Repetitive cerebral bleeding in an adult with Klippel–Trénaunay Syndrome

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SIRS: Klippel–Trénaunay Syndrome (KTS) is a congenital anomaly of unknown aetiology, characterised by vascular (98 %), cutaneous (72 %) and skeletal (67 %) symptoms [8]. Brain involvement has been described but is extremely rare [20] and is due to either bleeding or ischaemia. The underlying causes of cerebral bleeding are capillary or venous malformations [1] which usually occur in the hemisphere ipsilateral to the body involvement. To our knowledge this is the first reported case of KTS with repetitive cerebral bleeding without apparent macroscopic arterio venous malformations (AVM).

A 44 year old man with right hemispheric bleeding of unknown cause presented to the clinic on 2 February 1998. He was disorientated in time and space and quite aggressive. Vital parameters were all normal: 1.70 m, 71 kg, blood pressure 130/90, resting pulse 88/min, respiratory rate 12/min. He suffered from reduced verbal fluency, presevaration, impaired abstraction, poor judgement, poor memory and reduced sustained attention. No focal neurological symptoms could be detected. A large capillary malformation (port–wine stain) with telangiectasia, petechiae and varicose veins involved the entire right leg (see figure 1). No limb asymmetry or lymphangioma were seen on clinical examination. Abdominal examination revealed a hepatomegaly of approximately 16 cm.

The CT brain scan showed a hyperdense contrast–enhancing lesion in the right temporal lobe with surrounding oedema and slight mass effect, marked by enhanced choroid plexi and occipital cerebral calcifications (see figure 2). On MRI the lesion was T1/T2 hyperdense and enhanced with contrast. A t2* spin–echo–gradient sequence showed haemosiderin deposits rostral to the current bleeding, suggestive of a former haemorrhage in the same region. Cerebral angiography revealed no macroscopic AVM or abnormality of the venous system. A control MRI two months later showed no signs of a cavernoma, which could have been the origin of such a presentation.

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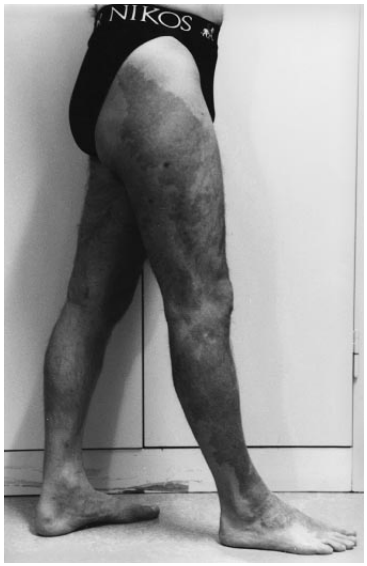

Figure 1: *Cutaneous capillary malformations (port–wine stain) and dilated varicose veins in Klippel–Trénaunay Syndrome.*

An EEG was abnormal with a right parieto–occipital δ focus without signs of elevated cerebral excitability. Transcranial Doppler sonography was normal. Opthalmological examination showed an asymptomatic weakness of the right inferior oblique muscle and papillary drusen, but no vascular abnormalities of the retina.

Laboratory investigation revealed a platelet count of 68,000/μL, reduced fibrinogen (87.0 mg/dL), elevated AT III (123 %) and reduced factor XIII (63 %). However the platelet aggregation (Born) was normal with collagen, ristocetin and ADP.

The presentation of this patient is consistent with a cerebral haemorrhage in KTS. According to Jacob this patient fits the diagnositc criteria for KTS [8]. He had capillary malformations (port–wine stain on the right leg), soft tissue hypertrophy (hepatosplenomegaly) and varicose veins (right leg).

In fact this patient's medical history dates back to early childhood, where a birth mark had been noted on his right lower leg. He suffered from frequent gingival bleeding and haematomas following minor trauma. Removal of varicose veins in the right leg became necessary in January 1987. The patient underwent a bone marrow examination due to the marked hepatosplenomegaly and pancytopenia. Histology showed myelofibrosis, activated haematopoesis due to peripheral haemolysis and a low–grade non–Hodgkin lymphoma (NHL) was suspected.

