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Problem Solving in Clinical Practice Paper Brexit Benefits? An Unusual Cause for Bruising in a Baby

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Abstract

This paper details the case of a 4 month old baby who presented acutely to A and E and was found to have bruising. It will highlight decision making dilemmas as they were encountered in the clinical environment and guide the reader to the final diagnosis through history, examination andinvestigations. There are controversies in the literature surrounding the final diagnosis that will be discussed. Finally the case is concluded with management and follow up details.

Introduction

On Christmas Eve evening a 4 month old baby boy is not responding appropriately at home and presents to the Accident and Emergency department. There is a brief non-specific history of two days of symptoms including pallor, being clingy and listless but still breast feeding well.

Initial examination follows the emergency ABCDE approach (Airway, Breathing, Circulation, Disability, Exposure). Assessment of A, B, and C is unremarkable except for cold peripheries with prolonged peripheral Capillary Refill Time (CRT), normal observations and a central CRT less than 2 seconds. Further assessment of D reveals he is alert, pupils equal and reactive to light with a high pitched cry. The anterior fontanelle is not bulging.

The initial review appears reassuring, however a brief episode of left eye deviation with a stiff extended left arm is observed. On exposure (E), abdominal examination is unremarkable but a 10 x 7cm bruise to the left upper chest, small bruise to left forearm, small linear scratch marks to the right temporal region and dried blood to the right external meatus are noted. These injuries cannot be explained and had not previously been noticed by the parents.

Differential Diagnosis after Initial Presentation

A summary of the case to date is a non-specific two day history prior to not responding appropriately at home, in a non-mobile baby with bruising and a possible seizure. What would be included in the differential diagnosis? See table 1 for diagnosis, indications and investigations used to exclude.

The investigations are organised as per table 1. IV ceftriaxone and aciclovir are given to cover for potential sepsis. A blood gas shows ph 7.227, bicarbonate 20.5mmol/L, base excess -6.3 and lactate 9.3mmol/L. He is given a 10ml/kg bolus of normal saline in view of his poor peripheral perfusion and

base deficit on blood gas.

Table 1. *Differential diagnosis following initial presentation.*

CATEGORY	DIAGNOSIS	INDICATIONS	INVESTIGATIONS TO EXCLUDE
Traumatic	NAI	- Bruising in a non-mobile child - Vague history with unexplained injuries - Seizures query due to head injury	IMMEDIATE -CT Head TO COMPLETE - Skeletal survey - Ophthalmology review - Involvement social services
Infective / Inflammatory	Intracranial sepsis – bacterial or viral	- History of 'not being right' for 2 days - Seizure - Bruising due to possible DIC	- FBC - CRP - LFT - Blood culture - Clotting - Group and save
Vascular	Hereditary haematological cause	-Unexplained, large and multiple bruises - Seizures possibly due to ICH - Male (clotting factor deficiencies commonly X-linked)	- Clotting - Clotting factors - Group and save
Neoplastic		- Bruising secondary to low platelets - Intra-cranial involvement leading to seizures	- FBC - UE - LFT - Bone profile - CT Head - Group and save

NAI = Non Accidental Injury, DIC = Disseminated Intravascular Coagulation, FBC = Full Blood Count, CRP = C

Further History and Subsequent Differential Diagnosis

What further information would be helpful at this point given these differentials? A full history including details about his pregnancy and birth, past medical details, development to date, social and family history.

- No history of fever, rash, respiratory symptoms,diarrhoea or vomiting to suggest sepsis.
- Birth in Paris, France at term by normal vaginal delivery after an uneventful pregnancy.
- There was no delay in separation of the umbilical cord.
- He has been exclusively breast fed since birth and is gaining weight appropriately.
- On day three of life, while living in Paris, he had a brief generalised tonic clonic seizure.
- The parents did not have any medical records but their understanding was a lumbar puncture, electroencephalogram (EEG) and magnetic resonance imaging (MRI) were normal and he was diagnosed with a benign neonatal convulsion.
- He has not suffered excessive bleeding post immunisations and has not been circumcised.
- No family history of bleeding disorders although mother suffers with menorrhagia that lasts nine days.
- In paternal family there is a history of epilepsy.

He is the first child of an Asian couple who are third cousins. Father is a dentist and Mother a housewife.

This contributes further to the differential diagnosis (see table 2).

