**?Neuroblastoma versus Wilm’sTumor by Prof. BaHakim:**

**Introduction in brief about abdominal masses in children**

* Although most of abdominalmasses in infants and children are benign, the finding of anabdominal mass should be taken very seriously.
* A complete history, meticulous physical exam, consultation with a pediatric oncologist and specific radiological studies like ultrasound, CT scan and/or MRI should be carried out.
* Some hints helpful for diagnosis will be there such as the age of the child and location of the tumor, and some abnormal physical findings might be their in association with the tumor (like those abnormal findings found in 20% of children with Wilm’s tumor)
* Here are examples of hints:

1. Most of abdominalmasses in a neonate are benign and most are related to urinary treat or G.I.treat like: Hydronephrosis, fecal (materials, full bladder due to obstruction multicystic kidney, polycystic kidneys, mesoblastic nephroma, renalvein thrombosis, pyloric stenosis, intestinal duplication.

* Here are examples of malignantabdominal masses in relation to age:
  + In neonate and infants up to one year of age: Neuroblastoma, Wilm’s, hepatoblastoma, sarcoma, etc.
  + Ininfants and young children (1 -3 years): Neuroblastoma,Wilm’s,hepatobl, rhabdomyosarcoma.
  + Children 3- 11 years: Neuroblastoma, Wilm’s, lymphoma.

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| **Neuroblastoma** |

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| Neuroblastoma and related tumours arise from neural crest tissue in the adrenal medulla and sympathetic nervous system. It is a biologically unusual tumour in that spontaneous regression sometimes occurs in very young infants. There is a spectrum of disease from the benign (ganglioneuroma) to the highly malignant (neuroblastoma). Neuroblastoma is most common before the age of 5 years |
| **Clinical features** | |

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| At presentation ([Box 21.1](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=B021001#B021001)), most children have an abdominal mass, but the primary tumour can lie anywhere along the sympathetic chain from the neck to the pelvis. Classically, the abdominal primary is of adrenal origin, but at presentation the tumour mass is often large and complex, crossing the midline and enveloping major blood vessels and lymph nodes. Paravertebral tumours may invade through the adjacent intervertebral foramen and cause spinal cord compression. Over the age of 2 years, clinical symptoms are mostly from metastatic disease, particularly bone pain, bone marrow suppression causing weight loss and malaise |
| **Management** | |

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| Localised primaries without metastatic disease can often be cured with surgery alone. |

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| Metastatic disease is treated with chemotherapy, including high-dose therapy with autologous stem cell rescue, surgery and radiotherapy. Risk of relapse is high and the prospect of cure for children with metastatic disease is still little better than 30%. Immunotherapy and the use of long-term 'maintenance' treatment with differentiating agents (retinoic acid) are now establishing a role in those with high-risk disease. |

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| **Wilms tumour (nephroblastoma)** |

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| Wilms tumour originates from embryonal renal tissue and is the commonest renal tumour of childhood. Over 80% of patients present before 5 years of age and it is very rarely seen after 10 years of age. |
| **Clinical features** | |

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| Most children present with a large abdominal mass, often found incidentally in an otherwise well child. |
| **Management** | |

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| In the UK, children receive initial chemotherapy followed by delayed nephrectomy, after which the tumour is staged histologically and subsequent treatment is planned according to the surgical and pathological findings. Radiotherapy is restricted to those with more advanced disease. |

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| Prognosis is good, with more than 80% of all patients cured. Cure rate for patients with metastatic disease at presentation (∼15%) is over 60%, but relapse carries a poor prognosis. |

* Here are signs and symptoms and abnormal physical findings and associations which are important in differentiating Wilm’s tumor Neuroblastoma:

