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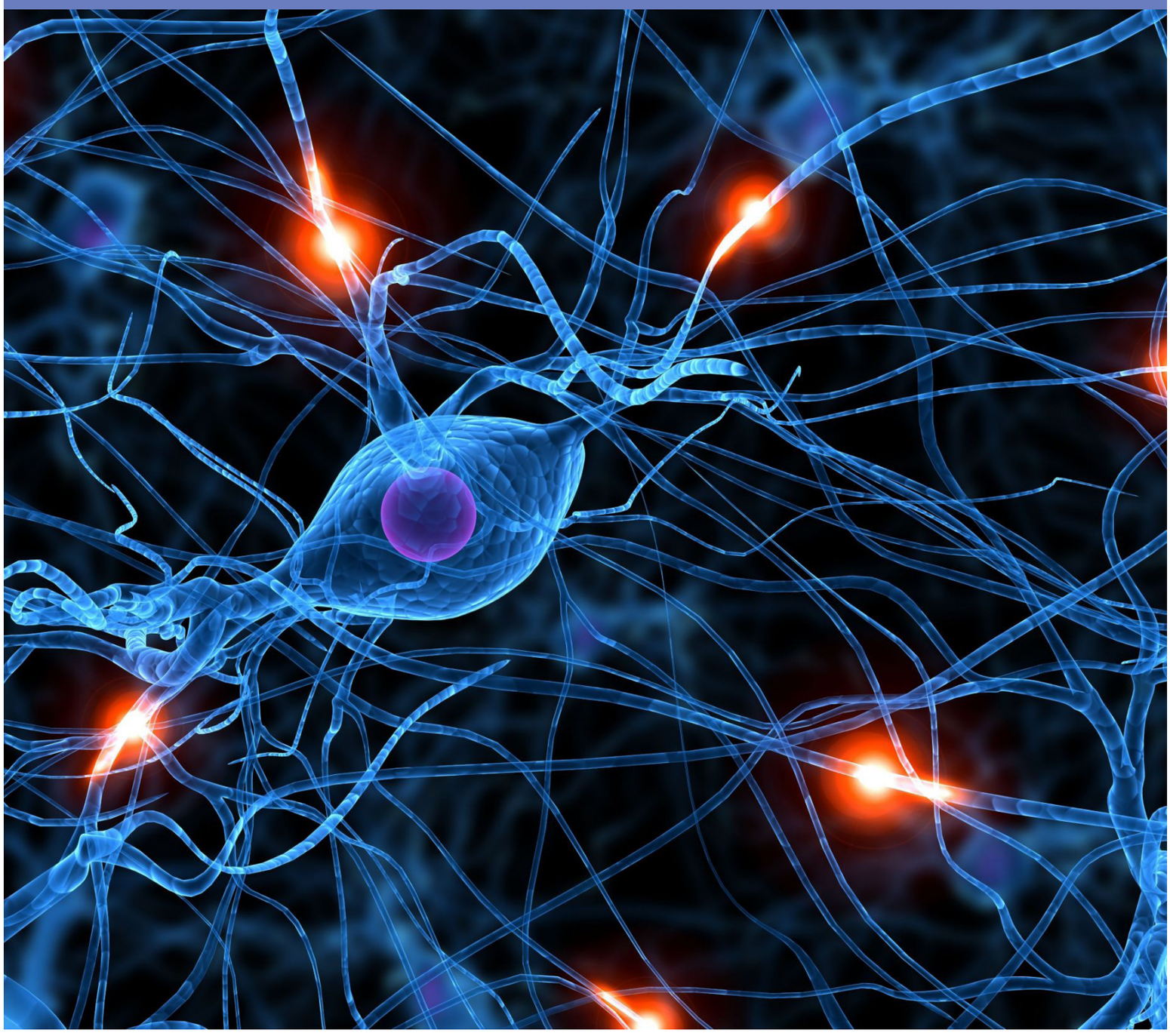

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Volume 7, Issue 7

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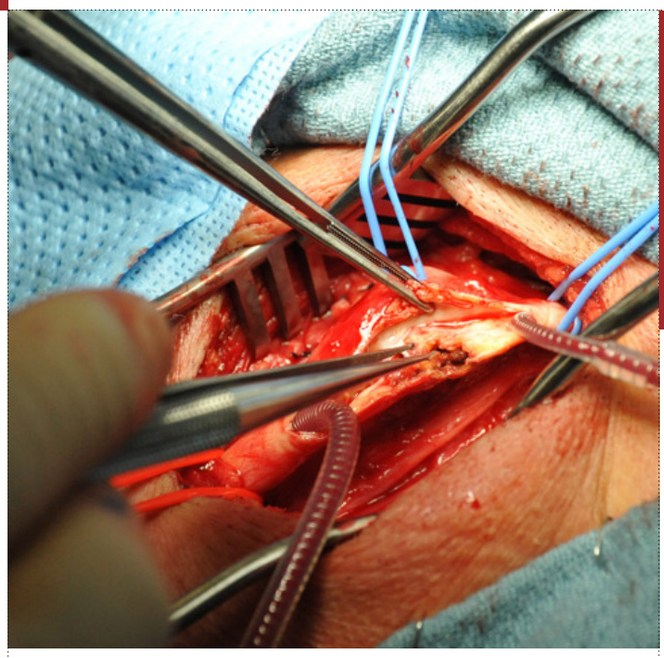
CAROTID ENDARTERECTOMY

H Nasr, S Shiralkar



Abstract

Carotid plaque instability is responsible for the high stroke recurrence rate following an ischaemic cerebrovascular event. Although improved outcomes have been demonstrated with medical therapy (e.g. statins, antiplatelets) with regard to event recurrence, surgical removal of the plaque by means of a carotid end-arterectomy (CEA) remains the best option for acute protection against further embolisation and vessel occlusion.

Urgent CEA for acute ischemic cerebro-vascular events has aroused controversy for many years. Previous reports suggested that urgent CEA was associated with high mortality and morbidity. This view was later challenged by recent evidence demonstrating that early CEA was not only safe, but also superior to medical therapy in carefully selected groups. What remains controversial is the role of early CEA in patients presenting with unstable neurological symptoms (crescendo TIA, progressive stroke and stroke in evolution).

Introduction

Carotid plaque instability can result in neurological symptoms that will range from amaurosis fugax, transient ischaemic attack (TIA), non-disabling stroke and disabling stroke. Carotid endarterectomy (CEA) is a prophylactic procedure to prevent death and disability related to neurological events caused by carotid atheromatous plaque embolisation. CEA is offered to two distinct groups:

1. The high risk symptomatic group

2. The low risk asymptomatic group

Those two groups differ in their presentation and indication for intervention as will be discussed later in this review.

In the symptomatic group, where the carotid plaque is unstable, urgent intervention is warranted to prevent further attacks. However, in the asymptomatic group where the risk of stroke is low, careful patient selection is of paramount importance so patients are not exposed to unnecessary surgical risk.

CEA for symptomatic patients

Two large studies: NASCET (North American Symptomatic Carotid Endarterectomy Trial) and ECST (European Carotid Surgery Trial) evaluated CEA against best medical therapy for the prevention of ischaemic stroke in patients presenting with symptomatic (neurological events within 6 months of recruitment) carotid stenosis (1, 2). A third study, the VA (Vetrans Affairs) trial was stopped prematurely because of the clear evidence supporting CEA reported by NASCET and ECST trials (3).

In all the symptomatic carotid trials the degree of stenosis determined the degree of benefit, where maximal benefit was conferred in the group with > 70% stenosis, and those with < 50% stenosis did not benefit from surgery. In patients with severe stenosis (70-99%), pooled analysis combining NASCET, ECST and VA trials found CEA to be associated with an absolute risk reduction (ARR) of 16% at 5 years and a relative risk reduction (RRR) of 67% (4, 5). There was no gender difference in procedural efficacy. These findings clearly demonstrated the efficacy and durability of CEA in symptomatic patients with severe carotid stenosis. In patients with moderate stenosis (50-69%), NASCET demonstrated that CEA conferred a small but significant benefit compared to medical therapy alone. However, the ECST trail showed that this group of patients did not benefit from surgery (1, 2). The discrepancy between the two trials was largely related to the difference in methodology of measuring the degree of carotid stenosis (Figure 1). The ECST method tended to overestimate the degree of stenosis when compared with NASCET (e.g. a 50% NASCET stenosis is equivalent to a 70% ECST stenosis). To overcome this problem the Carotid Surgery Trialists' Collaboration (CSTC) reanalysed the results of the ECST group according to the NASCET method. Following which, it was clear that the ECST results were similar to that of NASCET in that group of patients with moderate stenosis (ARR of an ipsilateral stroke at five years was 5.7%) (6). In patients with < 50% stenosis, CEA benefit was insignificant and CEA was actually harmful in those with < 30% stenosis (6).

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←	NASCET	ECST
Degree of ICA stenosis	(A-B)/A	(C-B)/C

Figure 1: Difference between NASCET and ECST in measuring degree of ICA stenosis.

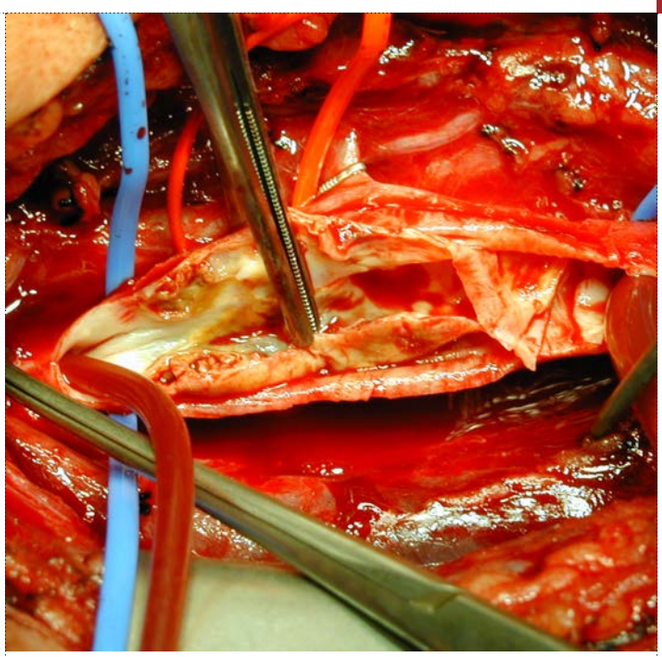
Timing of Carotid Surgery in Symptomatic Patients

The timing of CEA following a neurological event has been and remains the topic of debate within the neurovascular community. Early studies clearly demonstrated the harmful effects of urgent CEA following a neurological event with a high peri-operative stroke rate (26-60%) (7, 8). This was thought to be related to hemorrhagic transformation in the early period and it was hence advisable to delay surgery for six weeks, allowing maturation of cerebral ischaemia.

This policy of delaying surgery has been recently challenged. New evidence suggests that the risk of stroke recurrence after a neurological event is a lot higher than previously estimated. In the Oxford Vascular Study, the risk of stroke following a TIA was 8, 11.5 and 17.3% at 7, 30 and 90 days respectively (9), whilst others reported a risk of stroke in the region of 20% during the first 2 weeks following a neurological event (10, 11). Additionally, the data suggested that risk of event recurrence receded in the months and years following the index event. This could be related to plaque stabilisations and formation of collateral blood supply to the brain. These studies highlight the importance of urgent carotid intervention to prevent stroke recurrence.
Recently, the CSTC, using pooled data form NASCET, ECST and VA trials demonstrated that early CEA was not only safe, but also most beneficial if performed within two weeks of the index event (12). Surgery within two weeks prevented over 180 strokes per 1000 CEAs, whilst delaying surgery up to four weeks prevented just under 100 strokes and only 60 strokes will be prevented if surgery is performed within 4-12 weeks. The benefit becomes negligible if surgery is deferred more than twelve weeks. Interestingly, the decline in benefit with time was more pronounced in women highlighting the importance of urgent intervention in women.

Given the potential impact of urgent CEA on stroke prevention, many clinicians questioned the high peri-operative stroke rate reported by previous studies. A more recent systematic review of 12 studies revealed no difference in the rate of peri-operative stroke and death between early and delayed CEA in patients with stable neurological symptoms (10).

Having established that early CEA is safe and beneficial, current treatment guidelines recommend that CEA should be performed within two weeks in patients presenting with non-disabling neurological symptoms (13, 14).



CEA in patients with unstable neurological symptoms

As mentioned previously, there is enough evidence to support the urgency of CEA in patients with stable neurological symptoms (Amaurosis fugax, TIA and non-disabling stroke). However, the evidence is still ill defined in patients with unstable neurological symptoms (crescendo TIA, stoke in evolution and progressive stroke). There are no large prospective studies and most of the information regarding that group is from subgroup analysis in small or medium sized retrospective studies. Many of the prospective trials and case series have excluded this group of patients in their final analysis.

CEA in patients with unstable neurological symptoms has been associated with higher risks of stroke and death than delayed of early surgery in stable patients. In one study, the combined risk of stroke and death in patients undergoing urgent CEA with unstable neurological symptoms was as high as 7% compared to 2.4% in patients with stable symptoms (15). Other studies have suggested that with careful patient selection and if the surgery is performed in the correct instances, urgent CEA can be beneficial in that group of patients with sustainable long term benefits (16, 17).

Management of this group of patients remains a challenge, which highlights the need for large prospective studies to define clear guidelines on best clinical management.

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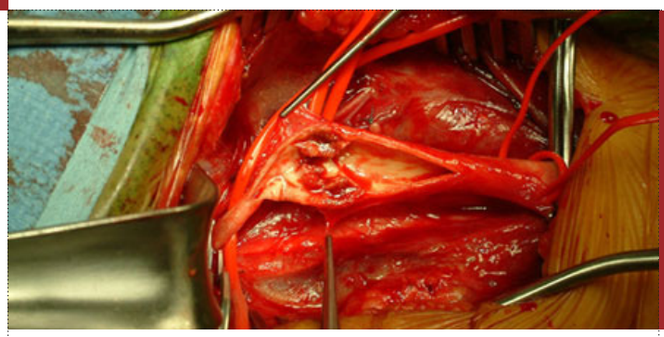


Carotid Endarterectomy
Patient Management

CEA for Asymptomatic Patients

Extrapolated data from the Asymptomatic Carotid Artery Surgery and Asymptomatic Carotid surgery trials suggest that at 5 years the stroke rate was 10% with medical management and 5% with CEA (18, 19). However, more recent studies suggest that the risk is actually 1% a year with appropriate medical therapy (20-22). In this group, patient selection is very important as the annual risk of stroke has been shown to vary from 0.7% to 6.3% depending on degree of carotid stenosis, carotid disease progression, contra-lateral carotid ischaemic event, presence of peripheral vascular disease, evidence of embolic events on Transcranial Doppler (TCD) (23-26). Therefore, routine CEA for asymptomatic patients is not justifiable without identifying each patient's risk of stroke with medical intervention versus CEA. It is important to note that most patients with asymptomatic carotid disease will be harmed with surgery.

The current European surgical guidelines recommend CEA for men < 75 years with 70-99% stenosis and a peri-operative stroke or death risk <3% and it should only be considered in younger fit women (27). On the other hand, the European Stroke Organisation recommends that carotid intervention should be avoided in all asymptomatic patients except in those with a very high stroke risk (>80% carotid stenosis with a life expectancy > 5 years) (28).

Conclusion

Significant atherosclerotic carotid artery narrowing is found in 20% of stroke and TIA patients. The onset of symptoms is thought to be related to carotid plaque instability, which also accounts for the high risk of event recurrence in the early period following the index event. Interestingly, this risk falls rapidly with time as the plaque heals. Therefore, early intervention is vital to prevent further neurological complications. Large randomised trials have clearly demonstrated the superiority of surgery over medical treatment, and current guidelines advocate early surgical intervention (within two weeks of the index event).

In addition to early intervention, other positive predictors of benefit from CEA have been identified. These include increasing degree of stenosis, male gender, age ≥ 75, neurological symptoms lasting > 24 hours, absence of contra-lateral ICA stenosis and plaque ulceration. Until we identify pharmaco-therapeutic agents that can acutely stabilise plaques, modify their activity and significantly reduce the risk of early event recurrence, CEA will remain to be the preferred treatment option for the majority of acutely symptomatic patients.

CEA for asymptomatic disease should only be offered to fit patients with high stroke risk, where the CEA stroke and death risk is lower than that on medical therapy alone.

Case scenario

A 75-year-old female presented to the accident and emergency department with right-sided weakness, however she retained function of the arm and was able to mobilise with assistance. She also revealed that 10 days ago, she had a similar episode that lasted for 30 minutes and resolved spontaneously, but did not seek any medical attention. A CT scan confirmed ischaemic changes in the left middle cerebral (MCA) artery territory. She was commenced on anti-platelet therapy, statins and anti-hypertensive medication. A duplex scan revealed a significant left internal carotid artery (ICA) stenosis (70-90 %). Unfortunately, a vascular surgeon did not see the patient for five days. She then developed a further stroke, but on this occasion the patient developed full hemiparesis. A repeat duplex showed complete occlusion of the left ICA.