Reactive Protein (Inflammatory marker), ICH = Intra-cranial Haemorrhage, UE = Urea and Electrolytes, LFT = Liver Function Tests

Table 2. *Differential diagnosis following subsequent history.*

CATEGORY	DIAGNOSIS	FURTHER INDICATIONS	INVESTIGATIONS TO EXCLUDE
Traumatic	NAI	- Injuries remain unexplained	Nil additional
Infective / Inflammatory	Intracranial sepsis – bacterial or viral	- No specific septic symptoms	Nil additional
Vascular	Haematological cause	- No delay in umbilical cord separation (associated factor XIII deficiency) - No personal history excessive bleeding - Maternal history of prolonged menorrhagia	Nil additional
Neoplastic	Unknown	- No weight loss - Feeding well	Nil additional
Metabolic	Unknown	- Consanguinity	- Serum amino acids - Urine organic acids - Lactate - Ammonia
Hereditary	Neonatal epilepsy disorder	- Previous seizures on day 3 - Paternal family history of seizures	TO COMPLETE -EEG - MRI Head

Initial Results

The CT head is performed urgently (figure 1). There is an acute left sided subdural and subarachnoid haemorrhage with possible parenchymal involvement. Discussion and review of the images by the neurosurgical team concludes that no immediate surgical intervention is required.

Evidence from an English tertiary neurology and neurosurgical centre concludes that subdural haematoma is frequently traumatic. It is more likely due to non-accidental injury if the patient is less than 4 months, the history is inconsistent, the patient is more seriously ill and there are other findings including fractures and retinal haemorrhage[1]. In this case, non-accidental injury remains high on the differential diagnosis and both further imaging to look for fractures and an ophthalmology opinion are required.

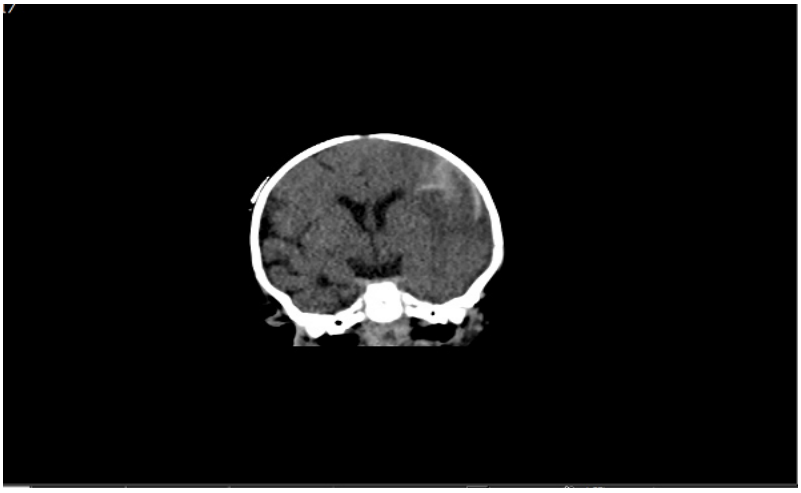

Figure 1. *CT head – coronal image*

Clinical Progress

Unfortunately, more seizures are observed and he is discussed with a neurologist. Phenytoin is given first line with a plan for phenobarbitone if seizures continue despite this.

Subsequently oozing is seen from both cannula and venepuncture sites. Blood results are still not available. Vitamin K is given on the assumption the clotting is significantly deranged.

The seizures continue and he is given phenobarbitone second line as discussed with the neurologist. The decision is made for intubation and ventilation with strict carbon dioxide monitoring on PICU (Paedatric Intensive Care Unit).

Urgent Blood Results are Available

Blood results;	
Haemoglobin 47 (g/L) Haematocrit 14%	Platelets 137 (10^9/L)
White Blood Cells 25 (10^9/L)	Sodium 134 (mmol/L)
Potassium 5.0 (mmol/L)	Corrected Calcium 2.64 (mmol/L)
Glucose 6.7 (mmol/L)	Bilirubin 72 (mmol/L)
Alanine Transaminase 43 (mmol/L)	Alkaline Phosphatase 295 (mmol/L)
International normalised ratio (INR) >10	Activated Partial Thromboplastin Time (APTT) >240 (secs)

He is significantly anaemic with very deranged clotting, a raised WBC count and mildly raised bilirubin.

Does he need blood products e.g. red cells, clotting factors? What effect will this have on his intracranial haemorrhage?

Guidelines for children over 4 months, as in this case, reflect those based on adults. The evidence should be based on the clinical picture of symptomatic anaemia rather than solely the laboratory value.

