

**A case study put together following the first time admission of a patient with CADASIL.  
The case study formed part of an assessment for a post-graduate paper in nursing.**

### **Introduction**

Diagnostic investigations collect information to clarify patients' health status, using personal characteristics and relevant history, symptoms and signs, physical examination, laboratory tests and additional diagnostic measures (Moons & Grobbee, 2002; Knottmerus, van Weel & Muris, 2002). Diagnostic goals include increasing the certainty of the presence or absence of disease, supporting clinical management, assessing prognosis and monitoring clinical course (Moons & Grobbee, 2002; Knottmerus et al., 2002). When comparing the appropriateness of a variety of diagnostic tests in meeting these objectives, it is important to recognise that additional tests, such as computed tomography (CT) or lumbar puncture, vary in accuracy, availability, invasiveness, and patient risk (Knottmerus et al., 2002).

As an adjunct to exploring the process of evidence-based diagnostic reasoning, the following dissertation will present a case study of an actual client whose presenting complaint induced several differential diagnoses and precipitated a diversity of diagnostic investigations. The case study will provide a systematic approach from presenting complaint to differential diagnoses and selection of diagnostic testing measures. As a definitive diagnosis is determined, the evidence-based diagnostic reasoning process will be outlined. In an effort to provide anonymity and facilitate the narration, the pseudonym, Keith, was chosen to represent the client.

#### **General Appearance / Presenting complaint / History and medications**

Keith, a 58 year-old male Caucasian, was brought to the hospital emergency department via ambulance with left-sided weakness, following a fall at home. Keith is of medium to slim build (BMI<24) with a healthy appearance, no prior hospital admissions, and is usually fit and well. Immediately before the fall, Keith had been working in his carport, stood to wash down the area and suddenly staggered sideways into a bush. Keith put out his left leg to stabilise himself and discovered the leg to be non-responsive. Subsequently, he fell over. Immediately afterward, Keith noticed that the entire left side of his body was non-responsive and called for help.

The evening before the fall, Keith had experienced a similar feeling of lower limb paresis when he was unable to get out of his chair on the first attempt. Keith had assumed that he was just tired at the time. Keith was not aware of feeling unwell in the moments preceding the fall, is orientated to time and place and denies any current or recent confusion, personality changes, photophobia or headache. With the exception of dietary supplements (vitamins), Keith does not take any medication, and has no known allergies. Admission vital observations reveal a blood pressure of 151/ 84, respirations 14, oxygen saturation 97% (on air), and pulse rate, regular, 87 beats per minute. Tympanic temperature is 37° (normal range: 36.3°-37.8°) and Glasgow coma scale rating is 15/15 (Smeltzer & Bare, 2000).

Keith works as a supervisor at the local oil refinery, is married and has two daughters, 29 and 31. Except for an episode of double pneumonia as a child, resolved with antibiotics and relocating to a warmer climate, Keith's health history is unremarkable. All childhood immunisations were completed and uneventful. Since emigrating from Scotland to New Zealand in his early twenties, Keith has maintained regular contact with his extended family and is unaware of any major health problems experienced by his siblings. Keith's mother is alive and well, his father died suddenly of a myocardial infarction at age 50 and his paternal grandmother died of a stroke (date and/or age unknown). Keith denies any familial or personal history of hypertension, hypercholesteremia or diabetes mellitus. An ex-smoker of approximately 25 cigarettes a day between the ages of 12 and 30, Keith has, since quitting, maintained a healthy eating and exercise regime and takes alcohol (one-two glasses of wine) only occasionally.

