Teaching Course 17

Neurological presentations of systemic disorders - Level 1

Stroke as first presentation of systemic disorders (Fabry, sickle cell disease, etc)

José Manuel Morão Cabral Ferro
Lisbon, Portugal

Email: jmferro@fm.ul.pt
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This teaching course text contains information on the epidemiology, specific stroke features diagnosis and treatment of stroke as the initial manifestation of systemic diseases

The topic is too vast and therefore we choose not to include cardiac and infectious diseases

We will review hematological diseases (myeloproliferative neoplasms), gastrointestinal and hepatic diseases, cancer, genetic causes of stroke, antiphospholipid syndrome, lupus and some of the primary vasculitis
Hematological diseases. Myeloproliferative neoplasms

The chronic myeloproliferative disorders, also referred to as myeloproliferative neoplasms (MPN), are a group of diseases in which there is an increased proliferation of one or more subtypes of myeloid cells. Those associated with stroke are polychythemia vera (PV) and essential thrombocythemia (ET) (Lacerda et al, 2014).

The Janus kinase JAK2 V617F mutation is present in the vast majority of patients with PV and in approximately 50% of those and ET. Compared to patients with ET that are negative for JAK2, those with the JAK2 mutation have higher red and white blood cell counts, lower erythropoietin levels and increased propensity for venous thrombosis (Scott et al, 2006). These ET patients are heterozygous for JAK2 mutation, whereas the majority of patients with PV are homozygous for JAK2 mutation (Beer and Green, 2009). The second more frequent mutation in MPN involves the CALR-gene. They appear to be absent in PV and present in 20-50% of ET patients (Barbui et al, 2015).

Vascular complications occur before the diagnosis of myeloproliferative neoplasms (MPN). In 612 patients from 4 European centers vascular complications were observed in 151 (25%) of the patients. Of these 66% occurred during the 2 years preceding the diagnosis of MPN. The majority were thromboembolic and included myocardial infarction (46), ischemic stroke (43), TIA (22), venous thrombosis (26). Bleeding was registered in 7, including 2 intracranial hemorrhages. Full blood counts showed that 44% had abnormal values at least 3 month prior to the diagnosis of MPN (Emblom et al, 2015).
Ong et al (Ong E et al, 2016) reported from the Hematology in Lyon registry 35 patients (4.3%) with a stroke history revealing MPN: 22 with an ischemic stroke, 8 with a TIA, 4 with CVTand one with hemorrhagic stroke. All patients had hemoglobin and/or platelet count abnormalities. Twelve had PV, 21 had ET, one myelofibrosis and one unclassified MPN. The JAK2 V617F mutation was present in 83% of the patients. In 18 (51%) there was an additional stroke mechanism: atherosclerosis (10), atrial fibrillation (1) and dissection (1). Stroke-MPN patients had higher levels of hemoglobin and were more frequently + for JAK2 mutation than the remaining MPN patients.

Polycythemia Vera

Main Clinical Characteristics

PV usually has an insidious onset, more frequently in the 6th decade of life. Many patients are led to diagnosis after the initial identification of erythrocytosis in a routine blood test. Patients who refer symptoms may have headaches, weakness, pruritus, dizziness, sweating, plethora, thrombosis and gastrointestinal bleeding (Lacerda et al, 2015). Approximately one third of the patients have thrombotic complications. Arterial events, predominantly ischemic strokes and transient ischemic attacks, account for approximately 30% of such thrombotic complications, followed in frequency by myocardial infarction, deep vein thrombosis and pulmonary embolism. Up to 25% of the patients have mucosal bleeding and bruising, which are usually not severe (Wehmeier et al, 1991). Approximately 10% of the patients have erythromeralgia, a burning sensation and erythema of the fingers, which is related to thrombocytosis and usually responds to low dose aspirin. In the brain an increase in the hematocrit above 45% is associated with a decrease in cerebral blood flow.
conductive to stasis and endothelial damage, interfering with nitrous oxide vasodilatory effects and therefore increasing the thrombotic tendency, even without associated thrombocythemia (Thomas et al, 1977; Fiermonte et al, 1993). Platelet counts > 1 000 000/µL are associated with hemorrhagic diathesis due to an acquired von Willebrand syndrome (Spivak et al, 2002).

Diagnostic Criteria and Risk Assessment

The distinction between PV and secondary polycythemias may be cumbersome. The 2008 WHO criteria help to differentiate between these entities. Polycythemias can be primary, due to clonal proliferation of bone marrow precursors, or secondary, due to reactive erythrocytosis. Secondary polycythemias include congenital and acquired syndromes, mostly erythropoietin mediated due to hypoxia, erythropoietin producing tumours or drug-associated (McMullin et al, 2005).

Diagnosis of PV requires meeting all three major criteria or the first two major criteria and the minor criterion (Arber et al, 2016) (Table 1). Briefly, the major criteria are significant erythrocytosis, bone marrow biopsy showing marrow trilineage myeloproliferation and JAK2 mutations and the minor criterion is subnormal serum erythropoietin levels. High risk patients are defined by any one of the following: age above 60 years, previous documented thrombosis, aspirin-resistant erythromelalgia, platelet count above 1000 X 109/L, diabetes or hypertension requiring pharmacological therapy, significant or symptomatic splenomegaly. Low risk patients should not have any of these risk factors (Harrison, 2010)
Table 1.
Diagnostic criteria of Polycythemia Vera according to the WHO (2016).

**Major criteria**

1. Hemoglobin >16.5 g/dL in men
   Hemoglobin >16.0 g/dL in women
   or,
   Hematocrit >49% in men
   Hematocrit >48% in women
   or,
   increased red cell mass (RCM) (> 25% above mean normal predicted value)

2. Blood Marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of JAK2V617F or JAK2 exon 12 mutation

**Minor criterion**

Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF)
Neurological symptoms in Polycythemia Vera due to microvascular circulation disturbances

The most frequent neurological symptoms in PV are headache and dizziness. The PV related headache has no defining characteristic and varies from a generalized headache to a unilateral intermittent throbbing migraine-like pain (Silverstein et al 1962). Other neurological symptoms resulting from microvascular circulation disturbances due to spontaneous activation and aggregation of platelets in the arterial circulation can occur even with normal hematocrit values and include: paresthesia, erythromelalgia episodic neurological symptoms such as atypical transient ischemic attacks proceeded by migraine-like headache, scotomata, blurred vision and transient ocular ischemic attacks. Most of these symptoms can be relieved with aspirin (Silverstein et al 1962; Michiels et al 2004, Michiels 2006 a,b, 2015).

Thrombosis and haemorrhage in Polycythemia Vera

In 1213 PV patients followed for 20 years, 14% had a thrombotic event prior to the diagnosis and 20% as the presenting symptom of the disease. Of these, ischemic stroke and transient ischemic attacks (TIAs) accounted for 70% of arterial thrombosis at diagnosis and 30% before diagnosis. On follow-up TIAs were the most common non-fatal event followed by myocardial infarction and ischemic stroke (Gruppo Italiano Studio Policitemia, 1995).

The central nervous system is the most frequent site of thrombosis, more common than coronary artery complications (Michiels et al 2004). CNS thrombosis can be arterial or venous. Thrombosis can precede the diagnosis by up to 2 years in 14-15% of patients; can be a presenting feature in 12-57% and occur in follow-up in up to 40% of patients. It is the
cause of death in 20-40% of PV patients. The rate of thrombotic events increases with age and a history of previous thrombotic event.

Cerebral venous thrombosis (CVT) are a frequent complication of PV (Ferro et al, 2004). CVT can present as headache, papilloedema, seizures or a focal deficit or a combination of the above, and in severe forms as encephalopathy or coma. Usually several sinus or veins are occluded simultaneously. PV should be searched in cases of cryptogenic CVT, as venous occlusion can antedate laboratorial and clinical manifestations of PV by several months. PV is an independent risk factors for the recurrence of CVT and other thrombotic events (Miranda et al, 2010)

Hemorrhage is less frequent than thrombosis and primarily involves the central nervous system. It can be a presenting feature in 6-58% of PV patients and cause death in up to 30 %. (Perkins et al, 1964; Gruppo Italiano Studio Policitemia, 1995; Passamonti et al, 2003; Passamonti et al 2004; De Stefano et al, 2008b).

**General Treatment Recommendations**

The current guidelines for all patients involve the careful assessment of cardiovascular risk factors and the use of low dose aspirin, unless contraindicated. Erythromelalgia also responds to aspirin. Aspirin is an irreversible inhibitor of platelet COX-1 activity. Other antiplatelet drugs are ineffective. Erythocytosis should be controlled by phlebotomy to maintain a hematocrit lower than 45% (Harrison, 2010).