In June 1994 the patient had sudden onset of Broca's aphasia and agraphia due to right dorsofrontal bleeding, as indicated by CT scan. At this time peripheral blood analysis revealed thrombocytopenia (90,000 μL), reduced factor

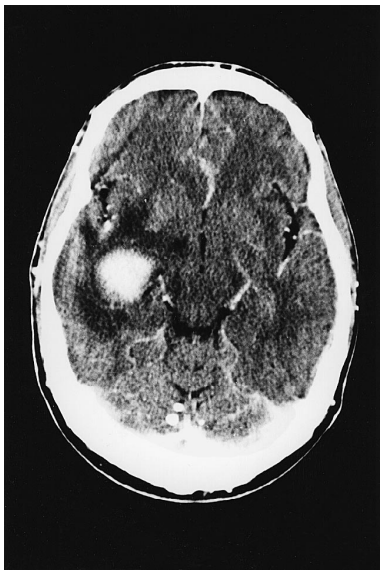

Figure 2: *Intracerebral bleeding in Klippel–Trénaunay Syndrome. The CT scan reveals a hyperdense contrast enhancing lesion in the right temporal lobe with surrounding edema and slight mass effect, marked enhanced choroid plexuses and occipital cerebral calcifications.*

XIII (44 %), reduced maximal amplitude and prolonged k time in thrombelastogram and prolonged bleeding time $<$ 10 min (Marx). Detailed neuropsychological testing showed severe reduced attention span and constructive abilities, poor memory, decreased reaction time, perseveration and reduced verbal fluency. All language impairments recovered within a year.

Progression of the NHL made polychemotherapy (CHOP-I) necessary, and this was started in June 1996. In the subsequent aplastic phase he developed a gram–positive sepsis and lower gastrointestinal bleeding caused by disseminated intravascular coagulation and severe thrombocytopenia (9,000/μL). An abdominal CT scan showed splenomegaly (28 cm) with multiple infarctions and hepatomegaly (24 cm) with a haemangioma in segment 7. The blood count improved after splenectomy in August 1996. The spleen (1,600 g) showed a soft, dark red cut surface and several subcapsular blister–like defects, which were caused by splenic infarctions. Histology of the spleen revealed distended sinusoids of the red pulp which were filled with atypical lymphoblasts and this together with the immunohistological findings suggested a monoclonal hepato–splenic Tγ–δ cell lymphoma, which was confirmed by polymerase chain reaction analysis [23].

What is unusual in this patient is the repetitive cerebral bleeding without any visible macroscopic AVM. Seven cases of KTS with haemorrhagic stroke have been published, all of them with an apparent AVM (see table 1). Our patient differs from this group by age, 44 years compared to a mean age of 21

Table 1: *Cerebral bleeding in Klippel–Trénaunay syndrome. Age in y = years, w = weeks. Gender: f = female, m = male.*

Author	Lesion/mechanism	Age	Gender	n=8
Jaksch 1986 [9]	Rupture of angioma	34 y	m	n=1
Oyesiku 1988 [18]	AV–fistula	12 y	f	n=1
Taira 1991 [21]	Aneurysm	8 w	m	n=1
Dunn 1993 [4]	AV–fistula, occlusion of the straight sinus	34 y	f	n=1
Suga 1994 [20]	Multiple angiomata (left cerebellar and pontine)	24 y	m	n=1
Makiyama 1994 [14]	Rupture of AVM	8 y	f	n=1
Spallone 1996 [19]	Fusiform aneurysm	28 y	f	n=1
Own case 1998	Coagulopathy, suspected microscopic AVM, repetitive right cerebral haemorrhage (1994, 1998)	44 y	m	n=1

years. In addition he suffers from deficient clotting due to the NHL. These factors together with the suspected co–existence of microscopic AVM increase the risk of bleeding. The occurrence of microscopic arteriovenous fistulae in KTS is controversial [12, 15, 16, 26]. A distinction between KTS and Parkes–Weber Syndrome has been suggested depending on the existence of such haemodynamically irrelevant AVM. Co–existence of microvascular AVM render cerebral bleeding in the affected hemisphere more likely if additional risk factors are present. Histologically the affected vessels in KTS show marked thickening of the medial vessel layer, hyaline degeneration of the lamina muscularis and patchy sclerosis of the intima [6]. In general, patients with peripheral bleeding suffer from spontaneous haemorrhages from dilated veins [1]. Peripheral bleeding can however be caused without apparent AVM [7, 22, 24, 25]. Reduced factor XIII, as been in this case, has been described with KTS [5]. Change in coagulation is mostly related to thrombocytopenia and low fibrinogen caused by their continous consumption in the altered vessels [3, 5, 11, 25]. Vascular abnormalities occasionaley involve the retina [2, 13, 17]. Severe haemorrhage is a risk in KTS patients and splenectomy might reduce the thrombocytopenia. In acute haemorrhage tranexamic acid has been reported to stop bleeding [10].

Our case has clinical features compatible with KTS involving the right hemicorps and repetitive right cerebral bleeding. This together with the underlying clotting defect raises the question of co–existent microvascular AVM, as discussed in the literature [12, 15, 16, 26]. Although KTS is not uncommon for dermatologists and pediatricians it is rare for neurologists. In all KTS patients with neurologic symptoms brain involvement should be thought of. MRI, MRI–angio or conventional angiography may lead to diagnosis of cerebral AVM. Laboratory screening of haemostatic parameters may reveal additional risk factors for haemorrhagic events.

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