#### **Diagnostic considerations at this time**

The presenting feature of sudden-onset hemiparesis indicates a brain injury, in particular, acute right hemispheric stroke (Bickley, 2003). The most sensitive neurological indication of impending danger, loss of consciousness, is absent (Smeltzer & Bare, 2000). The prior incidence of numbness or loss of sensation in

his lower extremities experienced the night before presentation is symptomatic of a Transient Ischemic Attack (TIA) (Bickley, 2003). The symptoms of a TIA usually resolve within 24 hours and are considered a warning sign of impending stroke (Bickley, 2003). There is however, a noted absence of confusion, visual disturbances, severe headache and/or difficulty in speaking or understanding speech, which are classical symptoms of stroke (Bickley, 2003). Vital signs are stable with no evidence of hypertension.

The clinical manifestations of a brain injury that are pertinent to this patient are sudden-onset neurological deficits and movement disorders (Bickley, 2003). As Keith denies a history of trauma, the mechanism of injury may be related to chemical exposure (occupational health hazard) and includes the possibility of arteriovenous disease, a tumor, an aneurysm, brain abscess or hemorrhage (Bullock & Henze, 2000). In addition, due to the absence of common risk factors for stroke, several genetically linked, and/or degenerative diseases often produce symptoms such as ataxia if the lesions involve the cerebellum or basal ganglia (Smeltzer & Bare, 2000). In particular, a number of the symptoms evident in early presentations of Multiple Sclerosis (MS) are consistent with Keith's recent history of weakness, fatigue, loss of balance and numbness (Smeltzer & Bare, 2000).

### **Clinical examination**

Although there is obvious (left sided) facial palsy, visual observations indicate an alert patient, comfortable at rest, with his wife present. Examination of the head and neck reveals normal visual fields and eye movements, equal pupillary reaction and normal facial sensation. Eyes are clear and bright, and conjunctiva and oral mucosa are moist and pale. Teeth are in good repair and non-tender. Facial movements are decreased in the left side and Keith's mouth is droopy, however, tongue and palatal movements are normal as is his hearing. Keith's trachea is central, jugular venous pressure (JVP) is one centimeter and carotid pulses are equal bilaterally. Chest is clear to auscultation, heart sounds normal with no rubs, murmurs or gallops evident. Temperature 37°, blood pressure 151/ 84, respirations 14, oxygen saturation 97% (on air), and pulse rate, regular, at 87 beats per minute. Abdomen is soft, non-tender, with active bowel sounds and nil urinary incontinence. Extremities are warm to touch with quick capillary refill, and skin turgor is normal. Pulses are present in all extremities.

The neurological examination reveals left-sided hemiplegia. The patient is alert, naturally concerned but able to respond appropriately to verbal cues and follow simple commands. Glasgow Coma Scale is 15. Cranial nerves are grossly intact. The tone, power, sensation, reflexes and coordination of Keith's right upper and lower limbs are normal, however, although left-sided response to pinprick is normal in both upper and lower limbs, tone, power, reflexes and coordination are absent.

### **Differential Diagnoses**

The clinical examination findings are consistent with the overall impression of a cerebrovascular event, or stroke (Bickley, 2003). However, this presentation is atypical due to the absence of hypertension, dyslipidemia, obesity, diabetes, smoking, drug or alcohol consumption, which are common stroke risk factors (Smeltzer & Bare, 2000). In addition, characteristics that are typically associated with right hemispheric stroke; spatial-perceptual disturbances, left visual field deficits and left-sided neglect are not evident in this presentation (Smeltzer & Bare, 2000). It is noted at this time that a significant bleed is unlikely due to the absence of clinical manifestations that are usually synonymous with intercerebral hemorrhage; hypertension, headache, visual disturbances or change in mental status (Smeltzer & Bare, 2000).

Causative factors in a brain injury include tumors, or neoplasms, characterised by a progressive uncontrolled proliferation of cells (Smeltzer & Bare, 2000). Many industries are associated with prolonged and repeated exposure to potential carcinogens (Smeltzer & Bare, 2000). Fuel manufacture, undertaken at Keith's workplace, involves a number of chemicals including arsenic, benzo(a)pyrene, benzidine and 2-naphthylamine which are common factors in tumor formation (Smeltzer & Bare, 2000).