Pharmacological therapy may be needed not only to control the red blood cell count, but also to lower the platelet count in patients with thrombocytosis. Hydroxyurea is usually reserved for high risk patients
above the age of 60 years, whereas younger patients should receive interferon and/or anagrelide (Harrison, 2010). Low risk patients may be managed with low dose aspirin and phlebotomy alone.

**Essential Thrombocythemia**

**Main Clinical Characteristics**

Essential thrombocythemia (ET) is a chronic myeloproliferative syndrome characterized by sustained (> 1 month) high platelet counts (>450 x 10^9/L) and increased number of mature large megakaryocytes in the bone marrow. ET has to be distinguished from other causes of high platelet count (thrombocytosis), which can be grouped in primary (polycythemia vera, myelofibrosis, myelodyplasia and acute and chronic myeloid leukemia), reactive and very rare genetic forms. The most common reactive causes of thrombocytosis are acute and chronic blood loss and anemia, chronic infections and inflammation, malignancy and splenectomy (Miller and Farquharson, 2010). ET is frequently diagnosed after the incidental finding of an elevated platelet count. Only 10% of the patients have splenomegaly at diagnosis (Harrison et al, 2005). A significant number of patients have coagulation abnormalities and approximately one quarter of high risk patients not receiving myelosuppressive drugs have thrombosis (Cortelazzo et al, 1995). The main predictive factors for thrombosis are age above 60 years and a history of previous thrombosis (Passamonti et al, 2008). Arterial thrombosis predominates, affecting the central nervous system (ischemic stroke, transient ischemic attack) and the cardiovascular system (myocardial infarction, unstable angina, peripheral arterial occlusion (Cortelazzo et al, 1995, Harrison et al, 2005). Venous events comprise primarily deep venous thrombosis and pulmonary embolism. Significant hemorrhage is less frequent than thrombosis and it affects
primarily the nasal, buccal and gastrointestinal mucosae (Cortelazzo et al, 1995, Harrison et al, 2005). It is typical for ET patients to have abnormalities in platelet aggregation and loss of large von Willebrand factor multimers, determining an increased hemorrhage time. However, these laboratory findings do not necessarily correlate with clinical bleeding (Elliott and Tefferi, 2005). Patients with ET may evolve to secondary myelofibrosis and have a low risk of progression to acute myeloid leukemia.

**Diagnostic Criteria and Risk Assessment**

The 2016 WHO criteria for the diagnosis of ET considers four major criteria (platelet count above 450 X 10^9/L; bone marrow biopsy showing increased mature enlarged megakaryocytes with hyperlobulated nuclei and very rarely minor increased reticulin, not meeting criteria for other myeloid neoplasms or myelodysplastic syndromes, mutation in JAK2, CAR or MPL mutation in JAK2, CAR or MPL) and a minor criterion (presence of a clonal marker or no reactive cause for thrombocytosis). For the diagnosis of ET, all four major criteria has to be present, or the first three plus the minor criterion (Arber DA et al, 2016)

High risk ET is defined by the presence of at least one of the following criteria: age above 60 years, platelet count above 1500 X 10^9/L, previous thrombosis and aspirin-refractory erythromalgia, previous hemorrhage related to ET, diabetes or hypertension requiring pharmacological treatment. Intermediate and low risk applies to patients lacking all these risk factors but with an age between 40 and 60 years, and below 40 years, respectively (Harrison, 2010).
Cerebrovascular manifestations of Essential Thrombocythemia

As for PV, neurological manifestations in ET are also due to large artery and vein thrombosis, microvascular ischemia and thrombosis (Jabaily et al, 1983; Kesler et al, 2000; Miller and Fraquharson, 2010; Enblom et al, 2015; Michiels et al, 2015). Strokes (Arboix et al, 1995) and cerebral venous thrombosis (Haan et al, 1988) are often the inaugural presentation of ET and may even antedate the diagnosis of ET by months.

The most common neurological symptom is headache, sometimes resembling migraine. Migraneous aura-like episodes are also common. Atypical (isolated dysarthria, diplopia or unsteadiness, hearing loss, transient focal deficits with prominent headache, very brief or sequential) or typical TIAs (amaurosis fugax, aphasia, motor deficits) are frequent, but seizures have been rarely reported. Erythromelalgia is a burning or painful sensation of the palms and soles and sometimes also of the toes and fingertips accompanied by a red-cyanotic skin discoloration of the affected skin. All these symptoms are attributed to microvascular ischemia and thrombosis, induced by activated platelets and by products released by the platelets (Michiels et al, 1993, 1996, a, b); 2015).

Other arterial cerebrovascular complications include ischemic strokes due to large artery and to small vessel disease (Jabaily et al, 1983; Arboix et al, 1995; Kesler et al, 2000; Mallada-Frenchin et al, 2004; Gonthier and Bogousslavsky, 2004). Nevertheless ET (and also polycythemia vera) are infrequent causes of ischemic stroke: 2 cases in 4697 strokes in the Lausanne registry and 6 out of 1099 in L’Aliança Registry.

Two unusual cases of progressive occlusive disease of the internal carotid with recurrent strokes or TIAs (Mosso et al, 2004; Kornblihtt et al, 2005)
have been reported. One of these patients had a Moya Moya angiographic pattern and was successfully treated with an internal carotid stent (Kornblihtt et al, 2005).

Thrombosis of the dural sinus and cerebral veins are frequent in ET and can be the inaugural clinical manifestation (Haan et al, 1988). The frequency of venous sinus thrombosis in ET is estimated to be 2%. In a cohort of 624 patients with cerebral venous thrombosis, 5 (0.8%) had ET (Ferro et al, 2004). Although the JAK2 mutation is rare in unselected cases of cerebral venous thrombosis (1-6%) (De Stefano et al 2008a; Bellucci et al, 2008; Shetty et al, 2010), this mutation is more frequent (RR 2.26) in ET patients with cerebral venous thrombosis (De Stefano et al, 2011). ET is a risk factor for the occurrence of further venous thrombotic events after CVT (Miranda et al, 2010).

**General Treatment Recommendations**

Similarly to PV, the current guidelines for all patients involve the careful assessment of cardiovascular risk and the use of low dose aspirin, unless contraindicated. High risk patients above 60 years should receive hydroxyurea, whereas younger patients may receive interferon or anagrelide instead as first line treatment (Harrison, 2010).

The treatment of cerebrovascular complications of ET should follow the general recommendation for the treatment of the different types of stroke. In general, therapies to reduce platelet count are added. For thrombosis of the dural sinus and cerebral veins, anticoagulation should be used in the acute phase and for 3-6 months thereafter and in longer periods in high-risk patients only. Platelet counts should be monitored frequently during unfractionated heparin treatment, to detect heparin-
induced thrombocytopenia, which can have a deleterious influence in the clinical course.

Table 2. WHO diagnostic criteria for Essential Thrombocythemia (2016)

Major criteria
1. Platelet count ≥450 x 10⁹/L

2. Blood Marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers

3. Not meeting WHO criteria for BCR-ABL11 CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

4. Presence of JAK2, CALR, or MPL mutation

Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Table 3.
Stroke as the 1st clinical manifestation of myeloproliferative neoplasms

Clinical hints

Stroke/TIA type

Multiple atypical TIAs including retinal symptoms
Cerebral venous thrombosis in middle-aged/elderly patients

Systemic manifestations

Erythromelalgia, splenomegaly

Routine lab findings

Increased erythrocyte or platelet counts
Selected references


Hepatic diseases

It is very rare that stroke is the first manifestation of a chronic liver disease. It may happen that liver disease, namely cirrhosis is undiagnosed at the time of stroke onset and is “discovered” during stroke work up. In the search of a cause in young or in cryptogenic stroke, testing for infection with hepatitis B and C is usually pursued.

Patients with liver disease have an increased risk of both thrombotic (both arterial and venous and bleeding events. There is a precarious hemostatic balance in these patients (Lisman et al, 2013). In cirrhosis there is thrombocytopenia, platelet function defects, decreased levels of procoagulants and anticoagulants and alterations in the fibrinolytic system. INR and aPPT may be prolonged. A recent US study using administrative data concluded that the risk of intracranial hemorrhage stroke is modestly increased in patients with cirrhotic liver disease (HR 1.8) (Parikh NS et al, 2015). Hemorrhagic stroke carries an increased risk of 90 days mortality (HR 3.89) among cirrhotic patients (Hung et al, 2015), in particular subarachnoid hemorrhage (HR 7.93).