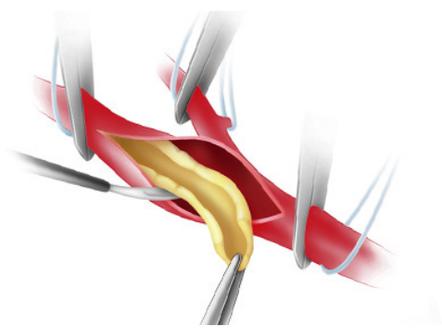
Learning points:

1. The patients' index event was actually 10 days prior to the accident and emergency attendance. Therefore, the patient should have been seen by a vascular surgeon immediately after admission to expedite intervention.

2. Initially, the patient would have benefited from urgent CEA, as she presented with a non-disabling stoke and significant ICA stenosis.

3. Despite starting best medical therapy, the patient developed a further stroke, which was disabling on this occasion. Consequently, CEA was not indicated anymore. Furthermore, the patient developed occlusion of the ICA, which is another contraindication for CEA.

This case highlights the importance of quick assessment and intervention in patients presenting with carotid related cerebral ischaemic events.



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Authors

Hosaam Nasr
Surgical Registrar, West Midland Deanery

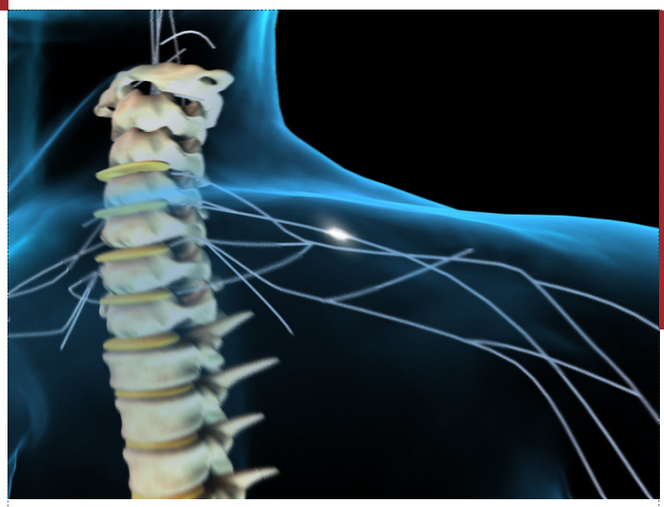
Sandy Shiralkar
Consultant Vascular Surgeon Russells Hall Hospital, Dudley

Correspondence

Sandy.Shiralkar@Dgh.Nhs.Uk

CASE-BASED DISCUSSION: DIFFERENTIATING CERVICAL CORD COMPRESSION FROM GUILLAIN-BARRE SYNDROME

C Johnston, P Crawford



Abstract

This article gives a brief history of a case of weakness and sensory disturbance, involving all four limbs, presenting to the medical admissions unit. This is followed by a discussion about which symptoms and signs can help to identify cervical cord pathology or a polyradiculopathy such as Guillain-Barre Syndrome (GBS). In particular, the features that may indicate an acute spinal cord compression requiring emergency management are highlighted.

Case History

Mr A is aged 62 and was admitted with falls, rapidly increasing leg weakness and clumsy hands. He had a two-month history of having what he describes as a cricked neck. He had shoulder and neck pain which had got worse over the subsequent months. He was advised to stop taking his statin. The distance Mr A could walk deteriorated and he felt unstable. Three weeks prior to admission he had a flu-like illness. Two weeks before admission he developed some tingling in the tips of his fingers. Three days before admission he got up during the night to pass urine and his legs gave way, he fell forward and banged his head which gave him two black eyes and a nose bleed; he then crawled back to bed. The next day he was unable to stand, his hands were numb and the grip was poor; there was no bladder problem. Hand function deteriorated over the following day until he was no longer able to hold a cup.

Case-based discussion: Differentiating cervical cord compression from guillain-barre syndrome
Patient Management

On examination Mr. A was alert and oriented. There was infra-orbital bruising. Cranial nerve examination was normal. Initially he needed assistance to stand and was able to mobilise short distances with a narrow-based, short-steppage gait. Tone was increased and he had mild distal weakness in all limbs. Reflexes were preserved with flexor plantar responses bilaterally. Sensory testing for light touch was normal but proprioception was abnormal in the feet.

Initial investigations included a plain x-ray of his thoracic spine showing diffuse moderate degenerative disc disease but no vertebral body collapse. He was given a provisional diagnosis of Guillain Barre Syndrome and imaging of the cervical spine was not immediately requested.

Discussion

How would you approach this patient if you were asked to review him?

There are important clues here that help you to identify acute cervical cord pathology or an acute polyradiculopathy such as GBS. They are easy to miss in the busy ED or medical admissions unit and this can result in delayed diagnosis of an emergency situation.

Start with the History.

1. Determine when his limb strength was last normal. Did the weakness come on acutely or gradually? What is the pattern of weakness? Is there any facial weakness or weakness of the neck?
2. Has there been any stiffness in the limbs?
3. Are then any sensory symptoms e.g. numbness / tingling / pins and needles? How and when did they start and how have they progressed since then?
4. Check for bladder symptoms. Has he had any nocturia, frequency, urgency or incomplete bladder emptying?
5. Details of the fall. Was he weak before the fall? What injuries did he sustain in the fall? Did his weakness, numbness or bladder function change acutely after the fall?

CASE-BASED DISCUSSION: DIFFERENTIATING CERVICAL CORD COMPRESSION FROM GUILLAIN-BARRE SYNDROME

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What to look for on examination (1)

1. Is there any evidence of injury? Look for bruising and check the spine for bony tenderness.
2. Look for upper motor neurone (spasticity, clonus, pyramidal pattern of weakness and hyperreflexia with extensor plantars) versus lower motor neurone signs (normal or reduced tone, weakness and areflexia).
3. Check the distribution of sensory loss in the limbs.
4. Always check for a sensory level.
5. Assess for cardiovascular or respiratory compromise.
6. Examine the abdomen for a full bladder.

The distribution of any bruising can give an indication of the mechanism of neck injuries. For example, black eyes or bruising on the forehead are classically seen in cervical cord injuries resulting from hyperextension of the neck. Cranial nerve signs including facial weakness, neck flexion weakness and ophthalmoplegia are against myelopathy. Back pain is not discriminatory as it can occur with either spinal cord pathology or GBS. (2)

A pyramidal pattern of weakness which occurs in a spinal problem gives increased weakness of the extensor muscle groups compared to the flexors in the upper limbs so look for weakness of shoulder abduction, elbow extension and wrist extension. In the lower limbs the flexors are weaker: hip flexors, knee flexors and dorsiflexors of the foot. Look for this pattern even when the weakness is predominantly proximal or distal. Reflexes can appear brisk in an anxious patient and testing for Hoffman's sign (Figure 1), abdominal reflexes, plantar responses and for clonus can help to determine whether they are pathologically brisk. Never forget that acute severe spinal injuries can be associated in the early stages with the absence of increased tone and reflexes, known as spinal shock. Rarely, reflexes can be present initially in Guillain Barre Syndrome but are quickly lost.

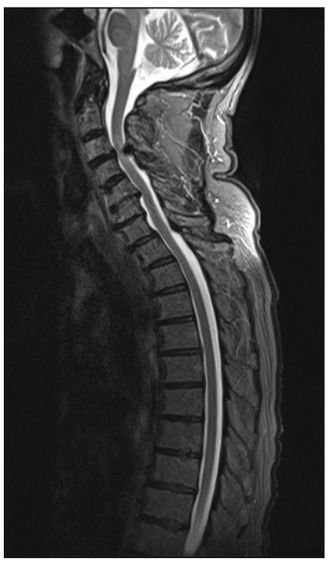


Figure 1: Sagittal T2.

Radicular symptoms can accurately identify the level of the lesion in the spinal cord. Patients may describe pains radiating from the back that are shooting, sharp and knife-like, hot or cold. It is important to note that spinal cord pathology can mimic GBS by presenting with distal ascending sensory disturbance and it is critical not to miss a sensory level. When testing for this use light touch and pin prick modalities and beware a high sensory level that can be easily missed. For example, lesions at C2 and C3 can cause facial numbness (behind ear and angle of jaw respectively). (2) There are physiological areas of increased sensitivity (across the inguinal ligament, just below the breasts and just above the clavicle) that may falsely indicate a sensory level. The sensory signs in GBS are often less prominent than the symptoms but can also resemble a spinal sensory level. Nevertheless it remains an important sign indicating the need for an urgent scan. Similarly, new bladder sphincter symptoms in this setting represent acute spinal cord pathology until proven otherwise with imaging.

Emergency Department Care

Mr A has a history consistent with an acute cervical cord injury. His neck should be immobilised and he should be on bed rest until MRI scan has been performed and stability of the cervical spine is established. Ask for an urgent Neurosurgical review, or Neurology in non-Neurosurgical centres.

CASE-BASED DISCUSSION: DIFFERENTIATING CERVICAL CORD COMPRESSION FROM GUILLAIN-BARRE SYNDROME

C Johnston, P Crawford

Case Presentation Continued

On examination the next day, he was again noted to have increased tone in all limbs. He had a pyramidal pattern of weakness and distal muscles remained weaker than proximal muscles. Reflexes were brisk but with flexor plantars. He had an ascending sensory level from the legs to just below the umbilicus. An MRI of his cervical spine confirmed cervical cord compression at C3/4, secondary to a modest disc bar, associated with posterior ligamentous and facet joint hypertrophy. High signal within the cord consistent with cord oedema from injury was seen at this level (Figure 1).

Treatment and Subsequent Management

Mr A underwent a C3/4 fixation with lateral mass screws. This was to prevent further deterioration although many people do improve subsequently. Mr A was treated by physiotherapists and occupational therapists. He improved so that on discharge he was walking with a frame. His hands remained clumsy but he was able to feed and dress himself. Further outpatient physiotherapy and occupational therapy treatment will be undertaken.

Could Mr A's spinal pathology have been picked up sooner?

Ascending sensory symptoms in this patient were one of the main reasons he was initially mis-diagnosed. Unless a patient presents with classical GBS including ascending weakness and sensory symptoms with areflexia and in the absence of bladder symptoms, brisk reflexes or a sensory level, an urgent scan should be arranged. It is much worse to miss a spinal cord injury than to arrange an urgent MRI that turns out to be normal. Table 1 summarises the clinical features that can help discriminate between GBS and spinal cord pathology.

Clinical Feature	Myelopathy	GBS
Back pain	+	+
Early bladder symptoms	+	(+)
Upper motor neurone signs	+	-
Neck flexion weakness	-	+
Facial weakness	-	+
Proximal sensory loss	+	(+)
Sensory level	+	(+)
Distal sensory loss	+	+

Table 1: Distinguishing spinal cord pathology from GBS.
Key: + = present, - = absent, (+) = unusual

Learning points

1. Both GBS and spinal cord pathology can present with distal ascending sensory features.

2. The presence of upper motor neurone signs, bladder symptoms, or a sensory level in a patient presenting with acute onset weakness of all four limbs should alert you to the possibility of cervical cord compression.

3. Bruising to the forehead or periorbital bruising can signify a hyperextension injury of the neck.

4. When the clinical signs are not discriminatory, review after a short interval. This can reveal evolving clinical signs and provide a clinical diagnosis.

5. Where acute cervical spine pathology is suspected, immobilise the neck and arrange urgent MR imaging of the cervical spine.

CASE-BASED DISCUSSION: DIFFERENTIATING CERVICAL CORD COMPRESSION FROM GUILLAIN-BARRE SYNDROME

C Johnston, P Crawford

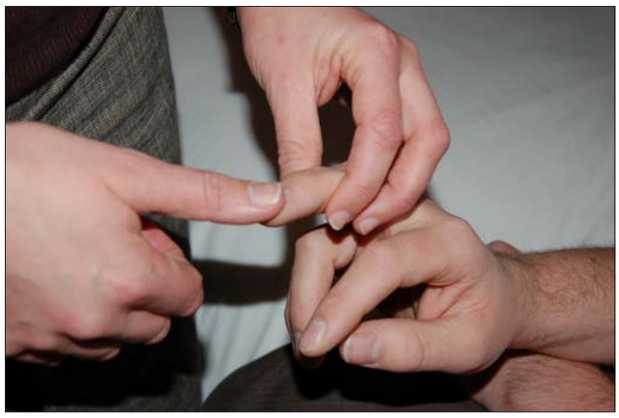


Figure 2: Testing for Hoffman's sign.

Support the hand so that it is completely relaxed and the fingers partially flexed. The middle finger is firmly grasped, partially extended, and the nail snapped by the examiners thumbnail. The sign is positive if there is quick flexion of both the thumb and index finger. (3)

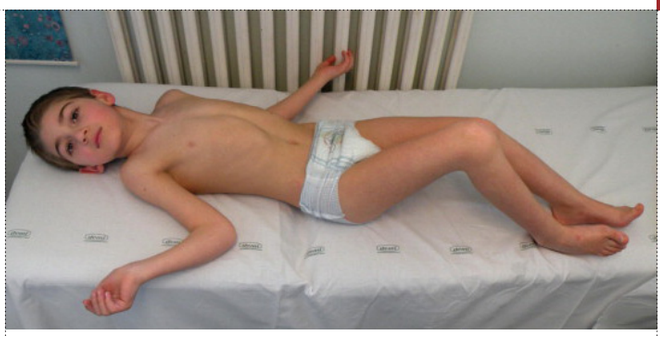
Questions

1. In a patient presenting with acute weakness and sensory disturbance of all four limbs, the following clinical features are consistent with acute spinal cord pathology and warrant urgent investigation with MR imaging. (True/False)

a. Back pain
b. Increased limb tone
c. Neck flexion weakness
d. Brisk reflexes with positive Hoffman's sign
e. Urinary frequency and urgency

2. The following statements are true of false?

a. Black eyes or bruising on the forehead is an important sign in a patient presenting with acute limb weakness and sensory disturbance.
b. A pyramidal pattern of weakness gives increased weakness of extensor muscle groups compared to flexors in the upper and lower limbs.
c. Reflexes can appear brisk in an anxious patient.
d. Sensory loss including the angle of the jaw goes against spinal cord pathology.
e. A patient presenting acutely to the Emergency Department (ED) with symptoms and signs suggestive of spinal cord compression should be admitted and then have MR imaging the next day.



Answers

1. a. F; b. T; c. F; d. T; e. T

Upper motor neurone features including limb hypertonia, hyperreflexia and bladder symptoms point to spinal pathology. Back pain can occur in spinal cord pathology or lower motor neurone conditions such as Guillain Barre Syndrome and is not discriminatory in its own right. Neck flexion weakness is not a feature of spinal cord pathology.

2. a. T; b. F; c. T; d. F; e. F

Black eyes or bruising on the forehead is seen in patients who have had hyperextension injuries of the neck. A pyramidal pattern of weakness gives increased weakness of extensor muscle groups compared to flexors in the upper limbs, but in the lower limbs the flexors are weaker. Reflexes can appear brisk in an anxious patient and testing for Hoffman's sign, abdominal reflexes, plantar responses and for clonus can help to determine whether they are pathologically brisk. The C3 dermatome includes the angle of the jaw. Patients presenting to ED with features of acute cord injury should be immobilised and have MR imaging of the spine as an emergency.

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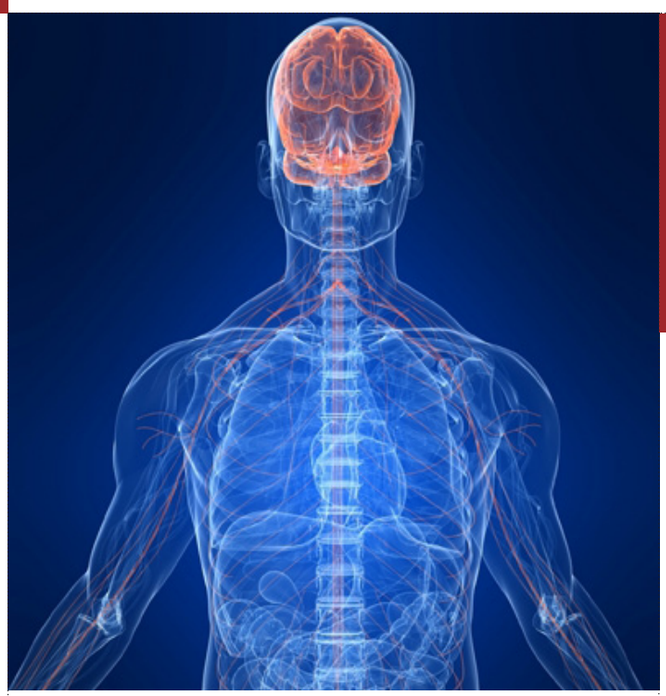
CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

M Atkinson, KPS Nair



Abstract

Spasticity is a common sign in multiple neurological pathologies including multiple sclerosis, cerebral palsy, stroke and spinal cord injury. It is characterised by a velocity dependent increase in tone and has significant negative effects on function as well as significantly contributing to a patient's disability. Treatment can improve patient's quality of life, improve appearance and hygiene as well as prevent the development of complications such as pressure sores (figure 1). In this article we will discuss the causes of spasticity, history taking and examination of patients with spasticity and management strategies.