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| **Neuroblastoma (adrenal medulla)** | **Wilm’s tumor (renal tissue)** |
| Age : 6m – 3y  Incident 7 in 1 million  Patient is irritable and chronically sick (skin on bones). Irritable due to metastasis to bones which is not visible but very painful and mimicking bone fracture. | Age : 6m – 3y  Incident 7 in 1 million  The patient looks happy, healthy and not irritable (The disease does not metastasize to the bone), and no loss of weight. |
| Some may have fever and intermittent watery diarrhea ( on and off ) because of vasoactive intestinal peptide (VIP) production. VIP induces secretory diarrhea, which might contribute weight loss. | No diarrhea because there is no VIP production. |
| On physical examination:  The child will be very thin    Abdominal ex shows : the mass is irregular, nodular and easily palpable (superficial palpation is enough for its detection). **In 75% of the cases the mass crosses the midline** علامه مميزه – مهمه meaning that both ipsilateral and contralateral lymph nodes are involved, which makes it stage 3. | The child usually looks healthy  Regular, smooth upon palpation. The **mass never crosses the midline**, unless in neglected cases (like stage 4).  Frequent or vigorous palpation might lead to mass rupture leading to its dissemination (because the mass is very fragile). |
| No congenital skeletal deformities,  but maybe associated with neurofibromatosis (café au lait spots) مهمه جدا , and hirschsprung disease. | It is associated with congenital abnormalities (20%): skeletal deformities, undescended testis, hypospadius or hemi hypertrophy of extremities or of body or of the face hypospadius.  NB : if any pt present with these congenital anomalies it mandutury to follow him or her up in the clinic every 3 m and do US every 6 m and do CT every 1 year untile the child reach 5 y to rule out Willms مهمه |
| Pt looks anemic : Anemia is due to the invasion of blasts to the bone marrow or due to chronic disease. | Pt looks normal |
| No hematuria | Chronic microscopic hematuria (25%), which does not lead to anemia (in adults RCC causes gross hematuria leading to anemia). On the other hand, many of them have polycythemia due to the secretion of erythropoietin by the tumor. |
| Episodic secretion of norepinephrine leads to episodic transient increase in blood pressure. | 25% of the cases will have continuous elevation of blood pressure. علامه مميزه اكثر لهذا النوع |
| Almost always unilateral in a few of cases. | Bilateral in some. |
| History of mother’s phenytoin ingestion is interesting. | Familial there is often a family history of renal disease. |
| Investigations :  X- ray : will show clacification in 50% | Classification in 10 % only |
| Urine analysis :  VMA high( in 90% ) |  |
| CT ( the best diagnostic test ) :  The mass is extra renal and it push the kidney away مهمه | The mass will be intra renal مهمه |
| CXR :  Will show no specific signs  NB : the pt might have respiratory distress because of the Ascitis that push the lungs | Will show lung masses ( cannon ball ))  NB: The respiratory distress might occur  NB : if the CXR is –ve do CT scan of the lungs (( it will show nodules in the lung ) |
| Both are associated with familial and genetic mutations. | |
| Treatment : for both Surgery + chemo + Rad  Willm has better survival rate ( 60% ) While NF has only ( 10 % ) | |

Note the following facts:

1. Malignant abdominal Masseswhich present in the majority of cases during infancy and before 3 - 4 years of age include: Wilm’s tumor, neuroblastoma (which is the most common intraabdominal maligncot tumor during the first year of life), also khabdomyosaecoma, and other tumors.
2. Babies are born with Neuroblastoma Or Wilm’s and both these tumors might not be palpable during the first few- to- 6 months of life. Then later in time the mothers will discover the tumor and will bring the baby to the pediatrician.
3. Most of these babies had already come to pediatricians in OPD and in ER for the usual minor illnesses or for checkups or for vaccines while the mass was in the abdominal. This might bring a serious question about why the tumor was not detected? By deep palpation of abdomen?