There are several possible mechanisms to explain the increased risk of ischemic stroke in liver disease patients, including a direct and indirect role of alcohol and of hepatic viral infections (Ferro et al, 2016). Alcohol abuse increases the risk of hypertension, atrial fibrillation and myocardial infarction. Hepatitis B virus seropositivity per se, does not increase the risk of stroke. There are a few reports of cerebral vasculitis and stroke associated with hepatitis B vasculitis, hepatitis B related-polyarteritis nodosa and Takayasu’s arteritis. Chronic hepatitis virus C accelerates atherosclerosis by a number of mechanisms including colonization and
replication within arterial walls, chronic inflammation, oxidative stress, endotoxemia, hyperhomocysteinemia, hypo-adiponectinaemia, insulin resistance and diabetes [63]. Other mechanisms that concur to stroke in hepatitis C are mixed cryoglobulinemia, anti-phospholipid and anti-neutrophil cytoplasmic (ANCA) antibodies and vasculitis (Castro Caldas A et al, 2014). Hepatitis C increases the risk of stroke, with an odds ratio of 1.58. Antiviral treatment reduces the risk of ischemic stroke (OR 0.62)(Hsu Yc et al, 2015).

Despite the increased risk of deep venous thrombosis, cerebral venous thrombosis is exceedingly rare in association with cirrhosis (Perez et al, 1999; Singhla A et al, 1999). In one of the reported cases there were several acquired deficiencies in natural anticoagulants.

Treatment of acute stroke and secondary stroke prevention in patients with chronic liver disease

Drugs used to prevent stroke, including anticoagulants, antiplatelets and statins are in general contraindicated in severe hepatic failure. They can be used with caution, with periodical clinical and laboratorial re-evaluation, if there is laboratorial evidence of liver disease. Aspirin is relatively safe in patients with chronic liver disease without esophageal varices. Cirrhotic patients with varices have a very high risk of bleeding while on aspirin, clopidogrel or anticoagulants, which therefore should be avoided. LMWH seem to have a good safety profile in patients with cirrhosis and thrombosis. VKAs have an unfavorable risk/benefit ration, in particular in those patients with a high INR prior to initiation of VKAs (Lisman et al, 2013). The experience with direct oral anticoagulants is limited. Some (e.g. dabigatran) are mainly eliminated by the kidneys and
can be used without need for dose adjustment in patients with moderate (but no severe) hepatic failure. DOACs have a lower risk of liver injury than warfarin. DOACs are also not associated with an increased risk of serious drug-induced liver disease. In fact the risk of transaminase elevations (> 3x ULN) is lower than with LMWH (Caldeira D et al, Heart, 2014). However DOACs appear to have a higher risk of GI bleeding than VKAs. Endovascular closure of the atrial appendage is a reasonable option to prevent recurrent stroke in patients with severe chronic liver disease and atrial fibrillation.

Concerning acute ischemic stroke treatment in patients with hepatic disease, IV rtPA can be used if INR is ≤ 1.7. Mechanical thrombectomy can be used and is indicated in patients with proximal internal carotid or middle cerebral artery thrombosis within 6 hours from onset. Alcohol induced hepatic disease was shown in an animal model to have a negative interaction with rtPA thrombolysis, as larger infarct volumes were observed in animals with alcohol induced hepatic disease. A probably explanation for this observation is delayed hepatic clearance of rtPA in hepatic disease, with brain recirculation of rtPA causing microcirculation and reperfusion injury.

Cerebral venous thrombosis can be treated with LMWH or by endovascular thrombectomy.

Hemorrhagic stroke, in particular intracerebral hemorrhage, is more frequent in patients with liver cirrhosis, more so if caused by alcohol. Neurosurgery is rarely indicated, except in space occupying cerebellar hematomas. Reversal of bleeding diathesis with fresh frozen plasma, activated factor VII or platelet concentrate is necessary before surgery.
In cases with subarachnoid hemorrhage due to ruptured aneurysm, endovascular occlusion of the aneurysm is preferable over surgical clipping.
Selected references


- Pérez, S, Casado I, García I, Gómez M, Ramirez JM, Luengo E. Hemorrhagic infarct as a result of cerebral venous thrombosis as a complication of cirrhosis. Rev Neurol 1999; 29:1355-6


Inflammatory bowel disease.

Patients with inflammatory bowel disease (IBD) have a remarkable thromboembolic tendency and are at increased risk of both venous and arterial thrombotic complications (Canero et al., 2011).

In hospital series of IBD, the prevalence of arterial and venous thrombosis is around 4%, while in autopsy studies, this percentage may be more than 30%. The incidence of thrombotic complications ranges from 0.5 to 6.7% per year (Bernstein et al., 2001; Papa et al., 2003). IBD is also a risk factor for recurrent venous thromboembolism (Novacek et al., 2010).

In a cohort of 49,799 Danish patients with IBD compared with 477,504 members of the general population, patients with IBD had twice the incidence of deep venous thrombosis and pulmonary embolism. Relative risks were higher at young ages (hazard ratio 6.0 below age 20), though actual incidence increased with age (Kappelman et al., 2011). In a retrospective case control study including 17,487 IBD patients and 69,948 controls had an increased risk of arterial thrombotic events. In particular women below age 40 exhibited a two-fold higher risk for stroke (Ha et al., 2009). Thromboembolism is more frequent in IBD than in other chronic inflammatory or chronic bowel disease (Miehsler et al., 2004). In the Nationwide Inpatient Sample Database including 461,415 patients with IBD 28,820 (6%) had a diagnosis of a thromboembolic event, 3.96% arterial and 2.4% venous. Of the ischemic events 22% were strokes (Kuy S et al, 2015).

Stroke in patients with IBD were already reported in the 30’. In 1986, Talbot and colleagues (Talbot et al., 1986) described a 1.3% prevalence of thromboembolic complications among 7,199 patients with IBD observed...
during a 10 year period in a single institution. Among the 92 patients with thromboembolic complications, 61 had deep vein thrombosis or pulmonary embolism. Nine patients had cerebrovascular thrombotic events. There were no subarachnoid or intracerebral hemorrhages. Several other case series (Lossos et al., 1995; Elsehety et al., 1997; Barclay et al., 2010; Benavente et al., 2011; Cognat et al., 2011) and case reports of arterial ischemic or cerebral venous thrombosis were published since then, with a frequency ranging from 0.6% to 4.7%. Recently a large studies and a meta-analysis confirmed the increased risk of stroke in IBD. In a Taiwan Insurance Database cohort comparing 3309 patients with Crohn’s disease with 13236 controls the HR for subsequent stroke was increased in IBD patients (HR 1.91), for patients older than 40, but not younger. Women were found to be at higher risk than men (2.39 vs. 1.50) (Keller JJ et al, 2015). However, other studies found that the risk of stroke was observed in both and older patients with IBD (Singh S et al, 2014). In a systematic review and meta-analysis of 8 studies, IBD revealed a trend towards a modest increase in the risk of stroke incidence (HR 1.29), somewhat higher in Crohn’s disease (1.32) than in ulcerative colitis (1.18). The risk was higher in women than in men (1.49 vs. 1.22) (Xiao Z et al, 2015).

Strokes are not related to the duration or the severity of IBD, but cerebrovascular events are more frequent during bouts of inflammation. Rarely, they can antedate other manifestations of IBD.

Pathophysiology

The prothrombotic state inn IBD has multiple contributors, namely blood coagulation, platelets, , prothrombotic mutations, vitamin deficiencies, inflammation and other immune mechanisms, endothelium and premature
atherosclerosis (Santos et al., 2001; Bermejo et al., 2008; Canero et al., 2011; Singh S et al, 2014).

The hypercoagulation state is related to raised levels of factor V and VIII, fibrinogen, fibrinopeptide A and PAI-1, and decreased levels of protein S and antithrombin. Thrombocytosis is common in IBD, secondary both to anemia and inflammation. Platelet function is disturbed and Von Willibrand factor, a potent mediator of platelet adhesion and aggregation, is increased. Prothrombotic mutations such as factor V Leiden and MTHFR were identified in some IBD patients with cerebrovascular complications. Vitamin deficiencies due to malabsorption, namely B12 and folate, cause hyperhomocysteinemia, in particular when combined with a MTHFR deficit. Cytokines, such as interleukin 1 and 6 and TNF-alpha can activate the coagulation cascade during periods of active inflammation. Other immune mechanisms include the co-existence of prothrombotic antibodies such as lupus anticoagulant, anticardiolipin antibodies, and atypical (non MPO, no PR3) ANCA antibodies, the later in ulcerative colitis.

Cardiovascular risk factors are not over represented in patients with IBD. So it is plausible that the increased risk of arterial thrombotic events is attributable to inflammation-mediated atherosclerosis. In some patients endothelial dysfunction was reported.