Indications for red cell transfusion include;

- Emergency surgical procedure with significant preoperative anaemia.
- Preoperative anaemia and other corrective therapy not available.
- Intraoperative blood loss >15% total blood volume (70-75 ml/kg).
- Haematocrit <24% and symptomatic anaemia.
- Acute blood loss with hypovolaemia not responsive to other therapy.
- Sickle cell disease and associated problems.
- Chronic transfusion programs for Red cell disorders e.g. β thalassaemia major[2].

This patient had cool peripheries but normal pulse and central CRT on admission. Ongoing observations showed mild tachycardia (160-180) which settled to normal limits (150-160), with normal blood pressure (101/48). There was no tachypnoea and he had good oxygen saturations. His haematocrit was 14% and there was evidence of acute intracranial and chest wall bleeding.

FFP (Fresh Frozen Plasma) is indicated when there is bleeding with prolonged PT and/or APTT or documented coagulation factor deficiency and that specific factor concentrate is not available [2]. Both the APTT and INR (PT) were prolonged in this case.

Cryoprecipitate contains the same levels of factor VIII, XIII, fibrinogen (I), von Willebrand factor and fibronectin as FFP but can be given in much smaller quantities so is appropriate if there is a risk of volume overload [2]. In this case, you may want to restrict the fluid administered due to concerns that this may exacerbate the intracranial haemorrhage. A study in preterm neonates with grade 1 intraventricular haemorrhage showed an increased odds ratio for extension to grade 3 or 4 if a red cell transfusion was given on the day the haemorrhage was detected. There is recognition the pathophysiology is multi-factorial and further research is required to assess if this is a causal link [3].

FFP and cryoprecipitate are given for the clotting abnormalities. A neurosurgical opinion advises there are no contraindications to giving a blood transfusion and therefore a red cell transfusion is also given.

Repeat blood tests show that the post transfusion haemoglobin is 64 g/L and clotting improving.

Results of further investigations are subsequently obtained including MRI (figure 2) that shows ischaemic changes on the left for which there is no obvious cause.

Ophthalmology review reveals left retinal haemorrhage, skeletal survey a left chest wall haematoma and no fractures, liver ultrasound in view of raised conjugated bilirubin shows changes suggestive of cholecystitis. None of these results indicate a specific diagnosis.

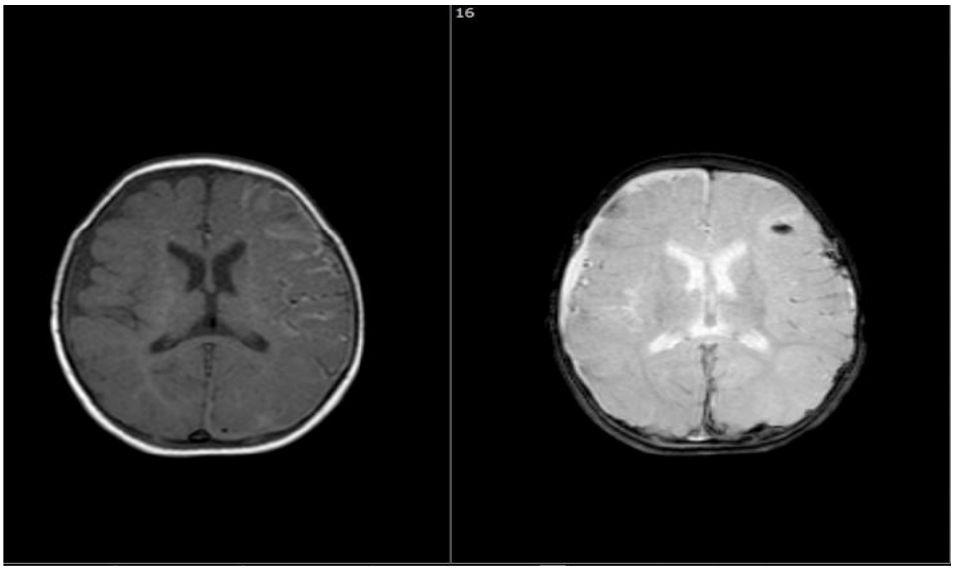

Figure 2. *MRI images, left T1 weighted, right T2 weighte.*

Final Diagnosis

Contact from the haematology department with final results from the extended clotting profile reveals severe vitamin K deficiency due to low factors II, VII, IX, X, and normal V, VIII (see figure 3). He is diagnosed with Vitamin K Deficiency Bleeding (VKDB) formerly known as Haemorrhagic Disease of the Newborn (HDN).