Unrelated to chemical exposure, Angiomas are tumors composed mostly of abnormal blood vessels (Smeltzer & Bare, 2000). Angiomas are a risk for cerebral hemorrhage due to the thin walls of the blood

vessels (Smeltzer & Bare, 2000). With the absence of common risk factors for stroke in Keith's case, the presence of chemically induced tumor or (ruptured) angioma, may produce neurological deficits such as hemiparesis (Smeltzer & Bare, 2000).

An intracranial aneurysm develops as a result of weakness in the arterial wall (Smeltzer & Bare, 2000). Symptoms that include hemiplegia, may be produced when the aneurysm enlarges and presses on nearby cranial nerves or brain tissue, or when the aneurysm ruptures causing subarachnoid hemorrhaging (Smeltzer & Bare, 2000). The presence of an intracranial aneurysm would be consistent with Keith's presenting complaint of unilateral weakness but is usually associated with loss of consciousness and deteriorating vital signs such as bradycardia or hypotension (Smeltzer & Bare, 2000). However, admission vital signs have remained stable and the patient is alert with no history of loss of consciousness, therefore the presence of a ruptured aneurysm is unlikely.

A frontal lobe abscess is a collection of infectious material within the tissue of the brain resulting from intracranial trauma, infection or surgery (Smeltzer & Bare, 2000). The clinical symptoms of hemiparesis related to a frontal lobe brain abscess, result from alterations in intracranial dynamics (brain shift, edema), infection or the location of the abscess (Smeltzer & Bare, 2000). The most likely cause for a brain abscess in Keith's case would be a spread of infection from nearby sites such as sinuses or other organs such as infective endocarditis or lung abscess (Smeltzer & Bare, 2000).

The blood vessel most often associated with stroke is the internal carotid artery where lumen elasticity is compromised by atheromatous deposits or plaques (Smeltzer & Bare, 2000). In arteriovenous disease, cerebral circulation is disrupted causing ischemia of the brain and producing sudden-onset neurological deficits such as, in Keith's presentation, hemiparesis (Smeltzer & Bare, 2000). Ischemia is also a common finding in the diagnosis of MS wherein neurological dysfunction is dependent upon the areas of demyelination and/or infarcts (Smeltzer & Bare, 2000). In the absence of stroke risk factors, the links to a possible diagnosis of MS in Keith's case include a recent history of weakness, numbness and loss of balance.

### **Diagnostic Tests**

Ascertaining the type and extent of brain injury is of primary concern to exclude the life threatening risk of intracranial bleeding (Benavente & Hart, 1999). Furthermore, the absence of intracranial bleeding must be affirmed before treatment is commenced (Benavente & Hart, 1999). In this case, a (non contrast) CT is used to visualise the presence (or absence) of infarcts, tumor masses and accumulations of fluid (Besson, Robert, Hommel, & Perret, 1995). Computed tomography is considered a non-invasive yet effective, primary diagnostic procedure to investigate the tissue structure of the intracerebral and extracerebral spaces (Malarkey & McMorro, 1996; Benavente & Hart, 1999).

Many neurologists regard the CT as the 'gold standard' in intracranial imaging for revealing the location of a clot, hydrocephalus, areas of infarction and extent of blood spillage within the cisterns around the brain (Besson, Robert, Hommel, & Perret, 1995; Mäurer et al., 1998; Fiebach et al., 2004). However, several studies are emerging wherein Magnetic Resonance Imaging and not CT, should serve as the gold standard (vonKummer, 2002). According to a study by Fiebach et al. (2004), MRI has a sensitivity rating of 95% and specificity of 100% for detecting intracranial hemorrhages.