**Arterial ischemic stroke**

Ischemic event can be both cerebral and ocular. Ischemic stroke occurs through several mechanisms: 1) large artery disease, including even a case of common carotid occlusion, 2) small vessel disease, e.g. corona radiata (Ogawa et al., 2011) or pontine lacunar infarcts, 3) cardioembolism, related to a) paradoxical embolism though a patent foramen ovale in
patients with lower limb, pelvic or mesenteric venous thrombosis, either
symptomatic or not, b) endocarditis (Kreuzpaintner et al., 1992; Chentarez et al., 2010), 4) vasculitis.

**Stroke and anti-TNF alpha therapy**

A few cases of arterial ischemic complications have been reported as a complication of anti-TNF alpha therapy (Vannucchi et al., 2011; Cohen et al., 2012).

**Vasculitis**

Systemic and organ specific vasculitis, namely cerebral, has been reported in association with IBD, especially with ulcerative colitis (Sheid and Teich, 2007). However cerebral vasculitis is very rare and only a handful number of cases, small case series and a few non-systematic reviews have been published (Sheid and Teich, 2007, Martin de Carpi et al., 2007). Vasculitis in IBD is immune mediated, via genetic susceptibility and HLA status, T lymphocyte mediated cytoxicity or immune complex deposition (Sheid and Teich, 2007). In another cases IBD is associated with primary vasculities (giant cell arteritis, Wegener, pANCA vasculities) (Jacob et al., 1990; Ronchetto and Pistono, 1993; Gobron et al., 2010) or with other immune diseases (Cogan syndrome, thrombotic thrombocytopenic purpura, and lupus) (Baron et al., 2002; Hisada et al., 2006; Chebli et al., 2000, Ullrich et al., 2009).

The clinical manifestations of cerebral vasculities in IBD are protean and include headache (Holzer et al., 2009), cranial nerve palsies, focal deficits such as hemiparesis, sensory disturbances, aphasia and visual defects, multifocal signs and vigilance or cognitive troubles, isolated or in combination (Sheid and Teich., 2007). The onset can be acute or
subacute. Presentation as a single stroke syndrome is infrequent. Levels of non specific inflammatory markers such as ESR or CRP may be elevated. Cerebrospinal fluid examination may reveal increased proteins or a mild pleiocytosis. Magnetic resonance imaging of the brain rarely shows large territorial infarcts. Acute lesions may be detected on DWI. The most common findings are deep white matter or periventricular white matter lesions, detectable in FLAIR or T2 sequences (Sheid and Teich, 2007). These lesions are not specific and per se do not allow a definite diagnosis of vasculitis, which relies on the demonstration of inflammation on a vessel wall. In several cases reported in the literature no imaging or biopsy of the vessels was obtained and therefore the diagnosis of vasculitis is only probable. Intra-arterial, MR (Schluter et al., 2004) or CT angiography can reveal multiples arterial stenosis or other aspects suggestive of vasculitis, but many of them can also be seen in non inflammatory vasculopathies and in the reversible cerebral vasoconstriction syndrome, in which the arterial stenosis usually regress in a follow up angiography performed 6-8 weeks later. Moreover angiography can be normal in vasculitis affecting only small arteries. In large artery vasculitis (Takayasu and giant cell arteritis), the temporal superficial, the carotid and the axillary arteries are accessible to ultrasound which may demonstrate inflammatory “halos”. Recently, appropriate MR sequences were reported to depict wall inflammation in medium size intracerebral vessels, such as the proximal segments of the middle cerebral artery (ref).

In a few cases of vasculitis associated with IBD, namely UC, necropsy of brain biopsy was obtained. In 3 cases necrotizing vasculitis was found (Glotzer et al., 1964; Nelson et al., 1986, Carmona et al., 2000), although in one of them hemorrhagic acute disseminated encephalomyelitis could
not be ruled out (Glotzer et al., 1964). In other cases only a lymphocyte infiltrate was found (Kraus et al., 1996).

Although the outcome is generally favorable, a few cases were rapidly fatal. The majority improved with steroids, but in some patients symptoms developed while they were already on steroids. In these patients cyclosporine, plasma exchange and more recently biologic agents (Ullrich et al., 2009) were used with variable success.

Cerebral venous thrombosis

Thrombosis of the dural sinus and cerebral veins are at least as frequent as arterial stroke in IBD. They appear to be more common in ulcerative colitis than in Crohn’s disease, but in some series the opposite was found (Cognat et al., 2011). Cognat and co-workers (Cognat et al., 2011) recently published eight cases from two centers in Paris and reviewed 49 other cerebral venous thrombosis associated with IBD confirmed by MR. Other cases not included in this review have been published (Milandre et al., 1992; Lossos et al., 1995; Papi et al., 1995; Barclay et al., 2010; Nudelman et al., 2010; Casella et al., 2011; Kothur K et al., 2012). The publications of Milandre et al (1992), Nudelman et al (2010) and Casella et al (2011) also provide a review of previous reports. When compared to patients with cerebral venous thrombosis with other causes, patients with IBD related cerebral venous thrombosis are younger and more often males.

The clinical presentation consisting of headaches, focal signs, seizures or encephalopathy and the site of the venous occlusions are similar to the usual cerebral venous thrombosis. They can occur from 2 months to 17 years after the first attack of IBD. Occasionally, the diagnosis of IBD is established only when cerebral venous thrombosis occur (Cognat et al.,
Although IBD may be asymptomatic when the venous thrombosis occurs, almost all patients had biological markers of inflammation, such as elevated leukocyte count, CRP or ESR.

When concomitant causes of cerebral venous thrombosis are systematically searched for, the majority had other risk factors such as oral contraceptives, severe iron deficiency anemia, anti-TNF-alpha treatment, thrombocytosis, hyperhomocysteinemia, folate and B12 deficiencies, infection, lupus anticoagulant and inherited thrombophilia (Milandre et al., 1992; Papi et al., 1995; Nudelman et al., 2010; Cognat et al., 2011; Casella et al., 2011).

Despite the potential risk of intestinal bleeding, treatment of acute cerebral venous thrombosis with full dose IV heparin or low molecular weight is effective and safe (Tsujikawa et al., 2000; Cognat et al., 2011). Endovascular thrombolysis was tried in a few cases, with favorable and safe outcome (Philips et al., 1999; Kothur et al., 2012). The prognosis is usually good, but a few cases were fatal (Cognat et al., 2011).
Selected references


Cancer

Epidemiology

Cancer is a known cause of stroke, both arterial and venous, ischemic or hemorrhagic. Strokes can be found in autopsy in up to 15% of patients with malignancies. Recent cohort and case-control studies confirmed an increased risk of stroke in patients with gastric cancer (HR 1.1) (Kuan AS et al, 2015), lung, pancreas, breast and colorectal cancer (Navi BB et al, 2015). Such risk appears to be higher in the first 3 months after cancer diagnosis. Cancer can also be a cause of stroke in the young adult (Aarnio K et al, 2015). As expected patients with stroke and cancer have a poorer prognosis and higher mortality Taccone FS et al, 2008; Aarnio K et al, 2015; Kneihsl M et al, 2016). The survival prognosis is worse in those with cryptogenic stroke (Navi BB et al, Stroke 2014)

Stroke can also be the initial presentation of systemic cancer. The % of cancers identified after admission for a first-ever ischemic stroke varies in recent studies from 0.8 (Taccone FS et al, 2008) to 4.3% (Selvik HA et al, 2015). In a cohort of 3247 cancer free patients with non-disabling stroke who were followed for two years the incidence of new cancer was 0.15, 0.80, 1.2 and 2.0 /100 patients at 1,6 12 and 24 months respectively. These figures were higher than in the general population at 12 and 24 months (SIR 1.2 and 1.4) (Qureshi A et al, 2015). Most of the cancers were located on the skin, followed by prostate, breast, lung and colon. The risk of death and also of recurrent vascular events was higher in patients who developed cancer. In the Bergen study (Selvik HA et al, 2015) the median time from stroke onset to cancer diagnosis was 14.0 months and 41.8% patients were diagnosed within 1 year, 13 (23.6%) within 6 months. The 7 most common cancer types were lung cancer (19.0%), prostate cancer
(15.9%), colorectal cancer (11.1%), breast cancer (11.1%), gynecological cancer (7.9%), lymphoma (6.3%) and metastatic cancer of unknown primary site (6.3%).