Key words: *Spasticity, Upper motor neurone, spasms, baclofen, botulinum toxin.*

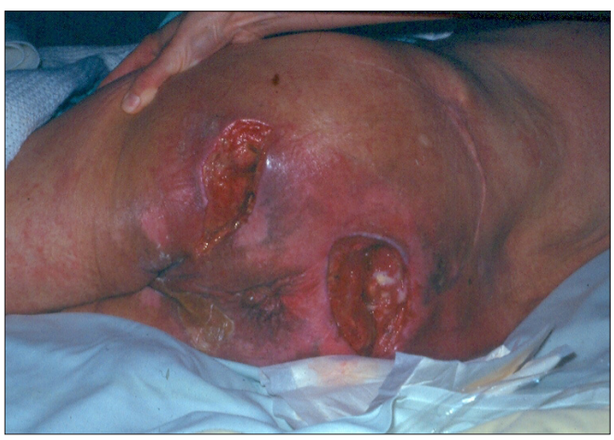


Figure 1: Pressure ulcers in a patient with spasticity.

Clinical Features & Management of Spasticity
Patient Management

What is spasticity?

Spasticity is one of the components of Upper Motor Neurone (UMN) Syndrome (table 1). (1) It is characterised by "a velocity-dependent increase in muscle resistance, in response to a passive stretch." (2) This is due to a disruption of the normal inhibition of stretch reflexes which control skeletal muscle tone. When a muscle is stretched 1a nerve afferents excite alpha motor neurones in the spinal cord causing reflex contraction of the agonist muscles and inhibition of the antagonistic muscles. When the upper motor neurones are damaged there is a reduction in the inhibition of this reflex and increased sensitivity of stretch receptors leading to increased tone (spasticity). Contractures can develop after prolonged periods of immobility due to accumulation of fibrofatty tissues in muscles, loss of elastic tissue and shortening of sarcomeres causing a permanent loss of joint movement (figure 2). (3,4)

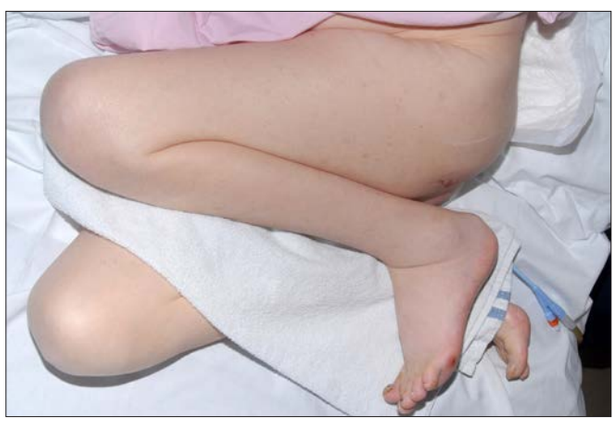


Figure 2: Flexion contractures in lower limbs due to spasticity.

CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

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Positive signs	Increase tone
	Hyperreflexia
	Clonus
	Exaggerated stretch reflexes
	Up going planter reflexes
Negative signs	Paresis
	Loss of dexterity

Table 1: Upper Motor Neurone Syndrome (1)

Patients with spasticity often experience spasms where any noxious cutaneous stimulation causes a reflex withdrawal. This is mediated by a polysynaptic reflex normally inhibited by descending pathways from the brain. Following damage to these inhibitory pathways, any cutaneous or visceral stimuli result in sudden and involuntary spasm which can be sustained or repetitive. (3, 4, 5)

What causes of spasticity?

Spasticity can be caused by any diseases affecting the Upper Motor Neurone (table 2).

Cerebrovascular accident
Traumatic spinal cord injury
Traumatic brain Injury
Spinal cord compression
Multiple sclerosis
Cerebral palsy
Motor neurone disorders
Hereditary spastic paraparesis

Table 2: Diseases which cause spasticity.

Worsening of pre-existing spasticity can be due to progression of primary disease (for example progressive MS), nociceptive stimuli (illustrated in table 3) or a new pathology different from the primary diagnosis. (3,6)

Visceral stimuli	Constipation
	Urinary tract infection
	Urinary calculi
Somatic stimuli	Ingrown toenails
	Pressure ulcers
	Injury (i.e. poor seating/orthotics)
	Cellulitis

Table 3: Nociceptive stimuli.

Evaluation

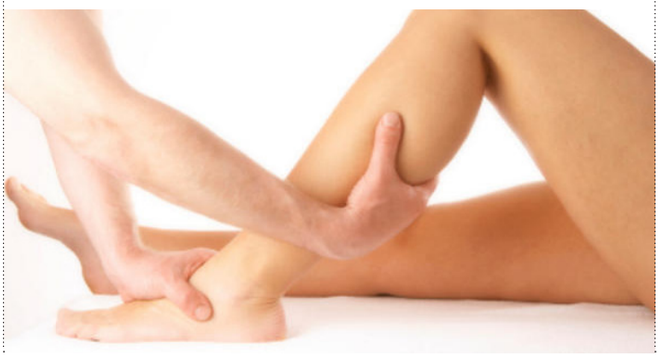
A detailed history and examination are needed during the assessment of spasticity to help identify the cause or exacerbating factor. It is also important to assess the severity of the spasticity and the impact this has on the patient's functionality.

History

A thorough history helps to differentiate between the different causes of spasticity. It can also help identify exacerbating factors (table 3). The pattern of spasticity can point to the location of the underlying pathology (i.e. spastic paraparesis due to spinal cord lesion, spastic hemiplegia due to brain lesion). The onset and any events at onset is useful to help differentiate acute (traumatic spinal cord injury) and more insidious pathologies (spinal cord compression). A history of transient neurological deficits may indicate multiple sclerosis and presence of associated features, such as fever and back pain, may indicate other pathologies such as discitis.

Examination

Aims of examination are to identify the cause of spasticity and its triggers. Examination can confirm the presence of spasticity and rule out other causes of increased tone such as rigidity. In spasticity the increased tone is velocity dependent, meaning the more force is applied to a stretch, the greater the resistance. There can also be a clasp-knife phenomenon where sustained force overcomes initial resistance and then a relaxation of muscle. This contrasts with the increase tone in rigidity which is equal in opposing muscle groups and is consistent throughout a range of movement.(7) In addition, a full neurological examination will help to identify the cause of spasticity. A thorough systemic examination will help determine exacerbating factors (table 3).



CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

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Impact

It is crucial to assess the level of impact spasticity has on the patient and their carers. Do they experience painful spasms, how disruptive is this to them? Does the spasticity affect their positioning/posture? Is there difficulty with hygiene tasks, bowel and bladder care or sexual relations? Do they have pressure areas? Conversely spasticity can have benefits. Trunk spasticity can aid sitting upright and standing, walking and transfers can be aided by spasticity in extensors of hips and knees.(3) It is vital that both detrimental and beneficial effects are taken into account in the assessment of spasticity.

Assessment

There are multiple tools for the assessment of spasticity, none of which are universally clinically accepted. (8,9) The most commonly used scale is the Modified Ashworth Scale (table 4). (3) There is evidence that it can be reliable if used by the same assessor. (1,3,10)

0	No increase in muscle tone
1	Slight increase in muscle tone
1+	Slight increase in muscle resistance throughout a range of motion
2	Moderate increase muscle tone throughout a range of movement. Passive movement is easy
3	Marked increase in muscle tone throughout a range of motion. Passive movement is difficult
4	Marked increase in muscle tone, affected part is rigid.

Table 4: The Modified Ashworth Scale (3).

Management

It is important to remember that the decision to treat spasticity is made primarily on an assessment of the impact of the spasticity on patient's disability and functionality. (1) The primary aims of treating spasticity are to improve disability and prevent future complications (such as pressure sores). The management of spasticity includes goal setting, elimination of triggers (table 3), non-pharmacological interventions, and pharmacological intervention.

The first step is to set treatment goals, which are meaningful for the patient. Examples of spasticity management goals are pain relief, improved gait, ease of activities of daily living, reduced burden of care, and prevention of complications. A successful spasticity treatment programme requires input from a multidisciplinary team.

Non-pharmacological interventions

Passive stretching and positioning is thought to decrease the excitability of motor neurones and can be delivered by therapists or carers. Limbs can also be kept stretched with splints or casts. Although the benefits of passive stretching are unproved at this time there is no evidence it is harmful. (11) There is evidence that exercises and standing may help to reduce spasticity (12) as well as providing other benefits such as improved psychology, bone mineral density and bladder and bowel functions.(3) Correct posturing reduces the aggravation of spasticity and prevents development of contractures.

Pharmacological Therapies

All antispasticity drugs cause weakness. These drugs should be introduced slowly and doses need to be titrated based on the response. Rapid dose escalation may cause side effects like weakness, drowsiness and falls. Good communication between physicians the multidisciplinary team and the patient (along with care-givers/family) is essential before commencing antispasticity drugs. Aims of treatment, side effects, dose escalation and expected positive effects all need to be communicated to ensure compliance. (3,13). Antispasticity drugs should not be stopped suddenly as this can lead to a rebound increase in spasticity as well as other withdrawal symptoms (such as hallucinations and occasionally seizures). (3,14).

CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

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Oral treatments

A 2004 meta-analysis found limited evidence on the efficacy of oral antispastic drugs and that reported side effects were high. (15) Despite this they remain the initial pharmacological treatment for spasticity. (1)

Baclofen

Baclofen is probably the most widely used oral antispasticity drug. As a GABA-B receptor agonist it down-regulates activity of the 1a sensory afferents, motor neurones and spinal inter-neurones. (3) Side effects include weakness, drowsiness and dizziness and occasionally urinary incontinence and sexual dysfunction. (1,3,13). Neonatal seizures have been reported in new born babies of mothers taking baclofen. It is excreted in breast milk, so should be avoided in breastfeeding and used with caution in pregnancy. (3)

Benzodiazepines

This class of drugs are GABA-A agonists. Drowsiness and behavioural side effects limit their use to treatment of spasms interfering with sleep. Clonazepam is a useful drug for the treatment of nocturnal spasms.

Gabapentin and Pregabalin

These are GABAergic drugs which are mainly used as adjuncts in the treatment of spasticity, especially when there are issues with neuropathic pain.

Tizanidine

An alpha-2 receptor agonist, tizanidine inhibits excitatory spinal interneurones. Side effects include dry mouth, sedation, QT prolongation and acute hepatitis (1,3,13).

Dantrolene

This drug is the only oral antispasticity drug that acts on muscles directly. It inhibits calcium release from the sarcoplasmic reticulum. It can cause hepatotoxicity, therefore liver function should be measured before commencing dantrolene and regularly during treatment. (3,13)

Cannabinoids

There is limited evidence that cannabinoids may prove improvement in patient reported outcomes in a small number of patients with spasticity secondary to multiple sclerosis. Concerns remain about the long term effects of treatment.(3)

Botulinum Toxins

Intera muscular injection with Botulinum toxins is used to directly treat the spastic muscle. It has been shown to be effective in reduction of spasticity of multiple aetiologies. It is especially beneficial when used in conjunction with physiotherapy interventions (1,13).

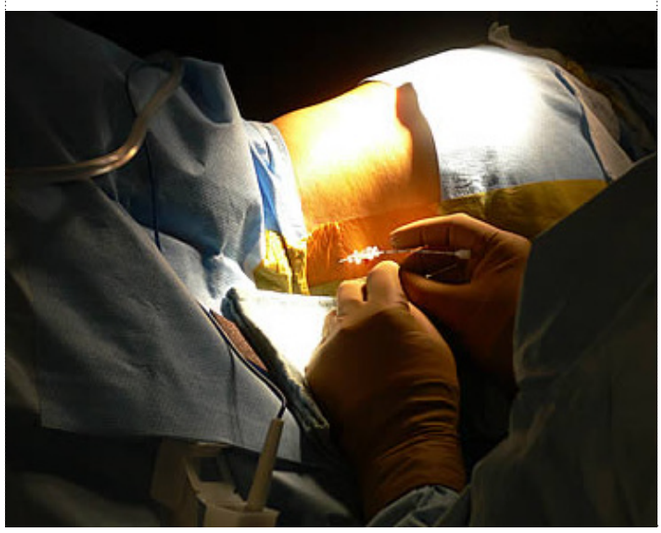
The therapeutically used toxins are extracted from toxins produced by the Clostridium Botulinium bacteria. Botulinum toxins irreversibly degrade SNAP-25 in the pre-synaptic nerve endings, preventing acetyl choline release therefore blocking neuromuscular transmission. Botulinum toxin causes selective weakness of the target muscle and is particularly useful for selective reduction in spasticity without the side effects of global weakness or sedation. Over 3-9 months nerves sprout back and the effect is reversed. (3) The injections can be repeated once every 3-4 months. Reported adverse side effects include muscle weakness, falls, pain, dysphagia and antibody development. (3,13)

Phenol Injection

Phenol causes protein coagulation in neural tissue when injected into nerves. Side effects include pain, dysthesia (abnormal often painful sensation to touch), oedema, skin sloughing and wound infections. Treatment with phenol also increases the risk of deep vein thrombosis and leukaemia. (3)

Intrathecal Baclofen

Oral Baclofen does not cross the blood brain barrier well. Therefore bioavailability of oral baclofen to the GABAergic neurones in the spinal cord is very low. Administrating the baclofen directly into the spinal subaracnoid space (Intrathecal baclofen) achieves therapeutic effect with far fewer side effects with a fraction of oral doses. (3) Intrathecal Baclofen is indicated for severe spasticity in the lower limbs despite treatment with two simultaneous oral anti-spasticity drugs A test dose of intrathecal bacofen is recommended before undergoing pump implantation. (1,3,13,16) Although well tolerated, intrathecal baclofen carries the risks of a general anaesthetic as well as those of catheter disconnection, obstruction and leakage as well as pump infection or erosion (figure 3). (1,3,13)



CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

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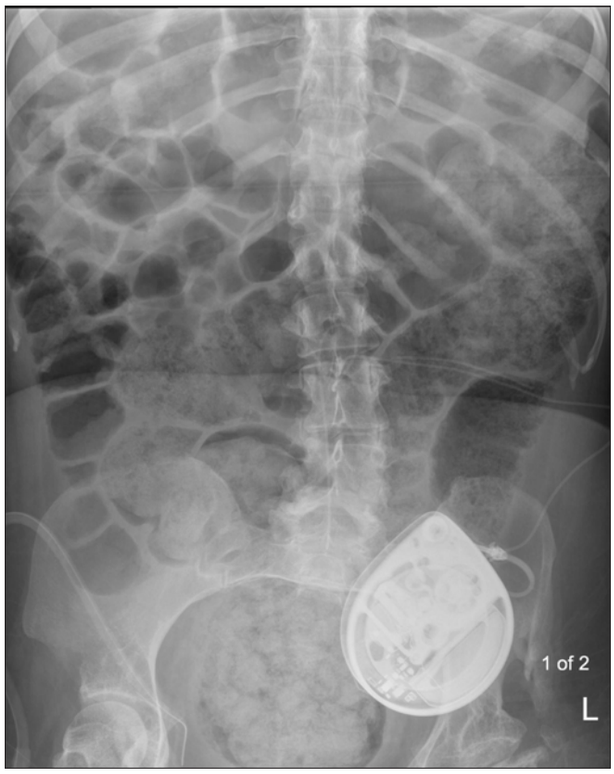


Figure 3: Abdominal X-ray showing intrathecal baclofen pump in situ.

Summary

Spasticity is one component of upper motor neurone syndrome. Untreated, it can cause pain, discomfort and reduced to mobility. Complications of spasticity include pressure ulcers and severe contractures. Treatment should start with eliminating the trigger factors and then progress to physiotherapy and pharmacological approaches. Oral antispasticity drugs should be started at a low dose and gradually titrated. In patients whose spasticity is resistant to oral treatments, intrathecal baclofen pump should be considered. An algorithm for treatment of spasticity is shown in figure 4.