* Neuroblastoma is very aggressive and is often discovered at an advanced stage and needs chemotherapy, radiotherapy and multiple surgeries. It has a poor prognosis, because more than 70% of the cases present with metastasis 80% might die, 20% might survive but with severe side effects of chemotherapy and radiotherapy.
* Wilm’s has good prognosis because majority have differentiated histology and majority don’t present with metastasis and the disease starts as malformation kidney tissue.
* Investigation (in order of importance):

1. CT scan with contrast: it can show Neuroblastoma and Wilm’s. In neuroblastoma the kidney will be healthy but only displaced with no anatomical distortion (the calcyeal system and the kidney’s structure is normal).
2. Histology is diagnostic in both Neuroblastoma and Wilm’s, but it’s only prognostic in Wilm’s. Very few cases of Wilm’s are anaplastic, but majority have favorable histology
3. 24 hours urine collection: will show high VA and VMA in 90 % of Neuroblastoma patients.
4. Bone scans to check for bone metastasis.
5. MIBG (iodine) I131is excellent investigation because it’s taken by tumor cells any where in the body even if it was very small metastasis.
6. In case of Neuroblastoma, it is indicated to do bilateral Bone Marrow biopsy to discover neuroblasts, which are arranged rosettes.

* Respiratory distress can be a complication of both Neuroblastoma and Wilm’s. In Wilm’s, it’s due to lung metastasis (sclerotic parenchymal invasion- called Cannon ball- that is usually resistant to chemotherapy and might require surgical removal and is a bad prognostic factor (stage 4). While in Neuroblastoma,the resp. distress is due to the huge mass compressing the diaphragm.
  + If there was any respiratory symptomit’s more suggestive of Wilm’s, and you need to do CXR and chest CT scan to check for parenchymal mets, whereas in NB it does not invade the parenchyma.
* Both metastasize to the liver.
* Wilm’s does not metastasize to the bone marrow.
* Neuroblastoma rarely goes to the brain.
  + 2% of Wilm’s have brain metastasis.
  + If the child has ataxia, nystagmus, and abdominal mass, it’s most likely that the mass is Neuroblastoma and in this case there is a good prognosis because it is not the tumor that spread to the brain but the IgG formed against the tumor and crossed the BBB, which mean patient has a better immunity. The IgG indicates that the child is using his immunity against neuroblastoma. مهمه جدا
* Rosette cells are found in neuroblastoma, medulloblastoma and retinoblastoma if they invade the BM.

Case : child present with continues wheezing , the investigations relived a mass posterior to the mediastarnum : what is the diagnosis ?   
in any mass posterioir to the mediastarnum in a child the diagnosis is : gangilion nuroblastoma

* NB : if the ganglion nuroblastoma pt present with signs of spinal cord invasion you should immediately send the pt to the neurosurgery to remove that mass , if no neurosergon give aggressive chemo

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| Non-Hodgkin lymphoma |

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| T-cell malignancies may present as acute lymphoblastic leukaemia or non-Hodgkin lymphoma, with both being characterised by a mediastinal mass with varying degrees of bone marrow infiltration. The mediastinal mass may cause superior vena caval obstruction. B-cell malignancies present more commonly as non-Hodgkin lymphoma, with localised lymph node disease usually in the head and neck or abdomen. Abdominal disease presents with pain from intestinal obstruction, a palpable mass or even intussusception in cases with involvement of the ileum. |
| **Investigations** | |

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| Biopsy, radiological assessment of all nodal sites (CT or MRI) and examination of the bone marrow and CSF.   |  | | --- | | **Case History 21.2 Pressure from a mass on local structures or tissue, e.g. airway obstruction secondary to enlarged lymph nodes** |  |  | | --- | |  |  |  | | --- | | A 14-year-old girl complained of a cough for 2 weeks which was non-productive and worse at night. She had seen her general practitioner and her chest was clear. She returned 2 weeks later, as she had noticed a swelling in her neck. On examination, she had a large anterior cervical lymph node which was non-tender. On referral to hospital, she had a chest X-ray, which showed a large mediastinal mass ([Fig. 21.10](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC021045)). |  |  | | --- | |  |  |  | | --- | | ***Differential diagnosis***   * T-cell non-Hodgkin lymphoma/acute lymphatic leukaemia * Hodgkin lymphoma   Her full blood count was normal. A biopsy of the mass was consistent with a diagnosis of Hodgkin lymphoma. |  |  | | --- | |  |  |  | | --- | | **Diagnosis:** Hodgkin lymphoma | |
| **Management** | |