**Mechanisms of stroke associated with cancer**

Cancer can be associated with stroke through several mechanisms namely:

1. Cancer hypercoagulability
   a. Platelets
   b. Coagulation
   c. Endothelium
2. Disseminated intravascular coagulopathy
3. Marantic endocarditis
4. Paradoxical embolism
5. Atrial fibrillation
6. Tumor seeding with embolism or mucin-secreting tumors
7. Infections
8. Traditional vascular risk factors
9. Compression and invasion of vessels
10. Intravascular neoplasm
11. Paraneoplastic
12. Cancer therapy
   a. Radiation
   b. Chemotherapy
Hemorrhagic stroke

1. Coagulopathy
   a. Leukemias
   b. Bone marrow invasion/failure
   c. Hepatic invasion/failure
2. Disseminated intravascular coagulopathy
3. Intracranial tumor necrosis and hemorrhage
4. Invasion of vessels
5. Cancer therapy

Recent studies emphasized the role of atrial fibrillation in causing stroke in cancer patients. Atrial fibrillation can occur after cancer surgery, but the association is not limited to the perioperative period. In the CHLC Lisbon Hospital registry of 109 patients with both cancer and stroke, 80% were hypertensive and 1/3 were on atrial fibrillation. Atrial fibrillation can occur after cancer surgery, but the association is not limited to the perioperative period. In the REGARDS study (O’Neal WT et al, 2015) including 15,428 participants, subjects with cancer were also more likely to have atrial fibrillation OR 1.19)

Type of ischemic stroke

In the majority of the studies no differences were found in TOAST stroke subtypes between patients with and without occult neoplasm (Cocho D et al, 2015; Aarnio K et al, 2015). Identification of marantie endocarditis is difficult because of the low yield of echocardiography (TT and TE) (Merkler AE et al, 2015)

Cancer patients with high D-dimers and no competing embolic or nonembolic etiologies have a predominant DWI pattern, consisting of

Predictors of occult cancer in patients with ischemic stroke

Besides local symptoms and signs directly due to the malignancy, cancer can produce several simple laboratory abnormalities (many of which are non-specific), which may indicate the need for further investigation, including neoplasm screening:

1. Blood cell count
   a. Anemia
   b. Out of range, low or high platelet counts
   c. Granulocytosis

2. Acute phase reactants, inflammatory markers
   a. High fibrinogen
   b. High ESR
   c. High PCR

3. Coagulation parameters
   a. High INR
   b. High D-Dimers
   c. High fibrin degradation products

4. High Lactic dehydrogenase

In recent series (Selvik HA, 2015) higher age, and smoking were associated with the diagnosis of cancer after stroke

Screening for occult neoplasm in arterial stroke

Routine screening for neoplasm in cryptogenic stroke and in ESUS is not cost-effective and is not recommended. Screening should be
individualized and based on clinical, laboratorial and imaging hints (see previous section)

**Screening for occult neoplasm in patients with unprovoked cerebral venous thrombosis (CVT)**

For unprovoked venous thromboembolism (VTE) prevalence of occult neoplasm (ON) is low (3.9%). ON prevalence is higher in recurrent events, smokers and aged > 59 years (Ihaddadene R et al, 2016). Routine screening with CT of the abdomen and pelvis did not provide a clinical significant benefit over limited ON screening (blood testing, chest Rx, screening for breast, cervical and prostate cancer) (Carrier M et al, 2015). A strategy including limited screening and a (18)F-FDG PET/CT was not associated with a higher rate of cancer diagnosis. In follow up, the risk of subsequent cancer was however low in patients who had a normal PET/CT (Robin P et al, 2016)

The frequency of occult neoplasm in patients with CVT appears to be low, although no prospective studies have been performed so far. A systematic review identified 11 studies reported on the frequency of cancer or hematological malignancies, including a total of 1780 patients. Cancer (including hematological malignancies) as predisposing risk factors was identifies in 99 patients (5.6%). None of these studies reported a systematic screening for occult cancer. There is also no data the influence of a systematic screening for occult malignancies in CVT patients on outcome (ESO CVT Guidelines, Eur J Stroke, in publication). The ESO CVT guidelines do not recommend routine screening for ON in patients with CVT, unprovoked or not
Treatment of acute ischemic stroke in patients with cancer

In the 2009-10 Nationwide Inpatient Sample of the 32,576 strokes treated with thrombolysis, cancer associated strokes had higher co-morbidity indexes overall but fewer vascular risk factors. There were no differences in in-hospital mortality and rates of home discharge or intracerebral hemorrhage (Murthy SB et al, 2013). A meta-analysis of six studies reporting on outcomes in 157,776 patients, of whom 1339 with malignancy, found no excess of intracerebral hemorrhage in cancer stroke patients treated with IV rtPA.
Selected references


Genetic diseases

Sickle-cell disease

Sickle cell disease is an important cause of stroke in children and young adults of African descent. Stroke can be ischemic or hemorrhagic, arterial and venous. Diagnosis of sickle-cell disease should be ruled out in all stroke patients of African descent by screening for hemoglobin S (screening for falciform cells, electrophoresis of hemoglobin S and eventually genetic confirmation: Val-Glu in np polipeptide B of Hg)

The Cooperative Study of Sickle Cell Disease (CSSCD), observing a cohort of more than 4000 adults and children found an overall stroke prevalence of 3.75 %. Stroke incidence varies significantly between the different sickle cell genotypes (SS>CS>AS), with the highest frequency in those with the homozygous hemoglobin (Hgb) SS genotype. Stroke incidence further varies by age and type of stroke. The CSSCD study showed the highest incidence of ischemic stroke in Hgb SS patients aged 2 to 9 years, with a second peak after the age of 30 years. In contrast, the incidence of hemorrhagic stroke peaked at ages 20 to 29 years and very rarely occurred in children or adults outside of this age range. Silent brain infarcts are also frequent and contribute to cognitive defects and decline. Silent infarcts are also a risk factor for stroke, as are prior transient ischemic attacks (TIA), low steady-state Hgb, recent acute chest syndrome, elevated systolic blood pressure, and abnormally elevated mean cerebral arterial flow velocities on transcranial Doppler (TCD). Risk factors for hemorrhagic stroke include low steady-state Hgb and high leukocyte count as well as association with history of hypertension, recent corticosteroid or NSAID use and recent transfusion (Lawrence C & Webb J, 2016).
Ischemic strokes in sickle-cell disease can be due to vasculopathy, which may in a few cases progress to a Moya-Moya pattern, cardioembolism or other causes. In a recent series of first ischemic stroke in sickle-cell disease, mean age was 7 and 32 in children and adults (29 cases) respectively. Vasculopathy (12 cases) was less commonly the cause in adults than in children. Other frequent cause was cardioembolism (7) (Calvet D et al stroke 2015)

In the acute phase laboratory assessment should include a complete blood count with reticulocyte count, blood typing, screening and a quantitative Hgb S measurement in preparation for potential simple and/or exchange transfusion. Imaging assessment should follow the current guidelines for acute stroke imaging, but non-invasive imaging or intracranial arteries and dural sinus/cerebral veins is advisable, due to the high frequency of intracranial arteriopathy and the possibility of CVT. A search for concomitant causes of stroke, namely cardiac (e.g. cardiac ischemia, paradoxical embolism) and large artery atheroma or dissection must be pursued.

While the benefit of red blood cell (RBC) transfusion in primary and secondary stroke prevention has been well demonstrated, the role of transfusions in acute stroke management is less clear. By decreasing Hgb S concentration and maximizing oxygen delivery through non-sickle RBCs, transfusion is thought to decrease vaso-occlusion, thus improving tissue perfusion and decreasing ischemic damage during stroke. A target goal post-transfusion hemoglobin of 10 g/dL, a Hgb S percentage of less than 30 % is recommended in the setting of acute stroke. For most patients with SCD, simple transfusion to the goal hemoglobin does not allow for a large enough packed RBC volume to sufficiently decrease the Hgb S
percentage, so exchange transfusion is recommended (Lawrence C & Webb J, 2016, Kassim et al, 2015)

Concerning the safety of thrombolysis in acute ischemic stroke in adult patients with sickle cell disease, a recent large case-control study concluded that thrombolysis is safe. From 2,016,652 stroke patients admitted to Get With The Guidelines-Stroke sites in the United States, 832 SCD and 3328 non-SCD controls with no differences in admission National Institutes of Health Stroke Scale or blood pressure were identified. Neither the fraction receiving thrombolytic therapy (8.2% for SCD versus 9.4% non-SCD) nor symptomatic intracranial hemorrhage (4.9% of SCD versus 3.2% non-SCD; P=0.4502) was different. There was no difference in a prespecified set of outcome measures for those with SCD compared with controls (Adams RJ et al, Stroke 2017). Coexistent SCD had no significant impact on the safety or outcome of thrombolytic therapy in acute ischemic stroke. Although the sample size is relatively small, this data suggest that adults with SCD and acute ischemic stroke should be treated with thrombolysis, if they otherwise qualify.

Concerning secondary prevention the main treatment to prevent ischaemic crisis is periodical TCD and repeated blood transfusions, with the target to decrease the levels of Hg S to less than 30%. Based on the results of the STOP trial (Lee MT et al, 2006), which showed a risk reduction from 10 to less 1%, repeated blood transfusions are recommended both in the primary prevention (I, A) and secondary prevention (I, B) of thrombotic events. The STOP II trial showed an increased risk of stroke if repeated transfusion were stopped after 30 months (Adams RJ, Brambilla D, 2005). This treatment policy should continue for at least 5 years or until the patient is 8 years old. The SIT
trial demonstrated a reduction from 14 to 6% new silent infarcts with repeated blood transfusions (DeBaun MR et al, 2014).