Clinical Features & Management of Spasticity
Patient Management

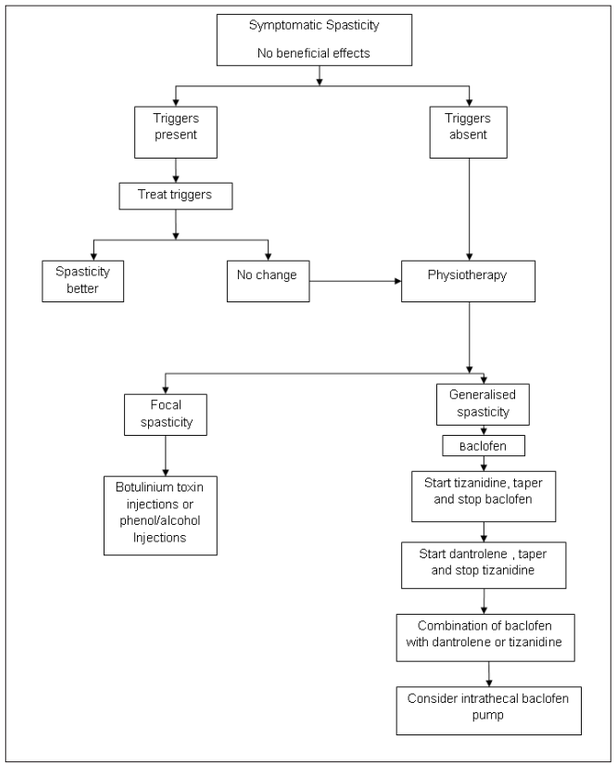
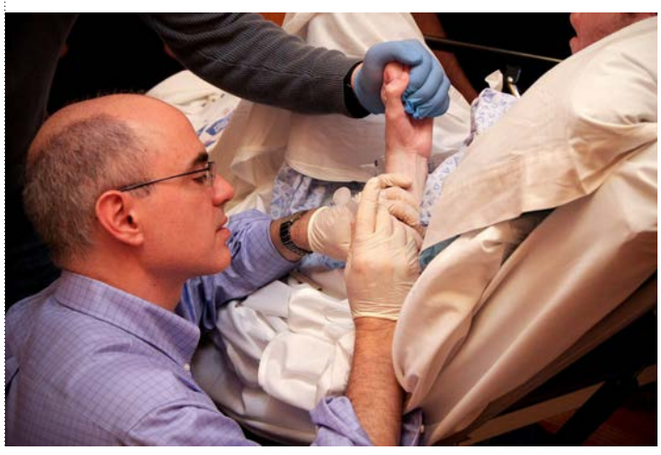


Figure 4: An algorithm for treatment of spasticity.



CLINICAL FEATURES & MANAGEMENT OF SPASTICITY

M Atkinson, KPS Nair

Test Yourself Questions

1) Which among the following is associated with spasticity?

A) Cog wheel
B) Gegenhalten
C) Pendular knee jerk
D) Clasp knife
E) Lead pipe

2) Which of the following is a trigger for spasticity

A) Urinary tract infection
B) Appendicitis
C) In growing toe nail
D) Pressure ulcers
E) All of the above.

Answers

1. Answer: D: Clasp Knife

Clasp-knife' phenomenon is where the spastic limb initially resists movement before giving away suddenly, rather like the resistance of a folding knife blade. During initial movement, the tone is high due to overactive stretch reflex. On sustained force, the Golgi tendon organs get stimulated resulting in the inverse stretch reflex relaxing the muscles with a 'give away' feel.

2. Answer: E: All of the above

Increasing spasticity can occur because of nociceptive, visceral or somatic stimuli. These are exaggerated reflex response to nociceptive stimuli and are mediated by polysynaptic inter-segmental spinal cord circuits. Common causes of exacerbation of spasticity are urinary tract infections and constipation. Identification and elimination of these triggers is an important part of management.

Authors

Dr Megan Atkinson
Foundation Year-2 Doctor
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffield S5 7AU

Dr KPS Nair
Consultant Neurologist
Royal Hallamshire Hospital
Glossop Road
Sheffield S10 2JF
Email: siva.nair@sth.nhs.uk

Correspondence details

Dr Megan Atkinson
Foundation Year-2
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffield
S5 7AU
Email: megan.atkinson@nhs.net
Telephone: 0114 267 0897

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ENCEPHALITIS

SK Chhetri, T Majeed

Abstract

This article discusses the clinical approach to a patient presenting with encephalopathy with a particular emphasis on encephalitis. We outline the common causes of encephalopathy followed by clinical features, investigations and treatment of patients with viral encephalitis. We also discuss common causes for delays and errors in diagnosis and treatment. Finally, we discuss the non-infective causes of encephalitis including paraneoplastic and autoantibody mediated immune encephalitis.

Case History

A 32 year old right handed lady is brought to the hospital with a 3 day history of fever, confusion and one witnessed episode of generalised tonic clonic seizure. There is no significant past history of note. There is no history of foreign travel. She is not on any medications. Clinical examination demonstrates a GCS of 14 (E4, M6, V4). There is no focal neurology of note. What would you do next?

Encephalopathy – A Clinical Syndrome

The patient has presented with encephalopathy, a clinical syndrome of diffuse brain dysfunction secondary to a number of infectious and non-infectious causes. (1) The hallmark of encephalopathy is an altered mental state. Other clinical features may include impaired cognition, fluctuation in alertness, lack of concentration and personality changes. The differential diagnosis is extensive (table 1); however a careful history, focussed examination and appropriately targeted investigations will prove rewarding in excluding and/or confirming most of the common causes. The patient's age, immunocompetence and tempo of progression are all important in the diagnostic process. The basic evaluation includes clinical and laboratory assessment for evidence of infection and metabolic derangements suggestive of a systemic process.

Neurological causes
Infections (see below)
Inflammation
Acute disseminated encephalomyelitis (ADEM)
CNS vasculitis
Degenerative disease
Creutzfeldt-Jakob disease (CJD)
Rapidly progressive Alzheimer's disease
Dementia with Lewy bodies
Neoplastic/Paraneoplastic
Primary and secondary brain tumours
Paraneoplastic Limbic encephalitis
Autoimmune
Autoimmune limbic encephalitis
Hashimoto's encephalopathy
Vascular
Ischaemic stroke
CNS haemorrhage
Seizures – e.g. non convulsive status epilepticus
Systemic Causes
Metabolic and endocrine
Uraemic encephalopathy
Hepatic encephalopathy
Hypoglycaemia
Electrolyte (e.g. calcium, sodium) disturbances
Nutritional and toxic disorders
Wernicke encephalopathy (Thiamine deficiency)
Alcohol including alcohol withdrawal syndrome
Recreational drug use
Vitamin 12 deficiency
Chemotherapeutic agents
Connective tissue disorders
Systemic lupus erythematosus (SLE)
Sjogren's syndrome
Infection – Septic encephalopathy
Cardiorespiratory failure

Table 1: Causes of encephalopathy.

Important aspects of the history and clinical evaluation

The short history of fever, confusion and seizure in a previously healthy individual would raise concerns for encephalitis. Encephalitis is inflammation of the brain parenchyma and is one of the causes of encephalopathy.(2) It affects all age groups and can result from a spectrum of infectious and non-infectious causes. The morbidity and mortality can be high, if left untreated or there are delays in treatment.

ENCEPHALITIS

SK Chhetri, T Majeed

History is the key to further diagnostic pursuits and every attempt must be made to ensure that a relevant history is obtained (Table 2). If the patient is confused, it is essential to take a collateral history from family members or friends. 'History not available as the patient is confused' often leads to errors in diagnosis and management. It is important to elicit history of personality and/or behavioural change from friends and/or relatives. Do not disregard concerns that a patient is irritable or 'not their usual self'. History taking should aim to unearth the following issues:

- *Sub-acute memory impairment, confusion and seizures might suggest limbic encephalitis affecting the limbic system. (3)*

- *Movement disorder e.g. orofacial dyskinesia, choreoathetosis or seizures may suggest autoimmune encephalitis.*

- *Skin rash may suggest infections like enterovirus, chickenpox, measles and mumps, particularly in children.*

- *Recent foreign travel – e.g. dengue or Japanese encephalitis may affect travellers from Asian subcontinent.*

- *Insect bites e.g. mosquito, tick bites (Lyme disease, tick borne encephalitis)*

- *Contact with individuals suffering from infectious diseases.*

- *Recent vaccination might suggest ADEM.*

- *Risk factors for immunocompromise caused by disease e.g. HIV and/or drug treatments.*

History
Prodromal illness
Behavioural and personality changes
New onset cognitive impairment or confusion
New onset seizures or movement disorder
New focal neurological symptoms
Skin rash
Recent vaccination
Contact with individuals suffering from infectious diseases
History of animal/insect bites
Travel history
Risk factors for immunocompromise eg HIV
Examination
Airway, Breathing, Circulation
Glasgow coma score
Seizure activity e.g. digit or eyelid twitching
Movement disorders
Skin rash
Bites from animals or insects
Neck stiffness
Kernig's sign
Papilloedema
Flaccid paralysis
Focal neurological signs
Systemic examination e.g. respiratory, gastrointestinal

Table 2: Historical and examination clues.

The immediate priority is to ensure that airway is protected and vital signs (oxygen saturation, pulse and blood pressure) are stabilized. The level of consciousness should be documented by using the Glasgow Coma Scale (GCS). If the GCS is low, for instance less than 8, the case should be discussed with intensive care unit. It is important to perform a thorough neurological examination to ensure that focal neurological signs are not missed. Neck stiffness or a positive Kernig's sign would indicate meningeal involvement. Digit or eyelid twitching might indicate subtle seizures and may easily go unnoticed. Fundus should be examined to look for papilloedema which would suggest raised intracranial pressure. The presence of flaccid paralysis indicates the possibility of polio, enterovirus or arbovirus infection. (2) Examine the skin for evidence of skin rash. Systemic assessment must be performed to look for evidence of concurrent illness like pneumonia.

Potential diagnostic traps:

- *Patients may present with confusion, altered or reduced consciousness, personality change, headache and fever. However, 28% of patients with encephalitis may not be febrile on admission. (4) Absence of fever does not exclude the diagnosis of encephalitis.*

- *Respiratory, urinary and gastrointestinal symptoms are not uncommon in patients with proven encephalitis. (2,4) It is important not to attribute behavioural and/or personality changes to systemic infections like urinary tract infection or gastroenteritis in an otherwise healthy patient, unless there is substantial evidence.*

- *Glasgow coma score is a crude tool to detect subtle cerebral dysfunction and a normal GCS does not exclude encephalitis. (5)*

- *Delay in performing lumbar puncture.*

- *A 'normal CSF' does not necessarily exclude the diagnosis (see below).*

Infectious cause of encephalitis

Limbic encephalitis (LE) usually presents with sub-acute (days to weeks) impairment of memory, confusion, agitation and disorientation. (3) Seizures may occur. In some cases, there is gradual onset of mood disturbances including depression and hallucinations which may be misdiagnosed as a psychiatric illness. Viral infections, particularly herpes simplex virus and autoimmune conditions are the most common causes of LE. (2,3) Encephalitis resulting from infection can present as acute viral encephalitis or postinfectious encephalomyelitis. (2,4,5) In one UK based study, 42% of patients with encephalitis had an infectious cause of which 19% had HSV and 5% each had VZV and Mycobacterium Tuberculosis. (4)

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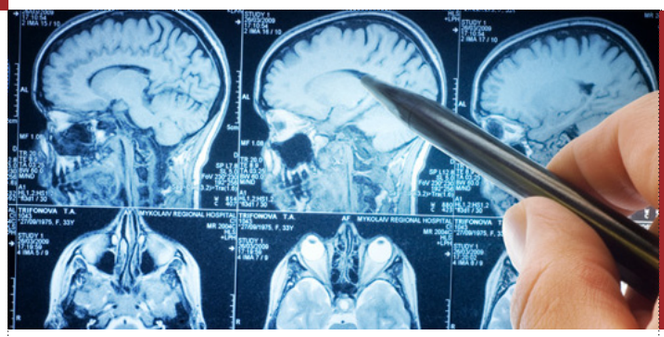

Encephalitis
Patient Management

Infections must always be considered and treatment instituted promptly, if there is any suspicion about the diagnosis. Fever, altered mental state and headache should raise alarm bells for infectious encephalitis. HSV is responsible for approximately 70% of cases of viral encephalitis with a mortality of nearly 70%, if untreated. (2) In an immunocompromised patient, the possibility of other infections like herpes simplex type 2, and human herpes viruses (HHV) (6) should be considered. Neuroimaging often demonstrates swelling and signal changes in the temporal lobes, best appreciated on MRI.

Herpes viruses
Herpes simplex virus types 1 & 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, HHV types 6 & 7
Enteroviruses
Coxsackie viruses, echoviruses, enterovirus, rhinovirus, parechovirus, Poliovirus
Other viruses
Mumps, measles, influenza, adenovirus, Japanese Encephalitis, HIV
Tuberculosis, Mycoplasma, Lyme disease, Neurosyphilis
Rare : Fungal, parasitic and rickettsial causes

Table 3: Infectious causes of Encephalitis (2).

What investigations would you arrange?

- *Routine blood tests including renal function tests, inflammatory screen and blood cultures should be requested. Atypical lymphocytes may suggest EBV infection.*

- *Hyponatremia may be suggestive of voltage-gated potassium channel (VGKC) antibody associated encephalitis, in the appropriate clinical setting (see below). (2,6)*

- *Chest X-ray should always be performed as there may be abnormalities suggestive of pneumonia including atypical infection, tuberculosis and malignancy.*

- *If atypical pneumonia is suspected, mycoplasma and chlamydia serology should be requested. Presence of cold agglutinins would indicate a diagnosis of mycoplasma. (2)*

- *HIV testing should be arranged as presentation and management of encephalitis is influenced by host factors including immunocompetence. For instance, in an immunocompromised patient, toxoplasma and syphilis serology should also be performed.*

- *Neuroimaging in the form of cranial CT or MRI should be performed to exclude a space occupying lesion and identify diagnostic patterns. MRI is the imaging modality of choice in cases of suspected encephalitis, although CT scan can be used if immediate access to MRI is not available. A normal scan, particularly early in the illness, does not exclude encephalitis. However, CT scan may show attenuation or areas of hyperintensity in one or both temporal lobes. MRI scan is more sensitive and may demonstrate T2 hyperintense lesions mainly in the temporal and orbital surface of the frontal lobes (Figure 1). There may be variable contrast enhancement with or without a haemorrhagic component. (2,7)*

- *Electroencephalography may demonstrate focal slowing or epileptiform discharges in the temporal lobes.*

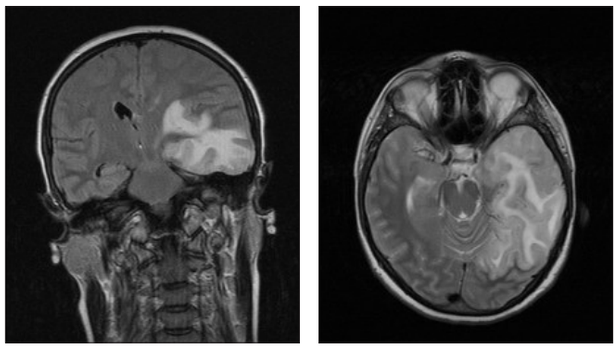

Figure 1: Coronal MRI T2 FLAIR (Figure 1a) and Axial T2 MRI of the brain (Figure 1b) showing hyperintensity involving mainly the left temporal lobe in a patient with HSV encephalitis.

If no contraindications to lumbar puncture are found on imaging or clinical grounds, cerebrospinal fluid (CSF) analysis should be performed which usually demonstrates raised CSF opening pressure, lymphocytosis and mildly raised protein. The technique and contraindications of lumbar puncture and CSF patterns in different conditions has been discussed previously in this journal. (8,9) Common contraindications include focal neurological symptoms and signs including seizures, papilloedema, pupillary changes; haemodynamically unstable patient; coagulopathy including platelet count of less than 50 x 10^9/L, INR of more than 1.4 and skin sepsis at the site of puncture. Delays in performing lumbar puncture can lead to delays in diagnosis and treatment. All patients with suspected encephalitis should have CSF analysis for cell count and culture, protein, glucose (with paired serum glucose), PCR for HSV1, HSV2, VZV, parechovirus and enterovirus.(2)

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CSF polymerase chain reaction (PCR) for herpes viruses is the gold standard for diagnosis with a sensitivity and specificity of more than 95% between day 2 and 10 of the illness.(7) EEG usually demonstrates non-specific slowing suggestive of encephalopathy. However, it may also show periodic lateralised discharges suggestive of HSV encephalitis or seizure activity.(2)

In a patient with risk factors for immunocompromise, the following additional investigations should be considered in the CSF. (2,7)

1. PCR for CMV, EBV, HHV6, HHV7

2. Acid fast bacillus staining and culture for tuberculosis

3. Culture for listeria monocytogenes.

4. Indian ink staining and/or cryptococcal antigen (CRAG) testing for Cryptococcus neoformans.

What are the pitfalls in interpretation of CSF results?

1. If the initial CSF analysis is non-diagnostic, a second lumbar puncture should be performed 24 – 48 hours later, as in 5 -10% of patients with proven HSV encephalitis, initial CSF findings may be normal. (2,7)

2. Polymorphonuclear cells may predominate early in the course of illness and may lead to confusion with bacterial infection. However, CSF blood glucose ratio is usually normal in viral encephalitis as compared to a low ratio in bacterial encephalitis. Always send paired serum samples for glucose along with CSF glucose.