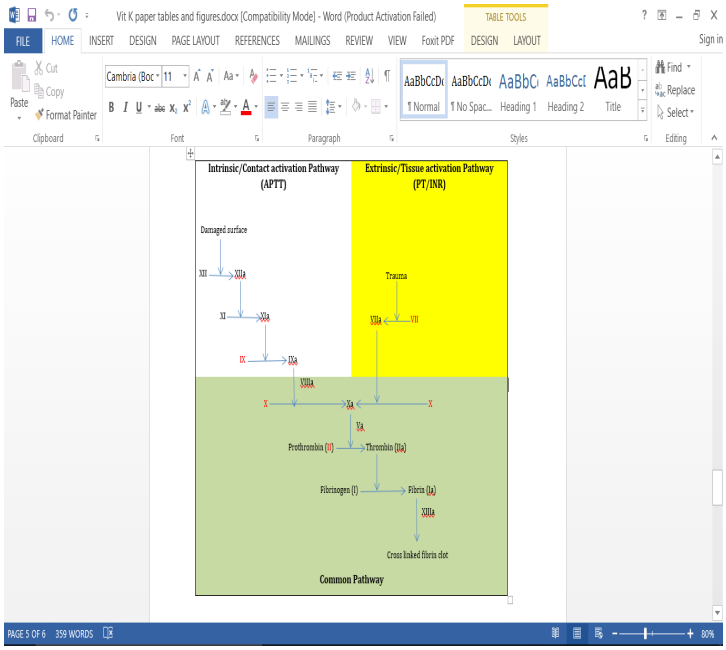

Figure 3. *Clotting pathway (Clotting investigation representing specific pathway)*

*INR is a measure of PT using World Health Organisation Internationalised Reference Reagent

Neonates are at risk of VKDB as they have poor vitamin K stores due to poor placental transfer, low levels of Vitamin K in breast milk (see tables 3 and 4) and poor production due to immature gut flora. At birth vitamin K levels in neonates are 40-60% of an adults and can take up to 90 days to normalize [4].

Table 3. *Vitamin K content of breastmilk, cow's milk and some infant formula milks*

Type of Milk	Content of vitamin k micrograms/100 millitres
SMA Pro First Infant from birth	Liquid 7[17] Powder 5.5[17]
Aptamil First Infant Milk	Liquid 4.5[18] Powder 4.4[18]
Cow and Gate 1 from birth First Infant Milk	Liquid 4.5[19] Powder 4.4[19]
Cow's Milk	0.3[16]-0.49[15]
Breastmilk colostrum Day 1-5	0.18[14]-0.23[15]
Breastmilk mature	0.12[14]-0.21[15]

Table 4. *Vitamin K content of some foods*

Foods	Content of vitamin k micrograms/100 grams
Roasted Chicken meat/skin	2.4[16]
Beef round roasted	1.9[16]
Cheddar Cheese	2.4[16]
Apple raw	2.2[16]
Banana raw	0.5[16]
Egg whole raw	0.3[16]
Peas boiled	25.9[16]
Baked Potato	2.7[16]
Broccoli boiled	141.1[16]
Carrots boiled	13.7[16]
Honey	0[16]

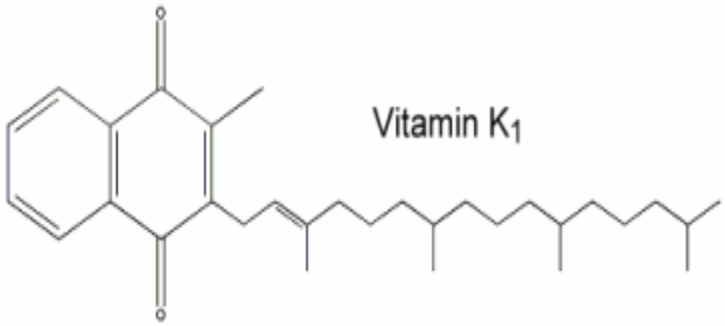

Figure 4. *Structure of Vitamin K*[21]

Classical VKDB presents within the first week of life with cutaneous, gastrointestinal, umbilical or circumcision bleeding. Late onset VKDB presents between three weeks and eight months of age and tends to occur in breastfed babies sometimes with coexisting liver disease or malabsorption. Intracranial haemorrhage occurs in greater than fifty percent of late onset VKDB [5]. In the US there are increased cases of VKDB due to refusal of prophylaxis[6].

