdural bleeding they had an average of 8.2 fractures, usually of different ages. The lack of subsequent injury is a significant pointer to the likelihood that the original abnormalities were not the result of inflicted trauma. Similar conclusions have been reached in relation to cases of temporary brittle bone disease without subdural bleeding (6).

If the combination of fractures and subdural bleeding does not result from non-accidental injury, what are the possible causes? Table 5 lists some possible metabolic causes of a combination of fractures and subdural bleeding together with some potentially relevant investigations. Fuller details of the investigation of this group of disorders are available (28). It is important to note that with all these disorders discrepancy between the clinical and radiological findings is a helpful pointer. These disorders may include an increased liability to bruising; we cannot avoid the paradox that lack of bruising with a fracture is suggestive of bone disease while bruising elsewhere or at other times may be a feature of the condition.

While it seems likely from our findings that the subdural bleeding and the fractures have a common cause other than non-accidental injury we cannot exclude the possibility that they result from unrelated simultaneous factors. There is a wide differential diagnosis for each. One difficulty is that there is no information on the frequency of occult fractures in the normal population; full skeletal surveys are undertaken only in the context of suspected child abuse. Similarly, there is little information on the incidence of subdural bleeding in unselected infants other than that of Rooks et al. (21).

Table 5 Metabolic disorders that could cause both unexplained fractures and subdural bleeding mimicking non-accidental injury.

Disorder	Some relevant investigations
Osteogensis imperfecta	Clinical examination Family history Fibroblast culture and collagen analysis Collagen gene mutation detection
Vitamin C deficiency	Plasma ascorbic acid Leucocyte ascorbic acid Ascorbic acid saturation test
Copper deficiency and Menkes disease	Serum copper Serum superoxide dismutase DNA testing for Menkes disease
Vitamin D deficiency	Serum calcium[a] Serum alkaline phosphatase[a] Serum 25-hydroxyvitamin D[a] Serum parathyroid hormone[a]
Prematurity	

[a]These investigations should also be undertaken on the child's mother.

One cause of fractures and subdural bleeding is osteogenesis imperfecta. This leads to spontaneous fractures but is also characterised by increased liability to bruising and to intracranial bleeding (29–33). This is generally ascribed to defective collagen in small blood vessels making them more liable to leak. However, ordinary osteogenesis imperfecta seems unlikely in our cases not least because there were no further unexplained fractures in the patients for whom follow-up information was available.

Other causes of collagen defects with fractures and intracranial bleeding are vitamin C deficiency and copper deficiency. Both vitamin C and copper are essential for the normal maturation of collagen. Scurvy has been recognised as a cause of intracranial bleeding since 1668 (34). Fractures, including metaphyseal fractures, occur in children with scurvy (35) and multiple spontaneous fractures occur in laboratory animals with scurvy (36). However, the investigation of vitamin C deficiency is not simple and requires attention to detail (36). None of our patients had been tested in any way for vitamin C deficiency.

Copper deficiency does cause fractures including metaphyseal abnormalities and asymptomatic rib fractures in infants (37, 38). Risk factors include preterm birth and multiple pregnancy. As far as we can ascertain, subdural bleeding has not been recorded in ordinary copper deficiency. However, subdural bleeding has been reported in Menkes disease, an x-linked recessive disorder of copper metabolism (39–41). Fractures including metaphyseal lesions are also well recognised in Menkes disease (40, 42). Neutropenia is a minor pointer consistent with the possibility of copper deficiency in six of our patients. Six patients had serum copper assays; all gave results within the reference ranges but the children's average age at the time was 4.7 months. A normal result at this stage does not exclude copper deficiency earlier and particularly in late intra-uterine life.

An increasingly well-recognised cause of fractures in young children is vitamin D deficiency (43, 44) but none of these patients had assays for serum 25-hydroxyvitamin D. None had classical radiological changes suggestive of rickets but these are seldom seen in infants aged <6 months (43). There is a similarity between the appearances of the metaphyseal lesions in some infants with multiple unexplained fractures and those of healing rickets (45). If vitamin D deficiency was a factor in the fractures reported here, could there be an explanation for the intracranial bleeding? One possibility is that a rachitic skull has an increased risk of deformity at or after birth with consequent underlying damage to blood vessels. Another possibility is that simultaneous vitamin K deficiency (also not excluded in these cases) contributed to the bleeding. Indeed there is some evidence of synergy of action between vitamin D and vitamin K (46). Late vitamin K deficiency is a well recognised cause of intracranial bleeding in the first 6 months of life despite the use of vitamin K prophylaxis (47–49). A further possibility is simultaneous vitamin C deficiency; the coexistence of rickets and scurvy has been recognised for many years (34). Recent years have seen recognition of the many roles of vitamin D other than on the skeleton. There is increasing awareness of its importance in haemostasis (50).

Eight of our patients were born at <37 weeks' gestation and of these five were born at <32 weeks. It is well recognised that such infants may have spontaneous fractures, particularly rib and metaphyseal fractures (51–53). In respect of their fractures our preterm infants could properly have been diagnosed as cases of osteopathy of prematurity (but were not at the time of presentation). The cause of this disorder is still unclear but vitamin D deficiency is not involved in most cases. Intracranial bleeding is well recognised in infants born preterm (54–56). One probable factor is hypoplasia and reticular fibre deficiency of intracranial arteries (56).

Heritable factors may contribute to the risk of the syndrome seen in our patients. Eight of our patients had a parent with hypermobile joints. In this respect the parents of our patients resembled those of infants who had temporary brittle bone disease without subdural bleeding (57). This finding is an additional pointer to a natural cause for this condition. It is important to note that a bleeding tendency has long been recognised in association with hypermobility disorders thought to be due to molecular defects of collagen. These include many variants of the Ehlers-Danlos syndrome, the benign joint hypermobility syndrome as well as most cases of osteogenesis imperfecta (58, 59). Fractures may be the presentation of Ehlers-Danlos type VII C (58).

We were concerned to note how many of our patients had, at the time of their presentation, inadequate investigation to exclude metabolic causes of the fractures or bleeding. Of the 18 surviving patients four had no serum calcium assays and six had no serum alkaline phosphatase assays. In those with abnormal findings none was investigated further. One patient (case 4) with a very high serum alkaline phosphatase was treated with calciferol but it was not thought at the time that this finding was relevant to the fractures. Ten patients had no recorded investigations for coagulopathy. In the eight who did, abnormalities were found in two but not taken further. It seems possible that a confident diagnosis of non-accidental injury inhibits consideration of the differential diagnosis of fractures and of bleeding.

In conclusion our review of 20 young infants with both unexplained fractures and intracranial bleeding provides strong evidence that non-accidental injury was unlikely in these cases. We found that many of these patients had inadequate investigation at the time of presentation to exclude underlying metabolic disorders. We provide an indication of the differential diagnosis of a combination of fractures and intracranial bleeding together with the principal relevant investigations. We hope that this will assist clinicians in the evaluation of such cases.

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