3. HSV encephalitis may have haemorrhagic CSF because of haemorrhagic necrosis of involved parenchyma and should not lead to suspicion of subarachnoid haemorrhage, in the appropriate clinical context.

4. CSF protein and white cell count may be spuriously raised from a traumatic tap. The white cell count and protein can be approximately corrected for the number of red cells in the CSF by subtracting 1 white cell for every 700 red blood cells/mm^3 in the CSF and 0.1 g/dl protein for every 1000 red blood cells.

5. Immunocompromised patients may not be febrile and may have a normal CSF but the diagnosis of encephalitis must be considered in the setting of altered mental state.

How would you treat a patient with suspected viral encephalitis?

Intravenous acyclovir at a dose of 10 mg/kg three times daily should be started, as quickly as possible, if there is any suspicion about the diagnosis or initial imaging studies and/or CSF is suggestive. If delays are anticipated in performing investigations, treatment should still be started as soon as possible, if the clinical suspicion is strong. Treatment with intravenous acyclovir reduces the mortality from 70% to approximately 20 – 30% and should be continued for a minimum of 14 days – 21 days. (2,7) Acyclovir has the potential to cause crystalluria resulting in obstructive nephropathy and therefore renal functions should be closely monitored whilst on the drug. Ensure that the patient is adequately hydrated to reduce the risk of renal impairment.

You have started the patient on intravenous acyclovir and the initial PCR has returned negative. What do you do? When do you stop acyclovir?

HSV PCR may be negative in the first few days of illness and if the clinical suspicion is strong, a second CSF should be taken 24-48 hours later. (2,7) Acyclovir may be stopped under the following circumstances in an immunocompetent individual. (2)

a. A definitive alternative diagnosis has been made or

b. HSV PCR on two occasions 24 – 48 hours apart is negative and MRI brain is not suggestive of encephalitis.

c. There is no impairment of consciousness, MRI brain and HSV PCR in the CSF performed more than 72 hour after onset of neurological symptoms is normal or negative and CSF white cell count is less than 5.

In a case of suspected encephalitis do not stop treatment on the basis of one negative HSV PCR.

Non-infectious Limbic encephalitis

Non infectious LE may be paraneoplastic, occurring in association with a tumour or non-paraneoplastic which is usually mediated by autoantibodies. (3) These conditions are uncommon; paraneoplastic LE and autoantibody associated encephalitis accounts for approximately 0.5% and 7% of all causes of encephalitis. (4) An autoimmune cause for LE should be considered early as institution of appropriate and timely treatment can improve clinical outcomes. In many cases of non-infectious LE, an autoantibody is likely to be pathogenic. Based on the target of these autoantibodies, LE can be broadly classified into the following groups: (3,6,10-14).

LE associated with classical onconeural antibodies against intracellular neuronal targets.

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These cases are almost always paraneoplastic in nature with limited treatment options and poor prognosis. (3,6,10) Common onconeural antibodies include anti neuronal nuclear antibody -1 (ANNA-1) or Anti Hu associated with small cell lung cancer (SCLC); ANNA-2 or anti Ri antibody associated with breast cancer and SCLC; Anti Yo antibody associated with ovarian and breast cancer; Anti-CV2 (CRMP) associated with lymphoma and SCLC; and anti Ma 2 antibody associated with testicular cancer. These onconeural antibodies are detected in roughly 60% of confirmed paraneoplastic LE, and therefore their absence does not exclude the diagnosis. (11) The consensus diagnostic criteria for paraneoplastic neurological syndrome requires the following. (10)

1. Sub acute onset (up to 12 weeks) of short-term memory loss, seizures, confusion and psychiatric symptoms suggesting involvement of the limbic system.

2. Neuropathological or neuroradiological evidence of involvement of limbic system.

3. Detection of well characterised onconeural antibodies or demonstration of cancer within 5 years of the neurological symptoms.

The neurological symptom predates the diagnosis of cancer in up to 60% of the patients by months or years (median time of 3.5 months). (11) Although paraneoplastic LE is rare, awareness of this syndrome may therefore enable earlier detection and treatment of cancer which may lead to better neurological outcomes.(11) A thorough search for underlying malignancy should be undertaken and various imaging modalities including positron emission tomography (PET) scan may be necessary, depending on the clinical syndrome. (12) Even if the initial screen is negative in a patient with LE and onconeural antibodies, it is important to follow the patient with interval screening, every 6 monthly for 4 years.(12) Treatment of paraneoplastic LE includes treatment of the underlying tumour, immunotherapy and supportive therapy.

LE associated with autoantibodies against neuronal surface antigens. These cases usually have an autoimmune basis but can be part of a paraneoplastic process. These autoantibody mediated LE carry a better prognosis if treated early and aggressively with appropriate immunomodulatory treatments like steroids, plasma exchange and immunosuppressant drugs. (6,13) Common autoimmune LE include VGKC antibody associated LE and anti NMDA receptor encephalitis.

VGKC antibody associated LE usually presents with sub acute memory loss, confusion and seizures. (6,13) The condition is more common in males (male to female ratio of 2:1) and the presenting age is usually more than 50 years. Hyponatremia occurs in 60% of the cases. MRI brain shows characteristic high signal in the medial temporal lobes (Figure 2) in 60% of the cases. (6) Less than 10% of cases are associated with tumour, commonly SCLC or thymoma. CSF is usually normal.

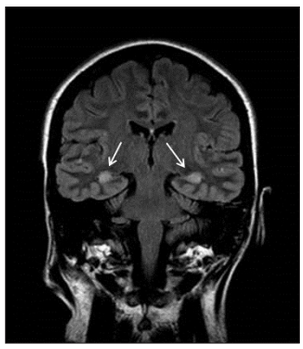
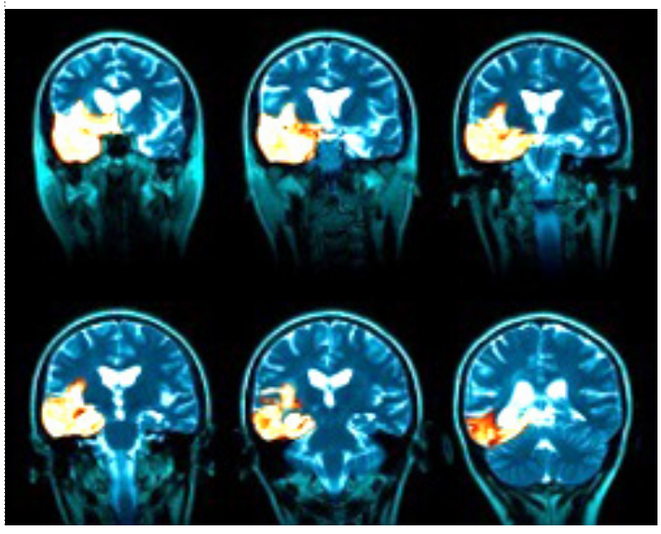


Figure 2: Coronal MRI T2 FLAIR (Figure 2) of the brain showing high signal changes in the medial temporal lobes bilaterally (arrows) in a patient with autoimmune encephalitis.

Anti NMDA receptor encephalitis usually occurs in females (male to female ratio of 1:3) and the median age of presentation is 25 years. (14) There may be a prodrome of fever, headache or a viral infection. The subsequent illness usually has two stages. The first stage is usually characterised by seizures, confusion, amnesia and a range of psychiatric symptoms including psychosis, anxiety, insomnia, delusions and hallucinations. The second stage occurring days or weeks later manifests with movement disorders, dysautonomia, hypoventilation and reduced responsiveness. MRI is often normal but high signal may occasionally be seen in the medial temporal lobes. CSF is frequently abnormal with lymphocytic pleocytosis and oligoclonal bands. 20 – 50% of female patients have ovarian teratoma. (14)



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Conclusion

Encephalitis remains a common medical emergency with significant mortality and morbidity, particularly if treatment is delayed. It is important to maintain vigilance for encephalitis when a patient presents with mental status changes, as early recognition and timely treatment can reduce mortality and prevent serious morbidity.

MCQ's (True or False)

1. The Glasgow coma scale is a sensitive indicator of cerebral dysfunction.

2. Viral infections account for 70% of cases of encephalitis.

3. All patients with encephalitis are not febrile on admission and/or do not have a history of fever.

4. A normal CSF white cell count excludes viral encephalitis.

5. Young females presenting with acute/subacute history of confusion, seizures and hallucinations should be investigated for anti NMDA receptor encephalitis.

Answers

1. False.

Glasgow coma score is a crude tool to detect subtle cerebral dysfunction and a normal GCS does not exclude encephalitis.

2. False.

There are a number of non-infectious causes of encephalitis including paraneoplastic and autoimmune etiologies.

3. True.

Absence of fever does not exclude the diagnosis of encephalitis as approximately 28% of patients with encephalitis may not be febrile on admission, particularly patients with autoimmune encephalitis.

4. False.

CSF analysis may be completely normal, particularly early in the illness. If there is a strong clinical suspicion of viral encephalitis, lumbar puncture and CSF analysis should be repeated 24 – 48 hours later.

5. True.

A sub-acute history of confusion, hallucinations, psychosis and seizures should raise suspicion for anti NMDA receptor encephalitis, as early treatment can be associated with favourable outcomes. Female patients with anti NMDA receptor encephalitis should be screened for ovarian teratoma.

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Authors

Dr Suresh Kumar Chhetri, MRCP
Specialist Registrar in Neurology

Dr Tahir Majeed, PhD, FRCP
Consultant Neurologist

Corresponding Author

Suresh Kumar Chhetri
Department of Neurology,
Royal Preston Hospital,
Preston, PR2 9HT.

Tel: 07795068968
Email: suresh.chhetri@nhs.net

INTERNUCLEAR OPHTHALMOPLEGIA & BRAIN STEM STROKE-CASED BASED DISCUSSION

H Ward, R Buccoliero

Abstract

Foundation doctors can be faced with a variety of neurological presentations whilst working on the medical wards. Whilst traditionally medical students and juniors can often feel that neurology is difficult to interpret, it is a requirement of the core curriculum (1), therefore developing a thorough and systematic approach to any patient is the most important first step. This case based discussion focuses on the diagnosis of a patient with internuclear ophthalmoplegia (INO) following an acute admission for sudden onset of diplopia. The article will look at her initial assessment, followed by the subsequent investigation and long term management of her newly diagnosed stroke.

Case history

The case is that of an 86 year old lady, Mrs. G, who presented to the stroke/ neurology unit complaining of diplopia, having attended Accident and Emergency. That morning she had awoken with 'a heavy feeling in her head', and as she had got out of bed to walk to the bathroom she noticed that she was unable to focus on things and was seeing double. She had been well the previous evening before going to bed.

What is the most likely cause of her diplopia?
How would you approach this patient?

Eye movement is controlled by six muscles, which in turn are innervated by three separate cranial nerves. Lesions causing diplopia could be due to trauma, space occupying lesions, vascular insufficiency, aneurysm, and neurological disease (Multiple Sclerosis-MS, Myasthenia gravis, meningitis) amongst other causes. Therefore a full neurological assessment is necessary.

Internuclear ophthalmoplegia & brain stem stroke-Cased based discussion.
Patient Management

Initial assessment

ABCDE

As with all patients of whom you are making an initial assessment, ABCDE (Airway, Breathing, Circulation, Disability, Exposure) should be carried out in order to ensure the patient is clinically stable before approaching a more detailed history and examination.

In this case the patient was alert, comfortable, able to communicate with no concerns. Observations were stable and it was possible to progress to more focused assessment.

What factors of the history are important?

Presenting problem:

- *Was the onset sudden or gradual?*
- *Has the visual disturbance changed over time?*
- *Is double vision noted on horizontal or vertical gaze, to one side or both?*

Associated symptoms:

- *Has there been any focal weakness, sensory disturbance, dizziness, headache, numbness, weakness, tremor, loss of consciousness, seizures, other eye symptoms, fatiguability of muscles?*

Previous Medical History:

- *Does she have known diagnoses of hypertension, diabetes, thyroid, epilepsy, cancers, head injury, Atrial Fibrillation (AF)?*

Family history:

- *Of neurological disease?*
- *Other relevant history – diabetes, stroke, cancer.*

Social:

- *Does she drive?*
- *Does she live alone, in what type of accommodation?*
- *Has she ever smoked, does she drink alcohol?*

Drug history

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History of presenting complaint

In this case study the patient had experienced sudden onset of the horizontal diplopia (having woken up with it), noticeable when she looked to the right side. She had experienced no loss of consciousness, dizziness or headache. She had noticed no focal weakness or sensory disturbance and her speech was normal. She noted no pain, redness or swelling of her eyes. Systemic review was unremarkable.

Past medical, family and social history

She was known to have hypertension, arthritis, an abdominal aortic aneurysm and recent admission to hospital with a lower respiratory tract infection. There was nil of note in her family history. She lived alone, was usually independently mobile with a stick. She had never smoked and drank alcohol only rarely.

Medications/Allergy

Her medications consisted solely of Ramipril, she had a known allergy to penicillin.

Which aspects of physical examination are important?

- *Weight and Body Mass Index (BMI).*
- *Blood pressure.*
- *Cardiovascular examination including evidence of hyperlipidaemia.*
- *Full Neurological examination including full inspection of eyes, eyelids, nystagmus .*

General examination

On examination pulse was regular of 100 beats/min and, heart sounds were normal. Blood pressure was 170/90 mmHg. Mild bilateral ankle oedema was noted, jugular venous pressure was not elevated. Her chest was clear, her abdomen soft and non-tender.

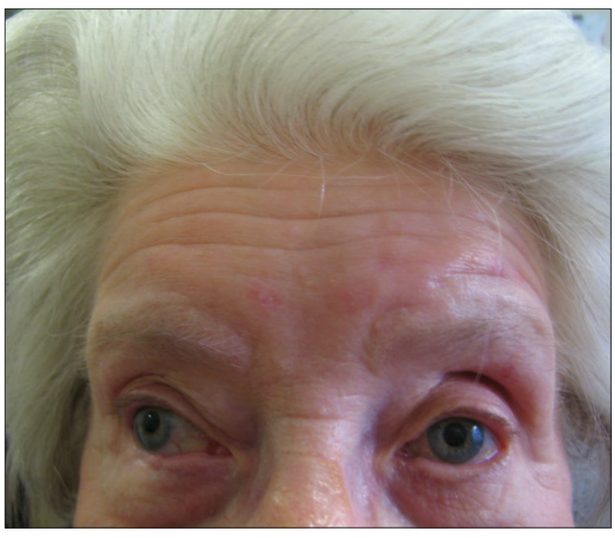

Figure 1: Patient unable to adduct the left eye while looking towards the right.

Neurological examination

On neurological examination her Glasgow Coma Scale was 15/15 and abbreviated mental test score was 10/10. Visual acuity was normal when each eye tested separately. There was no evidence of a defect in her visual fields. On inspection of her face a disconjugate gaze was noted. Her right eye was mild deviated to the right (she was known to have right eye squint), whilst her left eye focused directly ahead. On assessment of eye movements she was unable to adduct her left eye on right gaze (Fig.1). She reported diplopia on right-sided gaze and nystagmus was observed in the right eye on right gaze. Examination of the other cranial nerves was unremarkable. Her gait was mild unsteady. The evaluation of tone, power, tendon reflexes, sensory system, and co-ordination was normal in all four limbs.

Which Investigations would be necessary?

- *Full Blood Count – infective markers, anaemia of chronic disease*
- *Urea and electrolytes – baseline renal function*
- *Liver Function Test - transaminases*
- *Plasma glucose – screening for diabetes*
- *Lipid profile - hypercholesterolaemia*
- *Electrocardiogram – looking for AF, other abnormalities which may indicate cardiogenic source of embolus.*
- *Head Computed Tomography (CT) scan. In this patient, full blood count, urea and electrolytes were normal, total cholesterol was 6.0 mmol/l and electrocardiogram demonstrated normal sinus rhythm.*

When to do head CT scan?

Head CT scan should be done immediately (within 1 hour) in the following circumstances:

- *Indications for thrombolysis or early anticoagulation therapy*
- *On anti-coagulant therapy*
- *Reduced consciousness (GCS <13)*
- *Unexplained progressive or fluctuating symptoms*
- *Papilloedema, neck stiffness, fever*
- *Severe headache at onset of stroke symptoms*

INTERNUCLEAR OPHTHALMOPLEGIA & BRAIN STEM STROKE-CASED BASED DISCUSSION

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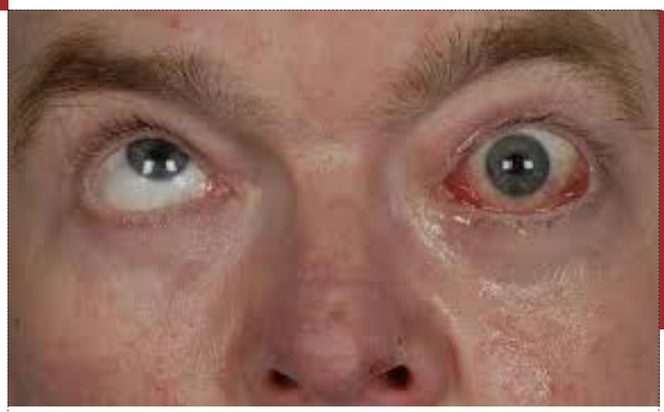


This patient did not fit within these criteria. National Institute for Health and Clinical Excellence (NICE) guidelines state that head CT scan should be carried out as soon as possible within 24 hours.