In addition to the CT investigation, which can indicate areas of infarction consistent with MS, an electrophoresis study of cerebrospinal fluid (CSF), via a lumbar puncture, will enable an analysis of cerebrospinal fluid to ascertain the presence (or absence) of oligoclonal bands (Smeltzer & Bare, 2000). Electrophoresis has a sensitivity rating of 95% in detecting oligoclonal bands, which are characteristic findings in MS (Bickley, 2003; Oberstein, Breuning, & Haan, 2004).

To investigate the possibility of chemical exposure, and/or tumor formation, a blood chemistry screen is used to evaluate the presence and levels of chemicals consistent with chemical poisoning, whilst assessing electrolyte balance, acid-base balance, renal function and osmolarity (Smeltzer & Bare, 2000). A full blood

screen is required to assess for contributing factors such as anaemia, inflammation, infection, polycythemia, haemolytic disease, the effects of ABO incompatibility, leukemia, and the status of dehydration (Malarky & McMorrow, 1996). In particular, the platelet count will be investigated to ascertain the presence of either thrombocytosis or thrombocytopenia, which are major causative factors in stroke (Malarky & McMorrow, 1996).

With a sensitivity rating of 95% in assessing the patency of the intra-cranial arteries, an ultrasound carotid Doppler will assess the patency of intra-cranial arteries and detect arterial stenosis, occlusion and plaques, common findings in arteriovenous disease (Ringelstein, 1995; Smeltzer & Bare, 2000). Chest x-ray and an electrocardiograph (ECG) will assess pulmonary and cardiac function and detect the presence of inflammation and/or infection, which may contribute to the development of a brain abscess (Smeltzer & Bare, 2000).

### **Diagnostic reasoning and formulation of a diagnostic decision**

The presenting complaint of sudden-onset hemiparesis, precipitated by a (probable) TIA, and followed by the clinical examination confirming unilateral motor deficit, formed the basis for the diagnosis of (atypical) stroke (Oberstein, Breuning, & Haan, 2004). Vital signs are stable, vision and/or mental status unimpaired with no history of trauma or confusion, frontal headache or seizures.

Keith is afebrile, denies a recent history of colds or chest infections, and chest palpation with percussion and auscultation were clear. An evaluation of the chest x-ray and ECG results are consistent with the clinical examination in that, no cardio or pulmonary abnormalities were detected. Except for a marginal rise in Keith's bilirubin count (not investigated), the initial full blood count indicated no chemical or haematological pathology for his symptoms.

Arteriovenous disease of the central nervous system is most frequently associated with atheromatous deposits within the internal carotid artery (Smeltzer & Bare, 2000). However, the ultrasound carotid Doppler was negative for plaques or haemodynamically significant waveforms thereby excluding arteriovenous disease as a causative factor in this presentation.

The CT scan revealed multi-focal white matter lesions, low attenuation, involving frontal, parietal and temporal areas. There is no midline shift, accumulations of fluid or masses evident and the basal ganglia, ventricles, gray matter and cerebellum appear normal. Based on these findings, the CT confirms the absence of an aneurysm and/or hemorrhage and excludes the differential diagnoses of a brain abscess or tumor masses. The stroke is deemed to be ischaemic with diffuse white matter lesions and subcortical infarcts (Bickley, 2003). Furthermore, the lesions evident on CT are suggestive of leukoencephalopathy, a disease of the white matter characterised by demyelination (Oberstein, Breuning & Haan, 2004).

Multi-focal white matter lesions are consistent with diffuse patches of demyelination typically found in patients diagnosed with Multiple Sclerosis (Smeltzer & Bare, 2000). In MS, demyelination occurs throughout the central nervous system causing lesions that interfere with nerve impulses producing a variety of neurological symptoms (Smeltzer & Bare, 2000). However, the electrophoresis study (lumbar puncture) was negative for oligoclonal bands, therefore a diagnosis of MS is excluded.