Other preventive measures include detection and treatment of hypertension and other risk vascular risk factors (IIa), prevention of iron overload and antiplatelets (IIa, B). The DOVE trial failed to demonstrate the efficacy of prasugrel in sickle cell disease (Heeney MM et al, 2016). Hydroxyurea and phlebotomy were evaluated in patients on transfusion/chelation therapy at risk of iron overload in the SWiITCH trial, which was closed for futility (Ware RE et al, 2011). More strokes occurred in the hydroxyurea/phlebotomy arm (10% vs. 0). However in the TWiITCH trial which enrolled children with abnormal TCD flow velocities (> 200 cm/s) but no severe vasculopathy on MRA, who had already 1 year of repeated transfusions, hydroxyurea was not inferior to repeated transfusions on preventing new infarcts, silent or symptomatic, and worsened vasculopathy (Ware RE et al, Lancet 2016). Hydroxyurea can be used if transfusion is not available/practical or if there is no evidence of vasculopathy. Bone marrow transplantation (IIb, C) is a promising intervention, which in the future may become the first option for secondary prevention of stroke and other ischemic events in patients with sickle cell disease.
References


Fabry's disease

Fabry disease (FD) is an X-linked lysosomal storage disorder characterized by deficient activity of α-galactosidase A (α-Gal A) due to mutations of the GLA gene (>800 described). The deficient α-Gal A activity leads to pathological accumulation of predominantly globotriaosylceramide into vascular endothelia, neural (peripheral and central), and renal cells, as well as cardiomyocytes. Early disease manifestations consist of peripheral nervous system (acroparesthesias, hypohidrosis) and skin (angiokeratoma) manifestations, whereas kidney, cardiac, and central nervous system complications develop in later life.

The risk of stroke is increased in FD, more so in man. Several cerebrovascular findings have been reported to be associated with FD. These include combination of large vessel and small vessel strokes, extensive white matter changes, cerebral infarctions in regions supplied by the posterior circulation, with associated dilatation of the vertebrobasilar vessels including extensive dolichoectasia, and high signal intensity of the pulvinar thalami on T1-weighted MRI.

In the prospective Stroke in Young Fabry Patients (SIFAP 1; Rolfs A et al, 2013) study only 0.9% of the young adult stroke patients were diagnosed FD. This low % was also found in other prospective studies. In the SIFAP study there were no differences in any MRI characteristic between stroke patients with and without FB, leading the authors to conclude that MR findings cannot be used to select patients to screen for FB (Fazekas F et al, Stroke, 2015).
Strokes are frequent and a major cause of disability in FD (Kolodny E et al, Stroke, 2015). The majority of strokes occur between the age of 20 and 50. Ischemic stroke predominate but hemorrhagic strokes can also occur. Silent strokes and white matter lesions are also frequent. Stroke can be due to small vessel disease, large intra and extracranial artery disease and cardioembolism (Viana-Baptista M. 2012).

The confirmation of the diagnosis of Fabry’s disease relies on genetic testing, although analyses of dried blood spots and whole blood samples are practical for screening for enzyme activity in male patients (but not in females) All suspected cases of FD must be confirmed using the gold standard mutation analysis, because there are polymorphisms present resulting in slightly reduced enzyme activity but no disease as the enzyme produced is fully functional. An example is the D313Y polymorphism which results in low enzyme activity but no apparent disease (pseudodeficiency) (Waldek S, 2017). More than 600 different mutations are known in the GLA gene. Mutations are not limited to active site residues, but include those predicting changes related to stability, and indirectly, to catalytic activity. Most mutations are “private”, i.e. individual or family specific, but few occur with sufficient frequency to permit genotype-phenotype correlation. Even within families, phenotypic heterogeneity is often present, suggesting the possibility of gene-environment interaction. The risk of stroke in Fabry’s disease seems, therefore, to be related to residual enzyme activity as determined by GLA mutations, as well as traditional vascular risk factors and other genetic and epigenetic factors not yet characterized fully (Kolodny E et al, Stroke 2015).

The etiological treatment of Fabry’s disease is enzyme replacement therapy with agalsidase 1mg/kg or 0.2 mg/kg EOW. Trials showed a
reduction in death and an improvement on several surrogate (plasma levels of GL-3a, accumulation in skin, kidney and heart) and renal, cardiac and peripheral nervous system clinical outcomes and Quality of Life. However, agalsidase does not change the risk of stroke/TIA or prevent the occurrence of white matter lesions and is of doubtful benefit in advanced disease (Rombach SM et al, 2013; Wyatt K et al, 2012).
Selected references


**CADASIL and other genetic small vessel arteriopathies**

Genetic forms of small vessel arteriopathies (e.g. CADASIL, CARASIL, RVCL - retinal vasculopathy with cerebral leucodystrophy, COL4A1 and A2 disorders) (Choi JC, 2015; Tan RYY, Markus HS 2015; Søndergaard CB et al, 2017) are an exceedingly rare cause of stroke, even in children and young adults. Clues to suspect the diagnosis of such entities include, besides a positive familiar history of stroke in young ages, multiple strokes, evidence of extensive white matter damage, which in CADASIL typically extend to the external capsule and temporal lobe, a pattern of white matter lesion distribution almost never seen in sporadic cerebral small vessel disease. Other clinical hints are migraine, depression and cognitive impairment in CADASIL and cerebral aneurysms, porencephaly, retinal tortuositites, kidney disease and cramps in COL4A disorders.

The information on how to manage acute stroke and prevent further strokes in these entities is scarce. In CADASIL it is not known if blood pressure control and aspirin prevent further strokes or the progression of white matter lesions. The safety (risk of intracerebral bleeding) of antiplatelet drugs in these patients is also questionable, because there are several reports of intracerebral hemorrhages in CADASIL patients (Oh JH et al, 2008) and several of these patients were on antiplatelet drugs (Khan et al 2015). There is one report of safe use of rtPA in a patient with CADASIL, who showed clinical improvement and no intracerebral hemorrhage (Khan MT et al, 2016)
Selected references

- Choi JC. Genetics of small vessel disease. J Stroke 2015; 17:7-16
MELAS

MELAS, a mitochondrial disease featuring myopathy, encephalopathy, lactic acidosis, and stroke-like episodes due to a point mutation in the mitochondrial DNA (in 80% of the cases m.3243A>G in the MTTL1 gene) can not only mimic stroke and rarely can also cause stroke, through a vasculopathy or cardioembolism. Stroke-like episodes (SLEs) are recurrent neurologic deficits resembling vasoocclusive strokes. However, SLEs are not restricted to vascular territories and have a predilection for the occipital and posterior parietal and temporal cortices, may evolve subacutely over hours to days, and have greater potential for reversibility. Their pathophysiology is incompletely understood. Current literature suggests a combination of neuronal mitochondrial energy failure and cerebrovascular angiopathy with dysregulated perfusion. Energy deficiency can stimulate mitochondrial proliferation in the smooth muscle and endothelial cells of small blood vessels leading to angiopathy and impaired blood perfusion in the microvasculature of several organs. Pathologic studies have provided evidence for a small vessel angiopathy: capillary proliferation and increased numbers of abnormal mitochondria in both endothelial and smooth muscle cells of the small arterioles of the brain. SLEs manifest with vasogenic oedema (DWI and ADC hyperintensity) or partial cytotoxic oedema (DWI hyperintensity, ADC hypointensity) in the acute and subacute stage, and with gyriform T1-hyperintensity (cortical necrosis) in the chronic stage.

In the sipaf1 study previously unidentified mitochondrial DNA mutations (m.3243A>G in the MTTL1 gene) 4 patients out of 3291 stroke patients (Tatlisumak T et al, 2016), but not proven to be the cause of stroke in these 4 patients. Clinical features indicating possible MELAS include
familial history with maternal inheritance, migraine, seizures, myopathy, deafness, short stature, and cardiomyopathy.