In this patient Brain CT scan showed no evidence of ischaemic event, haemorrhage, masses or midline shift.

Following further discussion with seniors and consideration of potential causes of this acute clinical presentation, a brain Magnetic Resonance Imaging (MRI) was requested. This revealed an acute brainstem infarct, anterior to the 4th ventricle and to the left of the midline that was interpreted being at the level of the left medial longitudinal fasciculus (Fig.2). Evidence of small vessel ischaemic disease was also observed.

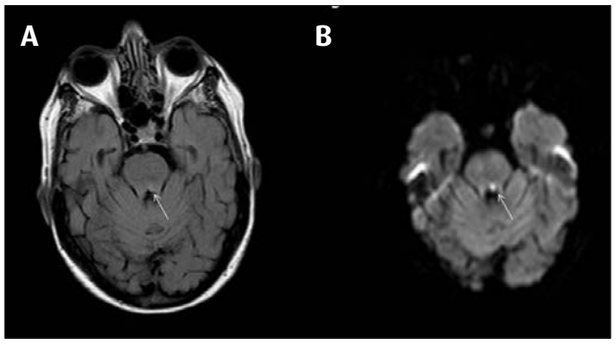


Figure 2: Magnetic resonance imaging (MRI) of the brain.

T2-weighted axial MRI image (A) shows a subtle high-intensity signal anterior to the 4th ventricle and to the left of the midline that was interpreted being at the level of the left medial longitudinal fasciculus. The Diffusion Weighted Imaging (called DWI) image (B), performed to assess if any abnormality is acute or not, showed clear recent small infarct in the area seen in T2-weighted image.

Internuclear ophthalmoplegia & brain stem stroke-Cased based discussion.

Patient Management

Diagnosis

The patient was diagnosed with a left sided brainstem ischaemic infarction.

Treatment

The management of this patient was twofold.

Firstly there was the rehabilitation therapy following stroke that involved physiotherapists, occupational therapists and in this case ophthalmologist. NICE guidelines recommend that following stroke patients should be offered 45 minutes of the necessary therapies for 5 days of the week until rehabilitation has been optimised.

Secondly there were secondary stroke prevention measures:

Lipid modification – *NICE guidelines state that for secondary prevention of cerebrovascular disease (CVA), 40mg Simvastatin should be commenced, unless there are interactions with patients' other drugs, in which case alternatives such as Pravasatin/Atorvastatin may be introduced.*

Improved hypertension control - *This patient was a known hypertensive already on Ramipril 2.5mg twice a day. She was noted to be hypertensive on admission. Blood pressure can be monitored and if it is persistently high in the time period after the stroke then ACE inhibitor can be increased or another anti-hypertensive introduced. In the immediate aftermath of the stroke hypertension would be tolerated.*

Anti-platelet therapy - *In the immediate aftermath of the stroke, Aspirin 300mg is given, this is then converted to Clopidogrel 75mg two weeks later on and will be lifelong therapy. If, as underlying cause, atrial fibrillation is identified anti-coagulation therapy would be considered after two weeks for disabling stroke or earlier for minor one.*

Patient follow-up

The patient was commenced upon a statin and clopidogrel for further stroke prevention. She was given an eye patch which improved her mobility/ stability as this omitted the double vision. She worked with physiotherapists and occupational therapists on the ward until symptoms improved and was discharged the following week. She was followed up by ophthalmology as an outpatient to monitor the degree of diplopia and manage this further.

INTERNUCLEAR OPHTHALMOPLEGIA & BRAIN STEM STROKE-CASED BASED DISCUSSION

H Ward, R Buccoliero

Discussion

Isolated diplopia is often not initially recognised as a potential stroke in the absence of other brainstem symptoms or signs although this patient was referred to the stroke unit due to the presence of vascular risk factors. She was presenting with the symptoms/signs of left Internuclear Ophthalmoplegia (INO) (5), diplopia, deficit of adduction with the left eye and nystagmus in the right eye on right gaze.

The two most commonly recognised causes of acute presentation are demyelination and brainstem stroke due to a lesion in the medial longitudinal fasciculus on the side of the adduction failure during lateral gaze. In this instance the cause was identified as an infarct in the posterior cerebral circulation with the patient's risk factors of age, hypertension and hypercholesterolaemia. Examination of eye movements was the key to diagnosis and location of the lesion within the brainstem.

Head CT brain was helpful in excluding a brainstem haemorrhage, but its sensitivity for showing small infarcts in the brainstem is low. Brain MRI scan has a much higher sensitivity for recent infarction on Diffusion Weighted Imaging and can also show silent lesions elsewhere or patterns of pathology as can be seen in demyelination (6).

The prognosis for INO due to stroke is usually gradual improvement in diplopia and this patient followed that path. Early rehabilitation was targeted to reducing symptoms of diplopia by eye patching and encouraging adaptation during tasks. The ward multidisciplinary team involved the orthoptists from the Eye Clinic to accurately test eye movements and contribute to management plans.

Although not the most typical presentation of stroke, due to a thorough approach it remained a differential diagnosis and was eventually identified as the cause.

Questions

1. The presentation of Internuclear Ophthalmoplegia is due to a lesion in which area?

a. Oculomotor nerve
b. Superior colliculus
c. Medial longitudinal fasciculus
d. Lateral geniculate nucleus
e. Optic chiasm

2. A 53 year old lady presents with sudden onset of right sided headache and double vision. On examination there is partial right sided ptosis and impaired movement of the right eye in elevation and adduction. The right pupil is larger than the left and does not react to direct light. What is most likely diagnosis?

a.Brainstem stroke
b.Posterior communicating artery aneurysm
c.Multiple Sclerosis
d.Horner's syndrome
e. Diabetes mellitus

3. Is the diagnosis of stroke mainly:

a. Clinical
b. Radiological
c. Clinical and Radiological
d. Biochemical
e. Microbiological

4. The risk factors for stroke include all except:

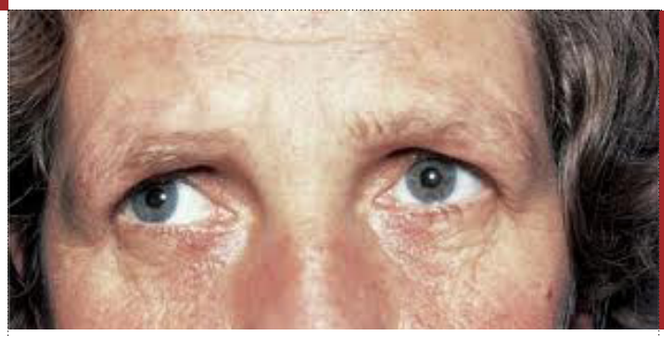
a. Dyslipidaemia
b. Sickle cell disease
c. Atrial fibrillation
d. Diabetes
e. Multiple Sclerosis

5. In the diagnosis of stroke head CT scan is useful for excluding:

a. Haemorrhage
b. Hydrocephalus
c. Alzheimer's disease
d. Epilepsy
e. Carotid artery disease

INTERNUCLEAR OPHTHALMOPLEGIA & BRAIN STEM STROKE-CASED BASED DISCUSSION

H Ward, R Buccoliero



Internuclear ophthalmoplegia & brain stem stroke-Cased based discussion.
Patient Management

Answers

1. Answer – c

Under normal circumstances, in order for the eyes to move together in a co-ordinated, conjugated manner, there is communication between the nuclei of the cranial nerves controlling their movement.

When the right eye abducts for example, this involves the lateral rectus muscle, supplied by cranial nerve VI (Abducens). At the same time the left eye must adduct in order to maintain conjugate gaze, and this involves the medial rectus muscle, supplied by cranial nerve III (Oculomotor). Abducens nucleus is situated in the pons, oculomotor nucleus is in the midbrain. Therefore there needs to be a connection between the two nerve nuclei, and this exists in the form of the Medial Longitudinal Fasiculus – a bundle of myelinated, rapidly conduction nerve fibres. If a lesion occurs in this area, the result is an ophthalmoplegia – typically with successful abduction of an eye into lateral gaze, but failure of adduction of the other eye. Also recognised is nystagmus, usually more noticeable in the abducting eye. INO can be unilateral or bilateral.

As described above, MS and ischaemic stroke are the two most common causes, other causes include traumatic injury, brainstem/ ventricle tumours, infection, hydrocephalus, lupus and Arnold-Chiari malformation. Management would therefore depend upon the aetiology.

The blood supply of the medial longitudinal fasciculus is derived from the anteromedial pontine blood supply, which is in turn supplied by the terminal vertebral and basilar arteries. In the case outlined above the MRI scan demonstrated an infarct in the brainstem indicating an inadequate posterior cerebral circulation supply.

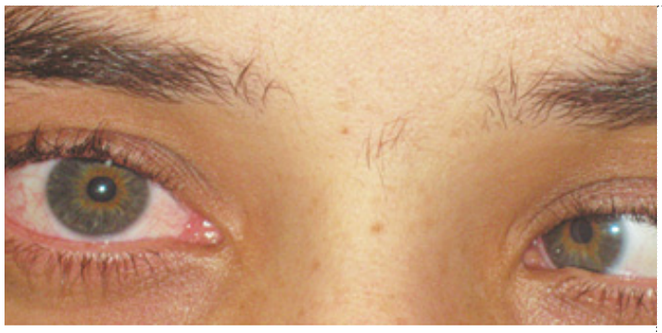
INO can be very disabling, particularly for multiple sclerosis patients who can experience it bilaterally seriously affecting their quality of life. Botulinum injections and surgical intervention can be considered, as well as conservative methods such as eye patches and occupational therapy support. Surgical methods include medial rectus resection and lateral rectus recession.

2. Answer – b

The combination of a ptosis with position of the eye in the 'down and out' position is typical of a third nerve palsy. The only ocular muscles not supplied by the Oculomotor nerve are lateral rectus and superior oblique. The eye is therefore in the position due to the unopposed action of these two muscles. As oculomotor nerve also supplies the levator palpebrae muscle, this explains why there is ptosis.

INTERNUCLEAR OPHTHALMOPLEGIA & BRAIN STEM STROKE-CASED BASED DISCUSSION

H Ward, R Buccoliero



Third nerve palsies can be categorised as surgical or medical. In a medical palsy the pupil is spared and the causes are most commonly diabetic or ischaemic. In a surgical palsy the pupil is involved, usually due to compression of the oculomotor nerve the parasympathetic supply, thus causing a dilated pupil. This is the case in this situation as the aneurysm is compressing the nerves and causing the surgical third nerve palsy presentation.

3. Answer – a

The diagnosis of stroke can, for the majority, be made clinically. In neurology in general, during the neurological assessment it is possible to gather the majority of information to make a diagnosis. If a good history is taken, it is possible to establish what the lesion is at this point. In stroke, the history will indicate a sudden onset of symptoms for example. If a good examination is carried out, it will then be possible to establish where the lesion is. Stroke commonly has a pattern of presentation that is recognisable.

By the end of the patient assessment it is often possible to be confident of a stroke, before imaging has taken place. Occasionally, as in the case above, there are other differentials which will need to be considered, therefore imaging plays an important secondary role.

4. Answer – e

All the others are recognised and modifiable risk factors for stroke.

5. Answer – a

As described above, the diagnosis of stroke is primarily clinical. However, there is no way of obtaining clinical certainty that the stroke is ischaemic or haemorrhagic without radiological assistance. The distinction between haemorrhagic and ischaemic stroke is crucial as it determines further management. In haemorrhagic stroke no medication will be introduced, whereas once ischaemic stroke is confirmed (by haemorrhage being ruled out), anti-platelet medication can be commenced to reduce the risk of further embolic events.

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Authors

H Ward
R Buccoliero
Department of Neurology
Harrogate District Foundation Trust
Harrogate
UK

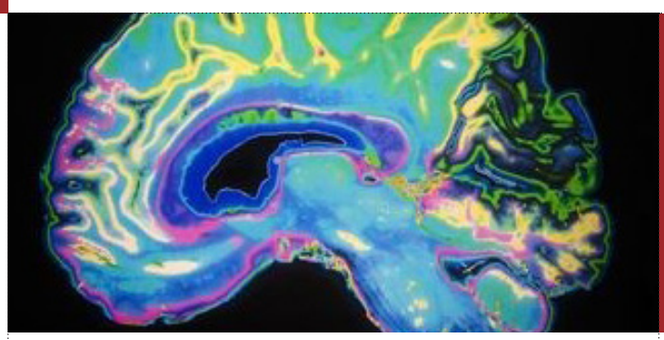
Corresponding Author

Dr Rosaria Buccoliero
Harrogate District Hospital
Harrogate
HG2 7SX

Phone number: +44(0)1423 553 038/4482
Fax: +44(0)1423 553 091
Email: rosaria.buccoliero@hdft.nhs.uk

INVESTIGATION & MANAGEMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

SA Zaidi, T Majeed



Investigation & management of Idiopathic Intracranial Hypertension.
Patient Management

Abstract

This case focuses the presentation, investigations and management of patient with Idiopathic intracranial hypertension. We emphasise the importance of early recognition, diagnosis and treatment of Idiopathic intracranial hypertension to prevent serious complications like visual loss.

Case Presentation

A 21 year old right handed lady with no notable medical condition in the past, presented with 2 weeks history of constant, generalised dull headaches. Headaches tend to increase with physical exertion and on bending forward. She also reported visual obscurations, occasional double vision and tinnitus affecting her right ear. She was not on any regular medications.

On Examination she was overweight and had bilateral gross papilloedema (Figure 1). Visual acuity was 6/24 in right eye and 6/9 in left eye. Visual field on confrontation revealed small peripheral scotoma on the right side. She had weakness of right lateral rectus consistent with partial right abducent nerve palsy. Rest of the neurological examination was unremarkable.

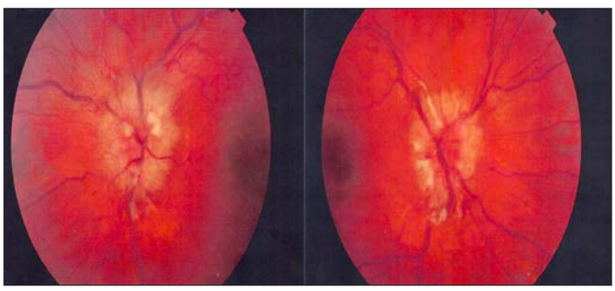


Figure 1: Severe bilateral papilloedema.

Following investigations were either normal or negative: Renal function, thyroid function, ANA, vasculitis screen, C-reactive protein, and erythrocyte sedimentation rate.

She had CT scan of brain which was normal. Her Lumbar puncture revealed CSF opening pressure of 40cm of water (normal value: 10-25 cm of water) with normal CSF constituents (protein 0.21g/l, cell count <1 and glucose 3.1 mmol/l). MR scan of brain and MR venogram were completely unremarkable (Figure 2 and 3).

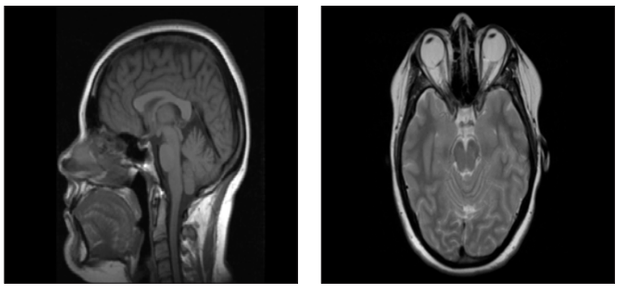


Figure 2: MR brain with no structural abnormality.

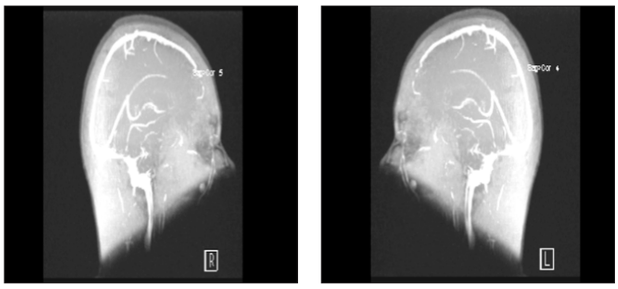
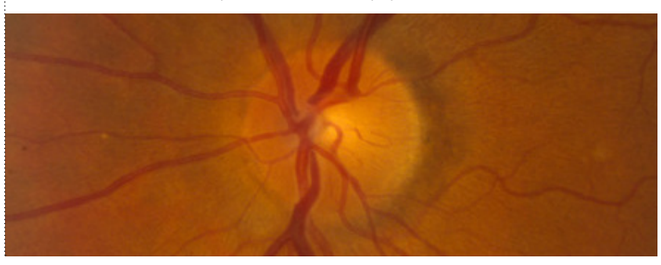


Figure 3: MR venogram with no evidence of thrombus formation.

