A 56-year-old man presented in 1997 with multiple joint pains involving small joints of hands and legs. He was worked up for joint diseases with investigations like rheumatoid factor and antinuclear antibody (ANA) which were negative. He was found to have high uric acid and treated as gout. Repeat examination in a tertiary hospital revealed splenomegaly of 10 cm and this led to hematological investigations. Investigations revealed hemoglobin (Hb) of 18.6 g/dL and hematocrit (HCT) of 58%. The total white blood cells (WBC) count was 40,200 cells.cumm and platelet count was 2,73,000. A bone marrow was done which was cellular, and lacked iron staining. A diagnosis of polycythemia vera (PV) was made.

Learning Points
Hyperuricemia is an important association of PV, and is due to the high cell turnover, especially in patients going into myelofibrosis. However there is no correlation between the bone marrow picture and the degree of hyperuricemia. Other presentations are splenomegaly, aquagenic pruritis, peptic ulceration and hyperviscosity central nervous system (CNS) features.

The ideal way to diagnose PV is by measuring red cell mass. However, surrogate markers of proliferation, such as hemoglobin concentration greater than 16.5 g/dL in females (or HCT above 50%) and hemoglobin concentration greater than 18.5 g/dL (or HCT above 56%) in male patients can be taken as diagnostic.

The hemoglobin need not be high in PV in the following conditions: early PV, less severe disease, or an elevated plasma volume and patients with complications related to PV (e.g. Budd-Chiari syndrome). Hence, these groups may not fulfill the classic polycythemia vera study group (PVSG) criteria for diagnosis.

Being a myeloproliferative disorder PV has increase in all 3 cell lines. This makes the causes of secondary polycythemia unlikely. The lack of iron staining in marrow is typical of PV (90% positive).

Janus kinase 2 (JAK2) mutations are diagnostic in 95-99% of patients with PV involving either exon 14 or 12. However, at the time the patient presented, these tests were not available freely.

Investigation and Treatment
The patient was put on allopurinol with which his joint pains decreased. He was treated with hydroxyurea for PV and massive splenomegaly. He took the medications for 3 months and then discontinued as counts decreased to normal.

Learning Points
Hydroxyurea causes decrease in counts and splenomegaly and our patient’s general sense of well-being returned as spleen size regressed. Resistance to treatment with hydroxyurea is an adverse prognostic factor, with a significantly higher risk of both death and disease transformation.

Investigation
The patient revisited several hospitals after 6 months with dragging sensation in the abdomen due to increasing spleen size and fatigue. In 2005, he was admitted in our hospital with massive splenomegaly and Hb of 8.6 gm/dL, packed cell volume (PCV) of 26.8%, total count (TC) of 3,400 and platelet of 2,73,000. The peripheral smear showed anisopoikilocytosis, tear drop cells, WBCs decreased and adequate platelets. Bone marrow was done which showed coarse reticulin with grade 3 fibrosis suggestive of PV spent state with myelofibrosis.

Learning Points
The factors that decide transformation into myelofibrosis include disease duration, age greater than or equal to 60 years, total white blood cell count more than 15,000/ml. The adverse risk factors for survival at any time after the onset of post-PV myelofibrosis included the following Hb less than 10.0 g/dL, Platelet count less than 1,00,000/ml, White blood cell count more than 30,000/ml. Our patient had all these criteria which might have contributed to his bad prognosis.

Treatment
At this stage, the patient was referred to a higher center, for bone marrow transplantation as it is the definitive treatment for myelofibrosis. Hydroxyurea was stopped and total counts and platelets were falling, and thalidomide at 100 mg/day and prednisolone in tapering doses was started.

Learning Points
Thalidomide has been evaluated as an alternative and found to be useful in 20–40% of patients, with reduction in splenic size, improvements in Hb concentration, WBC, and platelet counts, as well as transfusion independence. However, few patients are able to tolerate doses higher than 400 mg/day, because of side effects, which included
AN UNUSUAL CASE OF YOUNG STROKE

A 20-year-male student presented with a history of weakness on the right side of the body in the morning while in college, which completely recovered within one hour. That afternoon while writing an exam, he had difficulty in writing followed by right lower limb weakness for which he was brought to our casualty. There was no significant past history of similar episodes or history of risk factors for stroke.