In one case report SLE were rapidly reversed with high-doses of L-arginine (Siqquid I et al, Neurology 2015). Anti-epileptics not toxic to the mitochondria (levetiracetan) and dexamethasone were used in other cases. Several drugs have been tried to prevent recurrent stroke like episodes and new infarcts, including coenzyme Q10, L-carnitine, L-arginine, citrulline, idebenone, vitamins (C, E and B) and dichloracetate, all with inconclusive results. Allogenic stem cell transplant and mitochondrial replacement are new promising therapeutic techniques (El-Hattab AW et al, 2015; Fryer RH et al, 2016; Halter JP et al, 2015; Falk MJ et al, 2016).
Selected references


**Antiphospholipid syndrome (APS)**

The APS (Sapporo criteria, 2006) is present if at least one of the following clinical criteria and one of the laboratorial criteria are met:

**Clinical criteria**

- Vascular thrombosis: venous, arterial and/or small vessel thrombosis in any organ
- Pregnancy morbidity: unexplained fetal death, premature birth or spontaneous abortion

**Laboratorial criteria**

- Positive Lupus anticoagulant (LA)
- Medium or high titer (IgM or IgG) of anticardiolipin (aCL) or anti-β2 glicoprotein-I antibodies (anti-β2GPI)
- At least 2x, 12 weeks apart

APS is a risk factor for future thrombotic events, which will occur in around in 17% of APS patients within 5 years. The risk is higher in those with more than one laboratorial criteria present (any combination). Antiphospholipid antibodies are present in about 17 to 22% of young adult TIA/stroke patients. The presence of these antibodies seems to confer a fivefold higher risk of recurrence (Sciascia S et al, 2015). The studies investigating this problem have important methodological limitations: only 11% tested the 3 aPL antibodies, 1/3 accepted low titters aPL, only 1/5 performed testing 2 x, ½ studies were retrospective and there is also variability of test reproducibility.
Stroke and APS can be associated in three scenarios: 1) a patient with known APS suffers a stroke, 2) stroke is the 1st manifestation of APS confirmed by repeated laboratorial tests 12 weeks apart, 3) in a stroke patient laboratorial tests for APS are positive once but not confirmed in repeated testing. APS can cause both ischemic stroke and cerebral venous thrombosis. Ischemic stroke mechanisms include not only coagulopathy but also small vessel disease, large extracranial and intracranial arterial stenosis and Libman-Sacks Endocarditis. Clinical clues for the diagnosis of APS include previous thrombotic event, arterial or venous in any territory, fetal death, premature birth or spontaneous miscarriages.

A systematic review and meta-analysis on anticoagulation in patients with AP antibodies (Ruiz-Irastorza G et al, 2007), showed that patients with stroke and a single positive testing had no increased risk of recurrence, and that risk was successively higher in those fulfilling the criteria for APS and past venous thrombosis, an arterial thrombosis and recurrent thrombotic events. A few clinical trials compared anticoagulation aiming at different INR levels and anticoagulation with heparin to prevent thrombotic events in APS patients. In two studies which included APS patients with previous thrombosis, high intensity (INR 3-4) was not superior to moderate intensity (INR 2-3) oral anticoagulation. In the APPS study, which included stroke patients with positive lupus anticoagulant or anticardiolipin antibodies (on at least one occasion), no difference was found between oral anticoagulation and antiplatelet therapy (Crowther MA et al, 2003; Levine SR et al, 2004; Finazzi G et al, 2005). Currently, AHA/ASA Guidelines state that: 1) for patients with ischaemic stroke or TIA who meet the criteria for the APS, anticoagulant therapy might be considered (I;B); 2) for patients with ischaemic stroke or TIA who have an antiphospholipid antibody but who do not fulfill the criteria for
antiphospholipid antibody syndrome, antiplatelet therapy is recommended (I; B); 3) for patients with ischaemic stroke or TIA who meet the criteria for the antiphospholipid antibody syndrome but in whom anticoagulation is not begun, antiplatelet therapy is indicated (I; A). There is limited experience with the use of direct anticoagulants in the secondary prevention of thrombotic events in patients with APS and previous stroke. Most case series, but not all (Schaefer JK et al, 2014) report encouraging results with DOACS. DOACs seem to provide convenient, effective and safe prevention of thrombotic events in APS patients, but RCTs are needed, such as the ongoing RASP and TRAPS (testing rivaroxaban vs. warfarin) and ASTRO-APS (apixaban vs. warfarin), before their routine use can be recommended.
Selected references


• Schaefer JK, McBane RD, Black DF, Williams LN, Moder KG, Wysokinski WE. Failure of dabigatran and rivaroxaban to prevent thromboembolism in antiphospholipid syndrome: a case series of three patients. Thromb Haemost. 2014;112:947-50
Rheumatic diseases and primary vasculitis

A recent systematic review (1980-2014) and meta-analysis showed that the risk of any stroke is higher in most rheumatic diseases than in the general population, particularly <50 years. Rheumatoid arthritis and systemic lupus erythematosus increase ischemic and hemorrhagic stroke risk by 60% to 100% relative to the general population (Wiseman SJ et al, Stroke. 2016).

Because for most of the rheumatic diseases 1) the reported stroke cases are scarce, 2) the vast majority of stroke cases occur after the diagnosis of the primary disease and only exceptionally as the presenting feature, 3) there are no case-control studies to define the risk of stroke or to identify stroke features characteristics of each disease, 4) infarcts can be identified by neuroimaging, but they are often silent or the clinical presentation is that of an encephalopathy and not of a clinical stroke syndrome, we decided to limit our review to lupus and giant cell arteritis

Selected references

Lupus

The above mentioned systematic review showed an excess risk of stroke in systemic lupus erythematosus (SLE) [ischemic: OR, 2.11 (1.66-2.67); hemorrhagic: OR, 1.82 (1.07-3.09)] over the general population. Another meta-analysis including only population based studies showed that the pooled RR for overall stroke was 2.53 (95% CI 1.96 to 3.26), ischaemic stroke 2.10 (95% CI 1.68 to 2.62), intracerebral haemorrhage 2.72 (95% CI 2.15 to 3.44) and subarachnoid haemorrhage 3.85 (95% CI 3.20 to 4.64). Relative risk of stroke was highest among individuals younger than 50 years of age (Holmqvist M et al, 2015). In a large cooperative multicenter Spanish study enrolling 3658 SLE patients, 374 (10.9%) patients suffered at least a vascular event. In 269 (7.4%) patients, these events occurred after SLE diagnosis (86.2% women, median age 54.9 years, and SLE duration of 212.0 months). Strokes (5.7%) were the most frequent vascular events. Multivariate analysis identified age (odds ratio [95% confidence interval], 1.03 [1.02-1.04]), hypertension (1.71 [1.20-2.44]), smoking (1.48 [1.06-2.07]), diabetes (2.2 [1.32-3.74]), dyslipidemia (2.18 [1.54-3.09]), neurolupus (2.42 [1.56-3.75]), valvulopathy (2.44 [1.34-4.26]), serositis (1.54 [1.09-2.18]), antiphospholipid antibodies (1.57 [1.13-2.17]), low complement (1.81 [1.12-2.93]), and azathioprine (1.47[1.04-2.07]) as risk factors for CV events (Fernandez-Nebro A et al, 2015). A cohort study revealed that compared to non-CLE subjects, the risk of CVAs (smoking-adjusted hazard ratio [HR] 2.97 [95% confidence interval (95% CI) 1.13-7.78]) was also increased in patients with cutaneous lupus erythematosus (Singh AG et al, 2016).
Stroke is in fact a frequent (3-20%) complication of SLE. It may be the initial presentation, but in general stroke occurs in average 4 years after the diagnosis of SLE and usually in active SLE.

The ACR 1997 revised criteria for the diagnosis of SLE state that SLE can be diagnosed if any 4 or more of the following are present serially or simultaneously, during any interval:

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis (e.g. pericarditis)
- Renal disorder (e.g. cellular casts)
- Neurological disorder (e.g. psychosis, dementia)
- Hematological disorder
  - Leukopenia (< 4000)
  - Lymphopenia (1500)
  - Thrombocytopenia (<100 000)
- Immunological disorder
  - Anti-Sm
  - APL antibodies
  - Lupus anticoagulant
  - + VDRL
- Antinuclear antibody (ANA)
Therefore, the presence of any of these clinical findings or laboratorial abnormal results, particularly in a young adult stroke patient, may raise the possibility of SLE. Initially, the full criteria for SLE may not be met. Patients however deserve a careful follow up and repeated laboratorial testing, because the diagnosis of SLE usually “builds up” with time.

All types of strokes can occur (TIA, ischemic stroke - the most frequent -, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis). Ischemic stroke in SLE has heterogeneous mechanisms and a poor short-term outcome. Chronic inflammation leads to accelerated atherosclerosis and endothelial dysfunction, causing strokes through large extra or intracranial vessel disease. For the same reasons and also because of hypertension, stroke related to small vessel disease also occur. Cardioembolic strokes can be associated with AF, ischemic heart disease and with Libman-Sacks endocarditis, which affect 1 out of 10 patients with SLE and more often the mitral valve. Libman-Sacks endocarditis is influenced by the duration and severity of SLE, APS and the levels of anticardiolipin antibodies. An important contributing factor for stroke in SLE is the prothrombotic coagulopathy due to APS. Dissection is occasionally seen. Vasculitis is very rare. In fact in most of post-mortem examinations the most common finding is a non-inflammatory arteriopathy with endothelial proliferation, intima fibrosis and perivascular lymphocytes.