Thus far, the differential diagnoses of a brain abscess, tumor, aneurysm, hemorrhage and Multiple Sclerosis have been investigated utilising a systematic approach from presenting complaint to diagnostic testing. Unable to determine a definitive diagnosis at this point, Magnetic Resonance Imaging was completed. The MRI findings were consistent with the CT results in reporting extensive white matter changes in keeping with leukoencephalopathy and a right thalamus lesion in keeping with a focus of acute ischemia.

Leukoencephalopathy involves the disruption of sensory axons thereby producing, in Keith's case, unilateral paresis (Oberstein, Breuning, & Haan, 2004). Rare autosomal dominant forms of leukoencephalopathy have been reported but do not usually have stroke-like episodes or arteriolar pathology (Oberstein, Breuning, & Haan, 2004). In conference with a number of neuro-imaging specialists, the investigation of an autoimmune disorder, namely Cerebral Autosomal Dominant

Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) became a realistic target for future tests (Oberstein, Breuning, & Haan, 2004).

CADASIL is an inherited small vessel disease caused by highly stereotyped mutations in NOTCH3 and characterised by a history of migraine headaches, and mid-adult (30s-60s) onset of cerebrovascular disease progressing to dementia (Dichgans, 2002). Ischemic episodes (TIA or stroke), in the absence of hypertension, hypercholesterolemia or cardiovascular risk factors, are the most frequent presentation found in approximately 85% of CADASIL sufferers (Dichgans, 2002). A rare condition affecting only 400 families worldwide (and only 2 New Zealand families), diagnostic testing for CADASIL involves genetic testing for a Notch3 gene mutation (Connor & Ferguson-Smith, 1991; Oberstein, Breuning, & Haan, 2004).

With a definitive diagnosis of right hemispheric stroke in the absence of common stroke risk factors, Keith met the criteria for a probable diagnosis of CADASIL (Dichgans, 2002). In addition, although little is known about the disease process, a number of studies are emerging that link a high frequency of myocardial infarctions in the absence of classical cardiovascular risk factors, to the microvascular circulatory changes seen in CADASIL (Cumurciuc et al., 2006). As Keith's father died of a myocardial infarction at age 50, and his paternal grandmother suffered a fatal stroke, it is reasonable to suggest that there may be a genetic basis or predisposition to vascular disease (Cumurciuc et al., 2006).

There is a great deal of debate throughout the literature on the merits of investigations in accurately diagnosing CADASIL. An electron microscopic (EM) evaluation of a skin biopsy is considered the 'gold standard' method with sensitivity 45% and specificity 100% for diagnosing CADASIL (Joutel et al., 2001). However, according to several researchers; although positive results may be diagnostic, a false negative can also be produced (Markus et al., 2002; Ishiko et al., 2005). Joutel et al. (2001) dispute these findings suggesting that immunostaining skin biopsy samples with a monoclonal antibody specific for NOTCH3 could form the basis of a reliable and easy test. The study by Joutel et al. found diagnostic sensitivity at 96% and specificity at 100%. However, due to the high cost of screening, this test was not an option. Completed at a distant laboratory, genetic sequencing (chromosome analysis) for a NOTCH3 mutation provided a positive diagnosis for CADASIL.

### **Conclusion**

As a medical emergency, it is imperative to identify and classify the type of stroke, for example, hemorrhagic or ischaemic, in order to direct treatment and prevent further damage to the brain. The objective of diagnostic testing is to provide additional relevant information to compliment gathered data, such as the history of presenting complaint, and assist in gaining a definitive diagnosis. In this case study, diagnostic testing focused upon identifying the pathophysiology of stroke in an effort to establish the presence (or absence) of contributing factors to the brain injury. A number of diagnostic measures tend to be costly such as chromosome analysis, or invasive and risky such as lumbar puncture, and are therefore, often undertaken only when original investigations are inconclusive. In this atypical presentation, the absence of common stroke risk factors precipitated a systematic approach of exclusionary diagnostic testing wherein a diversity of diagnostic tools were necessary to produce a definitive diagnosis.

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