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| Multi-agent chemotherapy. The majority of patients now do well and survival rates of over 80% are expected for both T- and B-cell disease. |

**Bleeding disorders**

* It can be caused by

1. Platelets decrease in number or by platelet dysfunction that results in petechiae.
2. Coagulation protein deficiency, which usually results in ecchymosis. It can also be caused by vasculopathy, vasculitis that are very rare in children.

* In cases of bleeding, start with taking history about the child bleeds, and ask about family history (history of prolonged bleeding in parents and in siblings and uncles, history of heavy menstruation); if the bleeding is spontaneous or not; and assess the severity including the early age of onset (how early the child bled e.g. after circumcision).
* Note the following facts:

1. Regarding the extrinsic pathway and in the absence of liver disease and vitamin K deficiency and DIC, then the reason for bleeding in child might be due to factor 7 deficiency. The deficiency will be detected by abnormal (prolonged) PT only. The PTT will be normal.
2. Regarding the intrinsic pathway defects: we think of factor 8 (more common) and 9 deficiency (11, 12 can also be affected but these two are very rare and aren’t worrisome). These will be reflected as an increase in A PTT while other parameters are normal (PT is normal).

* The coagulation profile is considered prolonged if there is more than 4 seconds difference between the control and test, also note that PTT is the test to detect VW disease.
* Hemophilia is an X-linked disease, seen in males, while females are carriers. Hemophilia (intrinsic pathway disorder, factor VIII antigen (molecule) is normal but with defective function) is the most problematic in pediatric age group (increase in APTT).
* If a mother has 2 children with hemophilia or one child and one brother with hemophilia, then the mother might be obligate carrier but she needs to be tested by genes.
* You need to do genetic analysis to know if the mother is a carrier or not because 25% of mutations are spontaneous.
* The severity depends on the functioning amount. That is the percentage of the factor that functions in coagulation. For example, if only 1% of the factor functions then the disease is severe, and 1-5% is moderate disease, and more than 5% will have mild disease.
* In the common pathway disorders, factor I (fibrinogen), II (prothrombin), V and X will be affected causing an increase in both PT and APTT.
* If a patient came bleeding and had a normal PT (factor VII is normal); normal APTT (factor VIII and IX are normal); platelet count and function are normal; then think about factor XIII deficiency. Factor XIII function isn’t measured by PT or PTT, it’s the only one that isn’t measured by coagulation profile. It is tested by a clot-dissolving test (adding urea or acetoacetic acid (weak acids), if the clot dissolves, then there is factor XIII deficiency). After the clot-dissolving test that is suggestive for factor XIII deficiency, ask for factor XIII assay (measure of function).
* Classification of Hemophilia : severity range :
* <1% : Sever : usually the Baby bleed in early life مهمه جدا – علامه الشده
* 1-5% : moderate
* >5% : mild
* Case: a 4-5 year old child that have never bled before came with ecchymosis on both tibias (only site of ecchymosis). There is no need to do any further investigation because it’s localized to the tibia (traumatic).
* In anti-phospholipid syndrome (lupus anticoagulant): the coagulation profile shows a normal PT, and significantly prolonged APTT. Because most phospholipids acts on the intrinsic factors and Von Willebrand factor with a recent history of viral infection, then the child’s IgG might cross-react against phospholipid (coated by IgG). After any surgery, watch the child for thrombosis and prevent it by early mobilization and hydration. If the IgG cross-react with RBC causing hemolytic anemia it will result in ITP.
* Some children are referred by surgeon to hemotology clinic because of prolonged PTT. The child may need to undergo tonsillectomybut the surgery is cancelled or postponed because of pre-op screening tests showing prolonged PTT. But the history shows no past history of bleeding and family history shows no history of bleeding either. The hematologist will ask the lab to look for antiphospholipid antibody (IgG) by using mixing study. In the lab, the blood of the patient will be mixed with all the coagulation profile including Factors 8, 9, 11, 12, etc.
* If the PTT is done but still prolonged. This means that the patient doesn’t have any factor deficiency because all those factors were added to the blood of the patient but they didn’t correct the PTT. Then the blood will be tested for antibody like IgG while intrinsic pathway. The IgG is against phospholipid molecules, which are found in the platelet and also found in some factors.
* Conditions: the child can undergo surgery and will not have complications of