Controversies surrounding vitamin K started when Golding et al 1992 concluded that there was increased risk of childhood cancer with intramuscular vitamin K compared to oral or not being given it (p=0.002) [7]. Subsequent small studies and analysis in 2003 by the UK Childhood Cancer Study have not supported this association [8, 9]. In the UK, The National Institute for Clinical Excellence (NICE) recommendations originally from July 2006 are detailed in table 5[5].

Table 5. *UK Policy for Vitamin K [5].*

- Offer all parents intramuscular vitamin K (1 mg IM) for their baby.
- If IM dose is declined, offer oral (2mg at birth, 2mg at1 week, 2mg at 1 month if breastfed)
- If <36/40 or <2.5 kg exclusions apply – refer to local policy

The patient was born in Paris and was not given Vitamin K at birth. He received an unknown oral dose at the age of 1 month. He was also exclusively breastfed. Is this typical use of Vitamin K in France?

There is widespread variation in practice of vitamin k prophylaxis in France. In September 2014, Guidance was issued by *Agence Nationale de Securite du Medicament* in conjunction with Roche to bring French guidelines in line with European[10] (table 6).

Table 6. *French Policy for Vitamin K [10].*

- >36 weeks gestation1 dose IM at birth (1mg)OR 2 (3 if breast fed) oral doses at birth, between days 4-7 and at 1/12 (2mg)
- Less than 36 weeks gestation and birth weight over 2.5kg give 1mg IV or IM and repeat as guided by coagulation results
- Less than 36 weeks gestation and birth weight less than 2.5kg 0.4mg/kg IV or IM and repeat as guided by coagulation results

To further complicate the Vitamin K picture, the formulation of Vitamin K can affect VKDB. A study found that term babies receiving oral Vitamin K are often given the injectable preparation orally rather than Konakion MM (Mixed Micellular) Paediatric[11]. Worryingly case reports have shown late onset bleeding after three doses of injectable Vitamin K orally, suggesting that it does not provide adequate prophylaxis [12].

The French policy also recommends intravenous Vitamin K can be used in neonates born at less than 36 weeks gestation. However there is doubt about the efficacy of using intravenous vitamin K for long term prophylaxis in the preterm population as two cases of late onset VKDB have occurred following this. The safety of a peak in serum Vitamin K concentration following this route of administration has also not been assessed[13].

Management and Follow Up

To conclude this patient's story;

- He was ventilated for three days and required further maintenance phenobarbitone due to ongoing seizures.This was weaned over a few months and seizures have not recurred.
- Bloods all normalised including raised bilirubin and liver function tests. He was reviewed by a hepatologist as an outpatient and discharged.
- He was discharged eleven days after admission on oral Vitamin K daily until he is fully weaned onto solids. Incidentally the preparation used was the IV Konakion given orally.
- All immunisations are to be given subcutaneously to avoid haematoma formation.
- Child protection investigations completed with a follow-up chest X-ray at 6 weeks that did not show healing fractures.
- Metabolic investigations have been reported as normal.
- Genetic testing is awaited in view of his microcephally.
- At follow-up appointments, he clinically has a residual mild stiffness on his right side and developmental delay of about 3 months. He has microcephaly with his head circumference following the 0.4th centile but there is no birth comparison available.
- His parents have been given a very guarded long term developmental prognosis.

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Key Learning Points Quiz

1. Fresh frozen plasma is indicated when there is bleeding with? (choose 2 options)

A. Coagulation factor deficiency and the specific factor concentrate is available

B. Prolonged PT and/or APTT

C. Coagulation factor deficiency and the specific factor concentrate is not available

D. Prolonged PT and APTT

E. Prolonged APTT and INR

2. In the UK, all parents should be offered a choice of either IM or PO vitamin K?

True or False

3. Vitamin K deficiency bleeding can present up to 8 months of age?

True or False

4. Intracranial haemorrhage is more common in late onset vitamin k deficiency bleeding than classical?

True or False

5. Thorough investigation for suspected physical abuse in a child aged less than 2 years includes[20]? (select all appropriate answers)

A. CT head

B. MRI head

C. Skeletal Survey

D. Baseline Blood tests

E. Ophthalmology review

Answers to Questions

1. *B and C*
2. *False*
3. *True*
4. *True*
5. *A, C and E*

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