At presentation patient’s vitals were stable; there was evidence of right hemiparesis and right upper motor neuron (UMN) facial palsy. Electrocardiogram (ECG) was normal except for sinus bradycardia. The CT head showed hypodensities in the left medial temporal lobe. An MRI was done subsequently which showed evidence of multiple infarcts in the left side of the brain including the left temporal, cerebellum, corona radiate, genu of internal capsule and right occipital lobe, predominantly in the territory of left posterior cerebral artery (PCA). He was non-diabetic, BP and lipid profile was normal. He was non-alcoholic, non-smoker and did not have history of substance abuse.

He was diagnosed to have ischemic stroke when he was young.

Learning Points
Annual incidence rates of arterial ischemic stroke in adults lesser than 45 years old, range from 3.4–11.3/100,000 people per year. Ischemic stroke is more common in men than in women. Common causes in young adults are congenital and acquired heart diseases, hematologic conditions, vasculopathies, metabolic disorders, and drug ingestion. Young Indian population is believed to be more susceptible to stroke than western population. However, this data is based on studies conducted in urban population and in Indian Diaspora in foreign countries, and may be due to increased incidence of diabetes and lipid abnormalities.

Investigation and Treatment
Baseline investigations (CBP, FBS, lipid profile, LFT, RFT, Urine, PT, aPTT) were normal. As the most common cause of stroke in the young is cardioembolic, he was started low molecular weight heparin (LMWH) followed by warfarin while being investigated. Both transthoracic and transesophageal ECHO did not show any
evidence of valvular heart disease nor any evidence of intra-cardiac shunting. A 24 hour Holter assessment showed evidence of periods of sinus tachycardia and bradycardia, however there was no evidence of atrial tachyarrhythmias.

Learning Points
The most common cause of stroke in young being embolic, this patient was investigated for source of embolus. The trans-esophageal echocardiography (TEE) was done to rule out minor thrombi in left artery (LA), and Holter for ruling out paroxysmal atrial fibrillation (AF).

Investigation and Treatment
We also investigated for prothrombotic states, like antiphospholipid antibodies (APLA) which was negative. Homocysteine levels and Protein C and S were normal. Serologic tests including human immunodeficiency virus (HIV), venereal disease research laboratory test (VDRL), anticnuclear antibodies (ANA); were reported as negative. Carotid and vertebral artery Doppler study was also normal. As a part of young stroke work-up, since no cause was found, patient underwent CT angio of cerebral vessels which was normal. In view of absence of evidence of embolism, warfarin was stopped and patient was put on antiplatelets. At the time of discharge patient did not have any neurological deficits.

Learning Points
Initial evaluation of young stroke involves neuroimaging, cardiac, vascular, and hypercoagulable states in all patients. Magnetic resonance imaging (MRI) is more sensitive for acute ischemia than CT, particularly with use of diffusion weighted imaging in the hyper acute time period. In addition, brain MRI provides better visualization of the posterior fossa. Apart from brain imaging neurovascular imaging like magnetic resonance angiography (MRA) or computed tomography angiography (CTA) are also required to rule out vasculitis and aneurysms. If there is clinical suspicion of vasculitis or infection patient should be tested for ANA assay, HIV, VDRL. Rare syndromes like mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) should also be considered.

Anticoagulation is a standard practice in patients with embolic stroke, however in acute thrombotic stroke role of anticoagulation is controversial. Hence, for our patient we stopped anticoagulation after ruling out embolic stroke.

Investigation and Treatment
A month later, while on antiplatelets, he swayed to left side in a confused state of mind, had vomiting and had difficulty to recollect recent events. On examination, it was found that he had mild weakness of right side and abnormal finger test suggesting right cerebellar lesion. A repeat MRI showed infarcts all in posterior circulation and have occurred at different time intervals. Doppler study showed features suggestive of thrombosis/stenosis of distal left vertebral artery. In view of recurrent strokes and left vertebral thrombosis/stenosis, he was initiated on anticoagulation in addition to antiplatelets and statins. At the time discharge patient almost completely recovered. Repeat digital subtraction angiography (DSA) of cerebral vessels was planned as etiology of thrombosis was still unclear.

Learning Points
Optimal antithrombotic therapy for patients with intracranial stenosis is uncertain. aspirin should be used in preference to warfarin for patients with symptomatic intracranial arterial stenosis. However for basilar artery stenosis anticoagulation therapy might be better than antiplatelet drugs. Interventional therapies like angioplasty though feasible are still investigational.