Bleeding

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| von Willebrand disease (vWD) |

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| Von Willebrand factor (vWF) has two major roles:   * It facilitates platelet adhesion to damaged endothelium * It acts as the carrier protein for FVIII:C, protecting it from inactivation and clearance.   Von Willebrand disease (vWD) results from either a quantitative or qualitative deficiency of von Willebrand factor (vWF). This causes defective platelet plug formation and, since vWF is a carrier protein for FVIII:C, patients with vWD also are deficient in FVIII:C (see [Fig. 22.15](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC022055)). |

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| There are many different mutations in the vWF gene and many different types of vWD. The inheritance is usually autosomal dominant. The commonest subtype, type 1 (60-80%), is usually fairly mild and is often not diagnosed until puberty or adulthood. |
| **Clinical features** | |

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| These are:   * Bruising * Excessive, prolonged bleeding after surgery * Mucosal bleeding such as epistaxis and menorrhagia. 🡪 remember in hemophilia the bleeding will be in the muscles and joints مهمه جدا  |  | | --- | | **Management** |  |  | | --- | |  |  |  | | --- | | Treatment depends on the type and severity of the disorder. Type 1 vWD can usually be treated with DDAVP, which causes secretion of both FVIII and vWF into plasma. DDAVP should be used with caution in children <1 year of age as it can cause hyponatraemia due to water retention and may cause seizures, particularly after repeated doses, and if fluid intake is not strictly regulated. More severe types of vWD have to be treated with *plasma-derived* FVIII concentrate, as DDAVP is ineffective and recombinant FVIII concentrate contains no vWF. Cryoprecipitate is no longer used to treat vWD as it has not undergone viral inactivation. *Intramuscular injections, aspirin and non-steroidal anti-inflammatory drugs should be avoided in all patients with vWD*. | |

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| **Immune thrombocytopenia (ITP)**  **كلام الدكتور :**  **Usually healthy child with only petchi hemorrhage**  **PX :**is absolutely –ve  **Hx:** 3 weeks or more the pt will report mild viral infection ( ex : sore throat ) or reaction against some medication '  **pathophysiology** : the infection will trigger production of IgG that will attached to the platelets and the spleen will destroy them  **Lab :** usually normal except : low platlets 🡪 No need for bone marrow and the dz is clinically diagnosed  **Treatment :**  **If platlets < 20,000 :** it is an EMG and you have to admit the child and monitor for the brain hemorrhage And treat by giving Immunoglobulines  **If >25,000 :** follow up + steroids |

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| Immune thrombocytopenia is the commonest cause of thrombocytopenia in childhood. It has an incidence of around 4 per 100 000 children per year. It is usually caused by destruction of circulating platelets by anti-platelet IgG autoantibodies. The reduced platelet count may be accompanied by a compensatory increase of megakaryocytes in the bone marrow. |