History, examination findings and investigations were consistent with diagnosis of Idiopathic intracranial hypertension (IIH). She was started on Acetazolamide 250mg bd with gradual increment to maintenance dose of 500mg bd.However despite of increase in dose of Acetazolamide; she remained symptomatic with persistent headaches.Topiramate 25mg bd was therefore added to her treatment with good response and resolution of her symptoms.

At 6-months follow-up she remained asymptomatic. Visual acuity improved to 6/9 on the right and 6/6 on the left. Fundoscopic evaluation of her optic discs demonstrated complete resolution of papilloedema.



INVESTIGATION & MANAGEMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

SA Zaidi, T Majeed

Discussion

The patient in this case presented with headaches along features suggestive of raised intracranial pressure. Such clinical presentation can be secondary to space occupying lesion like brain tumors, AVM (arteriovenous malformations), venous sinus thrombosis or due to idiopathic intracranial hypertension. Further evaluation with neuroimaging and CSF analysis helps to differentiate among these conditions.

In our case, the presenting symptoms, age, sex and CSF pressure of >40 cm of water with normal neuroimaging, idiopathic intracranial hypertension is the most likely diagnosis.

Idiopathic intracranial hypertension (previously called pseudotumour cerebri/ Benign intracranial hypertension) is a syndrome of elevated cerebrospinal fluid (CSF) pressure of unidentifiable cause. The incidence ranges from 1-2 per 100,000 persons(1,2). Incidence is highest among obese women aged 20-44 years at an estimated 19 per 100000[2].Diagnosis of IIH requires modified Dandy criteria to be satisfied (1).(Table 1)

1. Symptoms, if present are only those of generalised intracranial hypertension.
2.Signs, if present are only those of generalised intracranial hypertension or papilloedema
3.Documented elevated CSF pressure during lumbar puncture in the lateral decubitus position
4.Normal CSF composition
5.No evidence of space occupying lesion or venous sinus thrombosis on imaging
6.No other causes for raised CSF pressure identified
*Adapted from reference 1

Table 1: Updated modified Dandy's Criteria*

History and Clinical Examination

Headache is the most common presenting symptom of IIH (3,4) .It is therefore important to take good history of headaches including character of pain, aggravating and relieving factors, postural effect and associated symptoms like visual disturbance (blurred vision, visual obscurations, and diplopia), tinnitus or dizziness.

Headaches in IIH are typically generalised, throbbing and episodic in nature, worse in lying position and aggravated by valsalva manoeuvres like coughing and straining. Pulsatile tinnitus is also common (up to 87% of patients in one study 5) and may be the presenting feature in some cases (5,6). Other common symptoms includes transient visual obscurations, blurred vision and diplopia. (Table 2).

Symptoms	Approximate Incidence (%)	Reference
Headaches	94	7
Visual obscurations	68	7
Pulsatile tinnitus	58-87	5,7
Photopsia	54	7
Neck, shoulder/arm pain	44-48	19
Retrobulbar pain	44	7
Diplopia	38	7
Abducens palsy	20	19

Table 2: Symptoms of Idiopathic intracranial hypertension.

Patients should also enquire about their regular medications and other medical problems as several studies have reported association of Idiopathic intracranial hypertension with medical conditions like SLE, Behcets disease, uremia and medications especially tetracycline, vitamin A and lithium (Table 3).

	Reference
Uremia	11
SLE	10
Behcets Disease	23
Hypothyroidism	13
Tetracycline	20
Vitamin A/Isotretinoin	21
Lithium	22

Table 3: Clinical associations with Idiopathic intracranial hypertension.

Although full neurological examination should be performed in all suspected cases of IIH, but fundoscopy, assessment of visual acuity and visual fields and examination of extraocular movements are vital to look for the features suggestive of raised intracranial pressure. Visual Acuity usually remains preserved in early stages of papilloedema but can deteriorate rapidly in advanced and severe cases. Visual field defects on perimetry are common and can occur up to 90% of patients. Abducent nerve palsy as false localising sign due to raised intracranial pressure is reported in 20% of patients (2,1).

Investigations

In all suspected cases of raised intracranial pressure it is critical to perform neuroimaging (ideally CT/MR brain and CT/MR venography) before attempting the lumbar puncture to exclude space occupying lesion and venous sinus thrombosis.

The lumbar puncture should be performed in lateral decubitus position as per Dandy's criteria. Normal limits of CSF pressure in obese patients remain unclear and there are conflicting studies. Whiteley and co workers recorded CSF opening pressure in 242 adults and found that 95% reference interval for CSF opening pressure was 10-25 cm of water. Whiteley and Warlow also proposed that in some patients up to 28 cm of water may be normal. Corbett and colleagues also found the cut off value of 25 cm of water (6).

In our patient CT scan and MR venogram were unremarkable. Her CSF opening pressure was significantly high therefore therapeutic drainage of CSF was performed to reduce the CSF pressure to <20 cm of water. Finding of elevated CSF pressure necessitates further investigations including CSF constituents, Serum inflammatory makers, autoimmune and vasculitis screen to exclude secondary causes of raised CSF pressure. Her investigations were entirely normal therefore she was commenced on treatment for IIH.

Management

Although not all patients require treatment as disease can be self limiting and symptoms may resolve either spontaneously or after initial lumbar puncture especially in patients with mild papilloedema. But significant decline in visual acuity and severe papilloedema in her case warrants immediate treatment as unnecessary delay in such cases could lead to permanent visual loss.

INVESTIGATION & MANAGEMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

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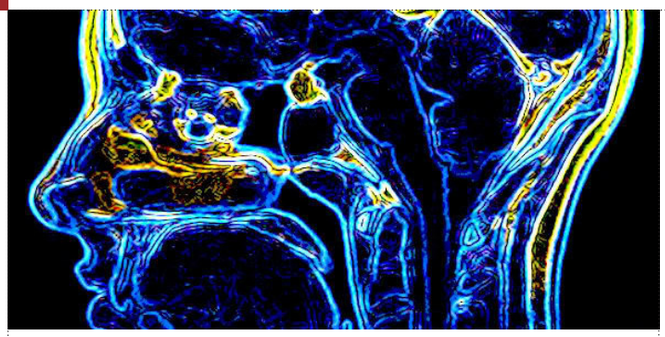

Pharmacological Treatment

Acetazolamide is generally used as a first-line medication in lowering the intracranial pressure in IIH. It reduces the CSF production by carbonic anhydrase inhibition. The usual initial dose of Acetazolamide is 250mg bd which is further titrated to maintenance dose of 1gm to 2gm per day depending upon patient's response and tolerability.

Topiramate has also been used to treat IIH due to its carbonic anhydrase inhibition effect and potential to cause weight loss. Efficacy of Topiramate is comparable to Acetazolamide (1,2). Our patient had partial response to Acetazolamide but after starting her on Topiramate, symptoms improved significantly. Diuretics like Furosemide or Bendroflumethiazide can be used as an alternative but they are less effective in reducing the CSF pressure.

Weight Loss

Association of obesity with IIH is well recognised (14,15).
It was reported that as little as 6.2% of weight loss results in complete resolution of marked papilloedema (15). Her BMI was 30, she was therefore referred for dietary advice and encouraged to join weight management programs.

Surgical Treatment

Surgical intervention is indicated if symptoms are refractory to maximal medical therapy or if there is severe or rapid visual impairment. As our patient responded well to medical therapy surgical treatment options were not considered.

Surgical treatment includes optic nerve sheath fenestration and CSF diversion procedures. Both procedures are effective in reducing the raised intracranial pressure in IIH (16,17); however CSF diversion procedures are preferred as post operative complication rate is as high as 40% after optic nerve sheath fenestration (18).

Lumboperitoneal (LP) shunt is the most widely performed CSF diversion procedure that facilitates excess CSF drainage with rapid resolution of symptoms, although complications like shunt failure are not uncommon.

Follow up

In view of the significant visual morbidity associated with IIH, careful follow-up with monitoring of visual fields, visual acuity and optical disc appearance is essential as the disease may deteriorate after initial period of stability.

Communication and professionalism

Communication whilst arranging and performing investigations is very important. Patients with headaches are extremely anxious about diagnosis. The possibility of 'brain tumor' as the cause of their symptoms is sometimes their major concern. It is therefore crucial to engage the patient in discussion about their investigations and management.

Prioritisation and organisational skills are essential in managing such patients. After recognising the features of raised intracranial pressure, prioritising the investigations, avoiding delays and initiating appropriate treatment can prevent serious complications like visual loss.

Questions

1. Treatment of IIH

a) Acetazolamide reduces the CSF pressure by increasing the CSF absorption.
b) Therapeutic goal in IIH focuses on symptomatic relief and preservation of visual function.
c) All patients with IIH require lumboperitoneal shunt.
d) Weight loss has no role in management of IIH.
e) Topiramate causes weight gain.

2. Investigations in IIH

a) Normal CT scan of brain exclude the possibility of venous sinus thrombosis.
b) Diagnostic Lumbar puncture should be performed in lateral decubitus position.
c) Inflammatory markers and autoimmune screen are not a part of routine investigations in patients with suspected IIH.
d) CSF constituents are usually abnormal in IIH.
e) Normal CSF opening pressure is 30 cm of water.

Answers

1. Answer 1b)
Treatment in IIH focuses on symptomatic relief and preservation of visual function. Visual impairment is the major sequela of IIH. Visual acuity can decline rapidly in patients with severe papilloedema and permanent blindness ensues if treatment is not offered immediately.

Acetazolamide is a carbonic anhydrase inhibitor. It lowers the CSF Pressure by reducing the CSF production.

Surgical treatment like lumboperitoneal shunt is indicated only if the symptoms are refractory to medical therapy or visual function is declining rapidly despite of medical treatment.

Weight loss has beneficial effects in IIH, loosing as little as 6.2% of weight can cause significant improvement in papilloedema.

INVESTIGATION & MANAGEMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

SA Zaidi, T Majeed

Topiramate act as carbonic anhydrase inhibitor and helps in IIH by reducing CSF production. It also promotes weight loss.

2. Answer 2.b)

The diagnostic lumbar puncture should be performed with the patient in lateral decubitus position to obtain true CSF opening pressure.

Plain CT scan of brain can not exclude venous sinus thrombosis. MR venogram or CT venogram are preferred investigations in such cases to look for thrombosis.

Association between IIH and inflammatory/autoimmune conditions has been reported in studies. It is therefore important to investigate these patients for such conditions.

As per diagnostic criteria for IIH, CSF constituents should be normal.

Normal CSF opening pressure is 10-25 cm of water, although in some cases up to 28cm of water is considered as normal.

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Authors

Syed Amir Zaidi MBBS, MRCP
Clinical Fellow Neurology at Royal Preston Hospital

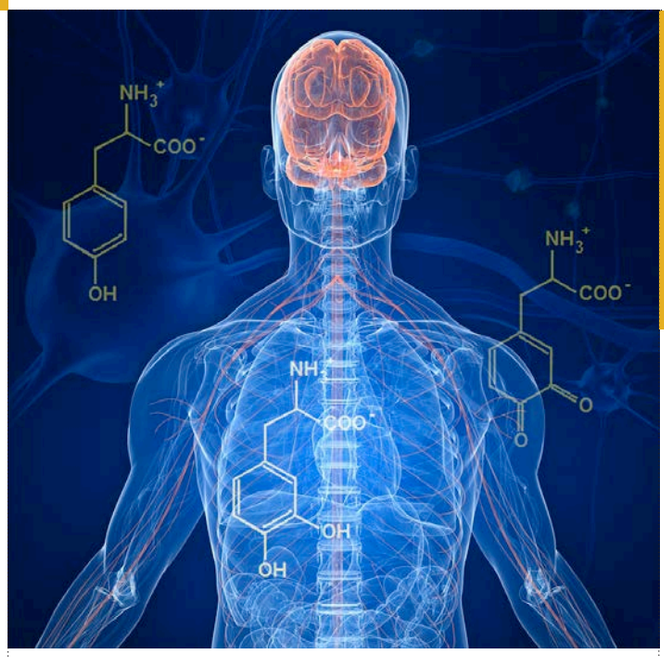
Tahir Majeed MBBS, FRCP, PHD
Consultant Neurologist at Royal Preston Hospital

Correspondence

Dr Syed Amir Zaidi
Clinical Fellow Neurology
Royal Preston Hospital
Email: drzaidi2007@gmail.com

GOOD CLINICAL PRACTICE: MANAGEMENT OF THE PATIENT WITH PARKINSON'S DISEASE ON THE ACUTE TAKE

A Lindahl



Good Clinical Practice: Management of the patient with Parkinson's disease on the acute take.
Good Clinical Care

Parkinson's disease (PD) is the second commonest neurodegenerative disease after Alzheimer's disease and affects about 2% of people over the age of 80. Although the incidence rises with age, however, it is not exclusively a disease of older people.

The diagnosis of PD and initiation and monitoring of treatment should be undertaken by a specialist, however, people with PD frequently need to see their GP and are often seen on the general medical or surgical take (either as a result of their PD or for unrelated conditions) therefore the non-specialist still needs to have an understanding of this common condition. Common causes of deterioration and distress in PD can be avoided or quickly managed by the savvy doctor and the aim of this article is to give you the tips you need to avoid the common pitfalls in the management of this complex condition.

Which of these people might have Parkinson's?

Mr A is a 48 year old right handed carpenter who has noticed it is increasingly difficult to use his screwdriver. He has also noticed a tremor of his right hand which occurs mainly when he is watching television in the evening.

Mrs B is an 72 year old lady who has had increasing difficulty walking over the last 4 months and has fallen on 6 occasions, often backwards. Her friends have noticed that she is more withdrawn and tends to have a rather blank expression. She has developed a tendency to get rather muddled but has little insight into this.

Mr C is a 60 year old man who has had a symmetrical tremor of both hands for 5 years. The tremor is most noticeable when he tries to hold a hot drink or when he bringing food to his mouth. It is also worse when he is anxious or when he drinks coffee. There has been little change in the tremor over the 5 year period but he is finding it increasingly embarrassing.

The correct answer is Mr A. Although he is young, his presentation is fairly typical of PD with a unilateral resting tremor and problems with the function of the same side (his difficulty using the screwdriver may be due to rigidity or difficulty with alternating movements- a feature of bradykinesia [see below]). Parkinson's presents unilaterally. Although it usually spreads to the other side, the side initially affected always remains the worst side. If a patient presents with bilateral symmetrical symptoms and signs it is unlikely to be PD – this is a so-called red flag.

Mrs B is unlikely to have PD as she is falling too early in the disease and has early cognitive problems, two more red flags. In her case it would be important to look for neck rigidity and a gaze palsy in case she has progressive supranuclear palsy although extensive cerebrovascular disease could give a similar picture. Mr C does not have PD as his tremor is bilateral, symmetrical and non progressive. The most likely diagnosis in his case is essential tremor.

Why is it important to make an accurate diagnosis? Firstly it allows the correct treatment to be offered and secondly it allows us to give the patient a more accurate idea about prognosis (which is clearly going to be vastly different in the three cases outlined above).

As the diagnosis of PD can be trickier than it looks, it is essential that people with suspected PD are referred to a specialist with expertise in the differential diagnosis of PD [NICE 2006]. It is also very important that patients are referred untreated (i.e. don't just give a trial of levodopa to see what happens!). Further details on the diagnosis of PD, red flags and differentials can be found in the excellent review by Quinn (1).

GOOD CLINICAL PRACTICE: MANAGEMENT OF THE PATIENT WITH PARKINSON'S DISEASE ON THE ACUTE TAKE

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What can a patient with PD expect?

PD is a progressive condition therefore a patient's priorities and problems will change over time. A 4-stage paradigm was proposed by MacMahon and Thomas (2) and is shown in Figure 1. The amount of time spent by patients in each stage is variable.

For example, the diagnostic stage may be relatively brief if a patient presents with very typical symptoms and signs and no red flags but longer if red flags are present and one of the atypical Parkinsonian syndromes is suspected (for example, dementia with Lewy Bodies, PSP, multisystem atrophy). During the maintenance phase, patients tend to respond well to medication and can live a fairly normal life.