Investigation and Treatment
A few weeks later, while transiently off anticoagulation in view of high International normalized ratio (INR) (greater than 5), he developed abrupt onset of numbness of left side of body lasting for one week. On examination, there was left Horner’s and mild cerebellar signs. Digital subtraction angiography (DSA) of cerebral vessels now showed features suggestive of vasculitis of posterior circulation with focal stenosis of right posterior cerebral artery at P1-P2 junction. In view of significant vasculitis seen in DSA, and repeat APLA being mildly positive, oral mycophenolate was added to anticoagulation and antiplatelets and discharged with diagnosis of primary central nervous system (CNS) vasculitis.

Learning Points
Primary CNS vasculitis is also called primary angiitis of the central nervous system (PACNS) and is a rare disease. The PACNS is primary involvement of blood vessels in the brain or spinal cord without evidence of systemic vasculitis. It affects small and medium-sized arteries of the brain parenchyma, spinal cord. Pathologic findings include the presence of Langerhans or foreign body giant cells, necrotizing vasculitis, or lymphocytic vasculitis. The cause of PACNS is unknown but, herpes zoster infection, Hodgkin lymphoma, Mycoplasma infection and HIV infection have been implicated. Even though cerebral angiography typically shows ectasia and stenosis usually in the small and medium arteries, PACNS should be diagnosed after excluding infection, systemic vasculitis. Firm diagnosis requires brain biopsy to identify other lesions or vasculitis mimics, particularly infection or malignancy.

Investigation and Treatment
A month later while on mycophenolate and anticoagulant and antiplatelets he developed sudden onset dysarthria associated with ataxic gait and confusion. He also had seizure for which he was diltiainultinised. INR was 2.38. CT head did not show any bleed but, MRI showed fresh infarcts. He was put on IV methylprednisolone and LMWH as mycophenolate and anticoagulation had proven inadequate to control his disease. As the patient was gradually improving, his oral anticoagulation was stopped since INR was 4.20 for one day.

On the subsequent day, he had worsening of right hemiparesis and facial nerve palsy. Considering the fact that the patient had developed recurrent strokes despite being on IV methylprednisolone, he was put on cyclophosphamide pulse therapy and IV immunoglobulin along with heparin were started on the same day.

There was a gradual and steady improvement in his neurological function over a period of one month. Next few weeks he joined back college. Over a period of two years he completed 18 doses of pulse cyclophosphamide. It was decided to change over to oral mycophenolate along with anticoagulation and antiplatelets. However monthly IVIG was continued for one more year. After successfully completing his education he is now gainfully employed.

Learning Points
Primary angiitis of the central nervous system (PACNS) was probably first described by Harbitz in 1922 as an unknown form of angiitis. Most data from India is in the form of case reports or case series. The pathologically vessel shows lymphomononuclear perivasculitis and focal fibrinoid necrosis of the vessel wall, involving both arteriolar
and venular components, especially small and medium sized vessels. However large sized vessels are spared. Less than 50% of cases have granulomas on biopsy so the term “granulomatous angiitis” is often confusing. It is defined by inflammation of the cerebral vasculature without angiitis in other organs.

The work-up and consideration of treatment for patients who may have PACNS must proceed simultaneously with plans for the systematic evaluation and exclusion of other disorders which mimic PACNS. Cerebral angiography and brain biopsy are the cornerstone for diagnosis of PACNS. Even though CTA and MRA are not very specific diagnostic tests; characteristic pattern showing multiple ectasia and stenosis referred to as “beading” should be the clue for the clinician to suspect PACNS.

The PACNS should be treated with a combination of glucocorticoids and cyclophosphamide. Most patients require oral steroids; IV methylprednisolone may be needed in sick cases. Either daily oral or intermittent intravenous cyclophosphamide can be used for treatment of PACNS. Patients should be closely monitored for severe immunosuppression.

Role of IVIG in PACNS is not been studied especially in adults, described only in case reports. Duration of therapy of PACNS is not clear; decision should be based on clinical response. There is no clear data on risk of recurrence after stopping immune suppression and combination of immune suppression.

Awareness of this condition is very important as it is amenable to treatment and can make a huge difference to the quality of life of the patient.

Final Diagnosis
Primary CNS vasculitis.