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| ***Clinical features*** |

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| Most children present between the ages of 2 and 10 years, with onset often 1-2 weeks after a viral infection. In the majority of children, there is a short history of days or weeks. Affected children develop petechiae, purpura and/or superficial bruising (see [Case History 22.3](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=B022008#B022008)). It can cause epistaxis and other mucosal bleeding but profuse bleeding is uncommon, despite the fact that the platelet count often falls to <10 × 109/L. Intracranial bleeding is a serious but rare complication, occurring in 0.1-0.5%, mainly in those with a long period of severe thrombocytopenia. |

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| **Case History 22.3 Immune thrombocytopenic purpura (ITP)** |

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| Sian, aged 5 years, developed bruising and a skin rash over 24 h. She had had an upper respiratory tract infection the previous week. On examination she appeared well but had a purpuric skin rash with some bruises on the trunk and legs ([Fig. 22.17](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC022060)). There were three blood blisters on her tongue and buccal mucosa, but no fundal haemorrhages, lymphadenopathy or hepatosplenomegaly. Urine was normal on dipsticks testing. A full blood count showed Hb 11.5 g/dl with normal indices, WBC and differential normal, platelet count 17 × 109/L. The platelets on the blood film were large; the film was otherwise normal. A diagnosis of ITP was made and she was discharged home. Her parents were counselled and given emergency contact names and telephone numbers. They were also given literature on the condition and advised that she should avoid contact sports but should continue to attend school. Over the next 2 weeks she continued to develop bruising and purpura but was asymptomatic. By the third week, she had no new bruises, and her platelet count was 25 × 109/L; the blood count and film showed no new abnormalities. The following week, the platelet count was 74 × 109/L and a week later it was 200 × 109/L. She was discharged from follow-up. |

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| **• In immune thrombocytopenic purpura, in spite of impressive cutaneous manifestations and extremely low platelet count, the outlook is good and most will remit quickly without any intervention.** |

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| ***Diagnosis*** |

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| ITP is a diagnosis of exclusion, so careful attention must be paid to the history, clinical features and blood film to ensure that another more sinister diagnosis is not missed. In the younger child, a congenital cause (such as Wiskott-Aldrich or Bernard-Soulier syndromes) should be considered. Any atypical clinical features, such as the presence of anaemia, neutropenia, hepatosplenomegaly or marked lymphadenopathy, should prompt a bone marrow examination to exclude acute leukaemia or aplastic anaemia. A bone marrow examination should also be performed if the child is going to be treated with steroids, since this treatment may temporarily mask the diagnosis of acute lymphoblastic leukaemia (ALL). Inadvertent steroid therapy in undiagnosed ALL mimicking ITP will compromise the long-term outcome of such patients. Systemic lupus erythematosus (SLE) should also be considered. However, if the clinical features are characteristic, with no abnormality in the blood other than a low platelet count and no intention to treat, there is no need to examine the bone marrow. |

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| ***Management*** |

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| In about 80% of children, the disease is acute, benign and self-limiting, usually remitting spontaneously within 6-8 weeks. Most children can be managed at home and do not require hospital admission. Treatment is controversial. Most children do not need any therapy even if their platelet count is <10 × 109/L but treatment should be given if there is evidence of major bleeding (e.g. intracranial or gastrointestinal haemorrhage) or persistent minor bleeding that affects daily lives such as excessive epistaxis or menstrual bleeding. The treatment options include oral prednisolone, intravenous anti-D or intravenous immunoglobulin and all have significant side-effects. Platelet transfusions are reserved for life-threatening haemorrhage as they raise the platelet count only for a few hours. The parents need immediate 24-hour access to hospital treatment, and the child should avoid trauma, as far as possible, and contact sports while the platelet count is very low.  Case : healthy child bleed since he was 1y old , PTT , PT , Fibrenogen , platlets count , Plat function : All normal  Diagnosis : Factor XIII deficiency  How to diagnose : take a clot from the ot and put it in a weak acid such as : 5 M urea Or accetoacetate 🡪 if it dissolve that is +ve for factor XIII deficiency |