Concerning intracerebral hemorrhage, hypertension, low platelet counts and uremia are contributing factors.

Management of stroke in the context of SLE should follow the general guidelines of acute stroke care and secondary prevention, plus the
treatment of SLE as recommended by a rheumatologist/internist (NSAIDs, steroids, antimalarial, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, immunoglobulin, plasmapheresis, rituximab, biological agents) depending on the staging and severity of the disease (see EULAR 2008 recommendations). SLE is not a contraindication for IV thrombolysis. Special attention should be placed on risk factors control and triple pharmacological secondary prevention (antiplatelet+ statin+ anti-hypertensive). Concerning anticoagulation only stroke patients with SLE and APS or a high risk cardioembolic condition should be anticoagulated.
Selected references


Giant cell arteritis

Large vessel arteritis are vasculitis which affect the aorta and the largest branches directed towards major body regions (to extremities and the head and neck and its main branches and divisions, including the cervical extracranial cerebral arteries. Takayasu arteritis (TA) occurs before the age of 50 and involves mainly the aorta, while giant cell arteritis (GCA) starts after the age of 50. GCA is much more frequent than TA (annual incidence 32-290 million/year vs. 0.4-2 million/year).

Takayasu disease is a large vessel (aorta and its branches) granulomatous giant-cell panarteritis, leading to occlusions and aneurysm formation. It affects mainly females of Asian origin, and is extremely rare in Caucasians.

The American College of Rheumatology Classification Criteria establishes that for the diagnosis Takayasu arteritis (TA) (pulseless disease) at least 3 of the following 6 criteria should be present:

1. Onset <40 years
2. Claudication of an extremity
3. Decreased brachial artery pulse
4. >10 mm Hg difference in SBP between arms
5. Bruit over the subclavian arteries or aorta
6. Arteriographic evidence of stenosis/occlusion of the aorta, its major branches or large arteries in proximal upper or lower limbs

PET can demonstrate the inflammation in the aorta and other affects vessels.
Neurological manifestations are present in more than half of the patients during the course of the disease, among which stroke. Stroke/TIA can also be a less typical initial presentation of TA.

A recent systematic review (Duarte MM et al, 2016) included twenty-one studies (16 studies were of cohort design) (3269 patients). The pooled stroke/TIA prevalence rate estimate was high: 15.8% (95% CI: 10.7%-22.6%). There was scarce information on the type of stroke, the characteristics of the affected individuals, and stroke-associated morbidity and mortality.

Giant cell arteritis (GCA) is a granulomatous large vessel vasculitis that usually affects the aorta and/or its major branches, especially the branches of the carotid arteries. GCA is the most common vasculitis in persons over 50 years of age, with a peak incidence between 70 and 80 years. Histopathological lesions are observed in all layers of the artery and lead to segmental and focal panarteritis with a polymorphic cell infiltrate that includes T cells, macrophages and multinucleated giant cells, a fragmented internal elastic lamina and intimal hyperplasia and sometimes granulomas. GCA is associated with polymyalgia rheumatic (PMR). In both PMR and GCA, systemic symptoms (fever, asthenia, anorexia and weight loss) and high ESR and CRP are the consequence of chronic inflammation. The typical features of GCA such as headache, scalp tenderness, jaw claudication, visual loss, scalp or tongue necrosis and also TIA or stroke result from the arterial topography of the inflammatory process, which involves common and external carotid scarring and narrowing and eventually occlusion or severe stenosis. The most frequent (30%) and severe ischemic complication of untreated GCA is visual loss caused by acute ischaemia of the optic nerve (AION), leading to permanent loss of vision in 15% of cases. Less often, patients with GCA may also experience
a stroke in the carotid or in the vertebrobasilar territories (−3%). The latter is usually more severely involved than the carotid system. Ischemic complications and strokes usually occur in the period of active disease and mainly affect the vertebrobasilar territory.

In a recent cohort and nested case control study using the UK Clinical Practice Research Datalink (Li L et al, 2017) 9778 newly diagnosed GCA patients in 1990-2014 were identified, and up to 10 non-vasculitis patients randomly matched to each case on age, sex, practice and years of history before cohort entry. Patients with GCA were more likely to have a history of vascular diseases and other comorbidities except myocardial infarction, type 2 diabetes, obesity and cancer, compared with non-vasculitis patients. Patients with GCA had increased risks for all types of incident vascular disease compared with non-vasculitis patients: adjusted hazard ratios were 1.57 (95% CI: 1.36, 1.82) for myocardial infarction, 1.41 (95% CI: 1.29, 1.55) for stroke, 1.75 (95% CI: 1.49, 2.06) for peripheral vascular disease, 1.98 (95% CI: 1.50, 2.62) for aortic aneurysm and 2.03 (95% CI: 1.77, 2.33) for venous thromboembolism.

A recent population-based stroke registry (Samson M et al, 2015) identified all cases of GCA with a biopsy proven diagnosis between 2001 and 2012. Among 57 retrieved cases, 4 (7%) experienced a stroke. Three were men and all had ≥2 vascular risk factors and were ≥80 years. The stroke was vertebrobasilar for ¾ patients and undetermined for the remaining one. The incidence rate of GCA-related stroke in patients ≥50 years was 0.76/100 000/year (95% CI 0 to 2.47), 1.36/100 000/year in men (95% CI 0 to 3.63) and 0.33/100 000/year (95% CI 0 to 1.45) in women. A case control study comparing GCA patients with and without stroke reported that stroke occurred at GCA diagnosis in 29 patients (73%),
whereas it occurred after diagnosis in 11 patients. Vertebrobasilar territory was involved in 29 patients (73%). Seven patients died within a few hours or days following stroke. Stroke, especially in the vertebrobasilar territory, is more likely to occur in patients with GCA who experience recent ophthalmic ischemic symptoms and who exhibit low inflammatory variables (de Boysson H et al, 2017)

Clinical hints for the diagnosis of GCA-related stroke essentially are the vertebrobasilar territory, old age, male gender, headache, neck, and shoulder or arm pain, a palpable, hard or tender temporal superficial artery, recent ocular ischemia, very high ESR or PCR.

The diagnosis should be confirmed by temporal superficial artery biopsy, taken on the symptomatic side. A large segment of the artery (5 cm) should be excised and multiple sections carefully examined, because of the segmental involvement of the artery by the vasculitic process. Biopsy should not delay (1 -2 weeks) the treatment with steroids, which can be started 1 -2 weeks before the biopsy. A contralateral biopsy is not routinely indicated. The biopsy can be guided by ultrasound. Ultrasound examination often shows an inflammatory “halo”, which is detectable on the superficial temporal, subclavian and axillary arteries. Ultrasound can also inform on the involvement of the anterior and posterior ocular circulation. PET shows inflammation of the involved arteries and of the aorta.

Prevention of vascular complications relies on the prompt recognition and diagnosis and emergent start of high dose corticosteroid treatment. Pulsed IV methylprednisolone may is an a option in already symptomatic (ocular or brain ischemia) patients. Otherwise patients should be started on 1mg/kg/day of prednisone, for at least a month and then tapered
gradually, aiming at 10-15 mg at 3 months, with reversal of systemic symptoms and normal ESR. In the long range, methotrexate can be used to reduce the dose of corticoids.

In TA patients, in whom the disease may remain active despite steroids, azathioprine, methotrexate, cyclophosphamide and mycophenolate can be tried. However the results of treatment trials with conventional immunosuppressive agents such as methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide have overall been disappointing. TNF-α blockers are ineffective in giant cell arteritis, while observational evidence and a phase 2 randomized trial support the use of tocilizumab in relapsing giant cell arteritis. Observational evidence strongly supports the use of anti-TNF-α agents and tocilizumab in Takayasu patients with relapsing disease. However biological agents are not curative, and relapse remains common (Muratore F et al, 2017)

Arterial reconstruction and bypass grafting may be necessary in up to 70% of patients with Takayasu arteritis to reverse some of the features of the disease, for example renovascular hypertension and hemodynamic stroke. In expert hands, reconstructive surgery has a good outcome, but revision surgery is often needed. Angioplasty and stent insertion have a higher rate of restenosis than surgical reconstruction, but may be appropriate for some patients. Elective procedures should be performed when disease is in remission (Mukhtyar et al, 2009)

In parallel, optimal vascular risk factor control prevention must be conducted and low dose aspirin should be initiated in all patients with GCA. Statins and anticoagulants should only be added if another indication (e.g. high cholesterol, AF) for their use co-exists
Selected references