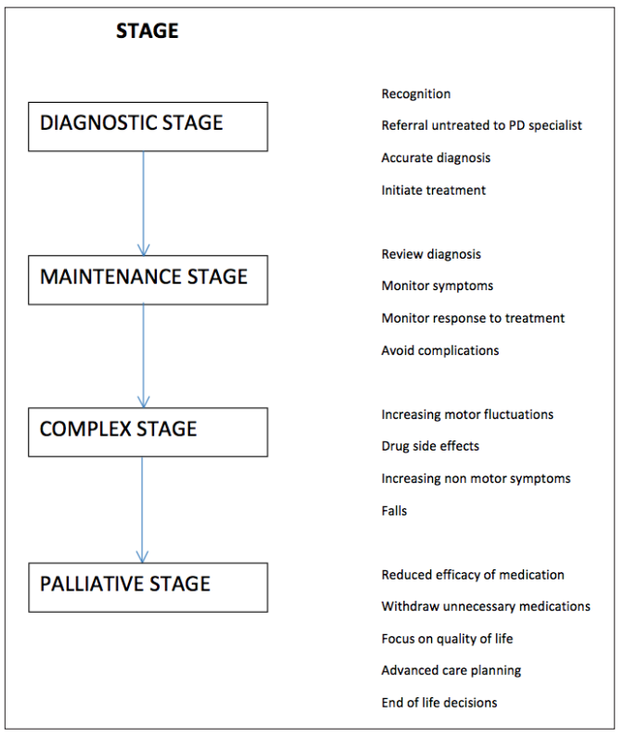


Figure 1: What a PD patient can expect: The 4-stage paradigm (adapted from MacMahon and Thomas (2)

During the complex phase, patients may notice a more unpredictable response to their medication with perhaps a wearing off effect at the end of the dose, involuntary movements (dyskinesia) at the peak of the dose, dose failures (where the medication fails to have any effect at all) or painful cramp (dystonia).

The non-motor symptoms of PD also become more prominent: the patient may start to fall, cognition may be affected (typically difficulty with executive and visuospatial function: difficulty planning their day, no longer being able to handle household bills and accounts etc.) and autonomic problems such as postural hypotension, urinary problems and constipation may become more prominent.

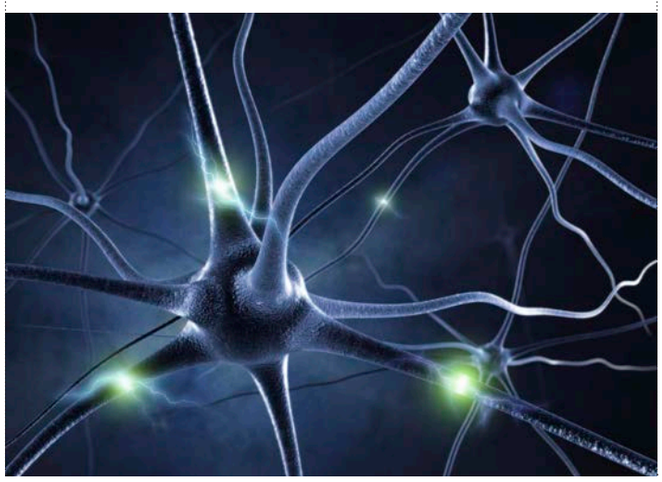
Depression and anxiety are very common and patients may start to develop neuropsychiatric problems. The commonly start as benign misperceptions (thinking there is someone in the room with them: a 'sense of presence' or perhaps thinking something has just run past them out of the corner of their eye 'a sense of passage').

This can progress to formed visual hallucinations (usually of children or animals but sometimes more disturbing, e.g. deceased relatives). These hallucinations can progress from the benign to the very disturbing (one former patient was convinced there were maggots crawling out of his food, resulting in severe weight loss and great distress).

In the palliative stage complex manipulations of drugs are no longer effective and increasingly drugs are withdrawn to eliminate side effects. The focus at this stage is to maximise quality of life by ensuring that the non-motor symptoms are optimally managed and to consider advanced care planning and end of life decisions.

What drugs are used to treat PD?

The NICE guidelines for the diagnosis and management of PD (3) state that it is not possible to identify a universal first choice drug in the treatment of either early or later disease and that the decision as to which drug to use should be an individualised one taking into account the patient's lifestyle and preferences.



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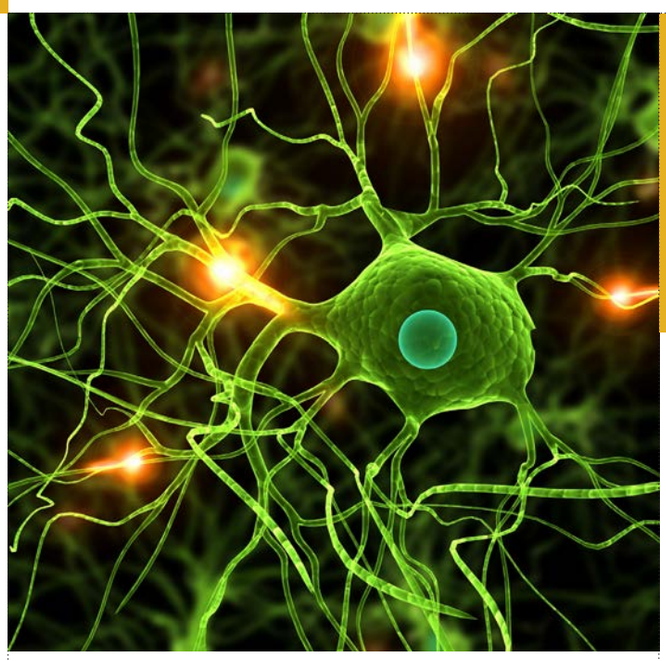

Good Clinical Practice: Management of the patient with Parkinson's disease on the acute take. Good Clinical Care

Why do PD patients come into hospital?

Woodford and Walker (4) looked at emergency admissions of PD patients over a 4-year period in a district general hospital serving a population of about 180,000. There were 246 admissions (129) patients admitted over this time period with a mean length of stay of 17.3 days. The commonest causes of admission were:

- *Falls (n=44, 14%)*
- *Pneumonia (n=37, 11%)*
- *Urinary tract infection (n=28, 9%)*
- *Reduced mobility (n=27, 8%)*
- *Psychiatric (n=26, 8%)*
- *Angina (n=21, 6%)*
- *Heart failure (n=20, 6%)*
- *Fracture (n=14, 4%)*
- *Orthostatic hypotension (n=13, 4%)*
- *Surgical (n=13, 4%)*
- *Upper gastrointestinal bleed (n=10, 3%)*
- *Stroke/transient ischemic attack (n=8, 2%)*
- *Myocardial infarction (n=7, 2%)*

It is therefore highly likely that as a foundation year doctor in medicine, surgery or general practice that you will encounter patients with PD.

Tips on how to approach the management of the PD inpatient

In many medical conditions, it will not matter greatly exactly what time the medication is prescribed or what formulation the patient received. This is absolutely not the case in Parkinson's disease. The PD patient admitted to hospital often has a turbulent time as their drugs may not be prescribed in the correct formulation, at the right dose and critically at the right time (often not coinciding with the nurses' drug rounds.)

For this reason, changes to drug management should only be made by the PD specialist team looking after the patient (liaise with either the Parkinson's disease nurse specialist or the consultant neurologist or geriatrician caring for the patient). In early disease, there are three categories of drug available: levodopa (the gold standard, converted into dopamine in the brain; common brands are Sinemet ® and Madopar ®), dopamine agonists (that mimic the action of dopamine) and the monoamine oxidase inhibitors (MAO-Is) selegiline and rasagiline (which block the breakdown of dopamine). There are differences in efficacy, side effect profile and drug interactions between the three classes of drugs. Selegiline in particular has many drug interactions and it is important to know that antidepressants cannot be co-prescribed with selegiline.

Rasagiline has a better side effect profile and fewer drug interactions than selegiline; however, it should not be co-prescribed with the antidepressants fluvoxamine and fluoxetine. The interaction between antidepressants and MAO-Is can result in the serotonin syndrome, a potentially life threatening reaction that can cause agitation, confusion, high fever, sweating, shivering, tremor, diarrhoea and hyperreflexia.

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This happens so frequently, that the patients' charity Parkinson's – UK (5) launched the "Get it on time" campaign in 2006 to highlight the issue. As the foundation year doctor you are in a prime position to try and avoid some of the common problems patients with PD encounter in hospital. The review by MacMahon and MacMahon (6) is worth reading for further detail. The key points are summarised below:

1. Check what PD medications the patient normally takes. Try and stick to their normal generic or brand if at all possible. If there are availability problems check with the pharmacist or PD specialist team as to what would be a suitable substitute. PD patients often bring their own drugs into hospital. If they are fit to self-medicate and your hospital has a self-medication policy it is advisable to let them do so.

2. Check that you understand which formulation of the drug the patient takes. For example immediate release and controlled release (CR) levodopa formulations are not interchangeable as the CR formulations have less bioavailability than the immediate release ones. The oral dopamine agonists ropinirole (Requip ®) and pramipexole (Mirapexin®) are now also available as once daily prolonged release medications (XL or PR respectively). Make sure you are clear what the patient's normal regime is.

3. Make sure you have clearly prescribed the correct dose.

4. Make sure you have prescribed the medication at the times the patient usually takes their medication not rounded up or down to the nearest drug round. Make sure also that the ward nurses are aware of the importance of medication timing and if necessary have access to pill timers or alarms to remind them if the regime is complex. Double check on ward rounds that medications are being given on time.

5. Make sure no-one prescribes drugs that exacerbate PD. It is common on some wards especially surgical wards to write up antiemetics such as cyclizine, prochlorperazine and metoclopramide routinely on the 'as required' side of the drug chart in case the patient develops nausea. Note that all of these medications are absolutely contraindicated in PD (not only do they make the PD much worse as they block dopamine, but they can also cause the potentially fatal neuroleptic malignant syndrome [NMS]). Domperidone, which can be given orally, via nasogastric tube or rectally, can be used or if intravenous or intramuscular antiemetics are required, ondansetron is an alternative. Most antipsychotic medications are also dopamine blockers (e.g. chlorpromazine, haloperidol, olanzapine, risperidone) and are contraindicated in PD for the same reason. Management tips for the confused PD patient are given below.

6. Ensure that no medications are prescribed that may make the patient confused or psychotic. Examples include anticholinergics that cross the blood-brain-barrier such as oxybutynin. Drugs that do not cross the blood-brain barrier such as trospium are preferred.

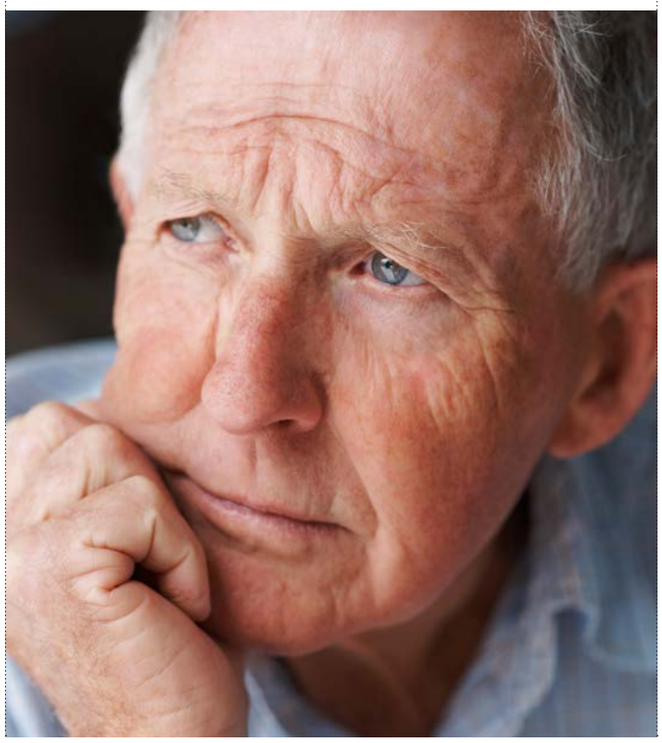
It sounds basic but attention to detail when writing out the drug chart at the time of admission and especially when drug charts are being rewritten can prevent a whole host of problems later. Clearly if a PD patient's PD control deteriorates during their admission it will prolong length of stay, could result in medical complications such as aspiration pneumonia and the effects of immobility and may even result in the need for institutional care.

Managing the confused PD patient

It is not unusual for elderly patients to become confused in hospital due to changes in environment, sleep pattern, reversal of day-night cycles and so on. This is also the case for patients with PD. Confusion may also occur in the context of intercurrent medical illness and metabolic disturbance. If a PD patient becomes confused it is therefore important to examine the patient, looking for any signs of infection especially aspiration and urinary tract infection which are both common in PD.

Constipation is common due to e.g. reduced mobility, dehydration, other medications and the fact that PD itself slows the bowel and this can result in discomfort and also absorption problems (drugs and nutrition). Perform a blood screen to check full blood count, CRP, electrolytes, glucose, liver function, mid stream urine (MSU) and a chest X ray to look for aspiration.

Check the drug chart to make sure that they have been receiving their PD medications (abrupt cessation of PD medications can result in NMS which also presents with confusion and agitation). If there is any suspicion of NMS it is important to check the creatine kinase daily, hydrate well and obtain specialist advice from a neurologist. Check the chart again to make sure that no dopamine blocking agents have crept on to the 'as required' part of the chart.



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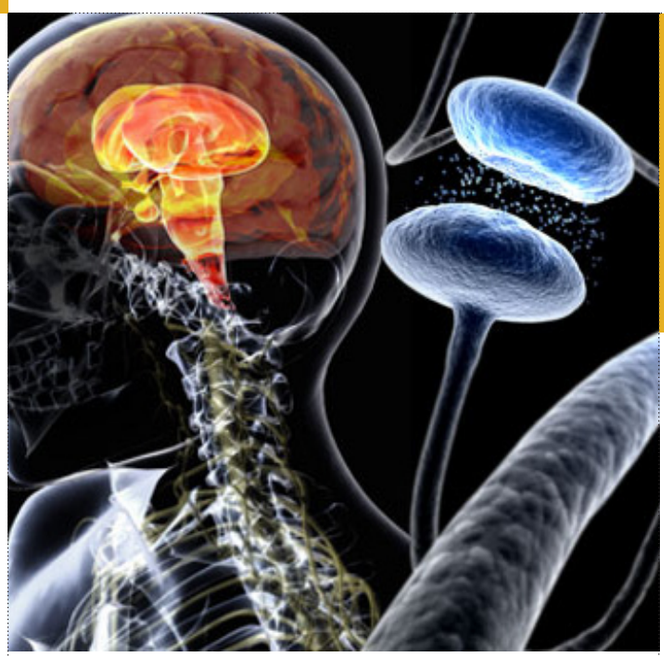

Before resorting to additional medication, see if a nurse or family member can calm the patient – nursing in a quiet side room with muted light is often better than a busy, noisy and brightly lit main ward. If the patient is a danger to themselves or others and medication is required, a short acting benzodiazepine such as lorazepam may be helpful.

If regular antipsychotic medication is required, seek the advice of the PD team. Clozapine has the best evidence base for the management of PD psychosis and relatively few extrapyramidal side effects but is subject to strict monitoring as it can cause agranulocytosis. It can only be prescribed by a registered prescriber and patients must be enrolled on a compulsory monitoring programme. For this reason, quetiapine, which has relatively few extrapyramidal side effects, is often used.

Good Clinical Practice: Management of the patient with Parkinson's disease on the acute take. Good Clinical Care

What if the patient is nil by mouth?

Clearly there are circumstances where patients are unable to take food or medication orally, e.g. after a stroke or if admitted for surgery. If the admission is elective, such as for planned surgery, it is wise to obtain advice from the PD team in advance. If patients are admitted non-electively then if at all possible a nasogastric tube (NGT) should be inserted and the patient's usual medications given down the tube.

Levodopa/DDI preparations can be switched to an equivalent dose of dispersible Madopar® for ease of administration down NGT. Controlled release preparations are not suitable for NGTs and advice should be taken from the PD team. Dopamine agonists can be switched to the rotigotine transdermal patch (a dose equivalent table is shown in Figure 27). In special circumstances the PD team may decide to use the subcutaneous dopamine agonist apomorphine but it is important to appreciate that this should only be initiated by a specialist experienced in its use and in settings where there are nurses trained in its administration.

Managing the non-motor symptoms of PD.

Ropinirole (mg / day)	Pramipexole (salt mg / day)	Rotigotine (mg patch/24 hours)
3	0.375	2
4	0.75	4
6	1.5	6
8	2.25	8
12	3.0	12
16	3.75	16
24	4.5	16

Figure 2: Dopamine agonist switching table (adapted from 7)

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Problem	Recommendation	Notes
Depression	Low threshold for diagnosis SSRI e.g. citalopram, mirtazepine	SE likely with tryicyclics-worsen constipation, cognitive and autonomic dysfunction. **NB Increased risk of serotonin syndrome with selegiline and all antidepressants and with rasagiline and fluoxetine or fluvoxamine**
Psychosis/hallucinations	PD team to review PD drugs Avoid treatment if mild and tolerable to patient Consider quetiapine 25mg, increased in 25mg steps to usual max 75 mg PD team may refer to psychiatry for consideration of clozapine or ChE-I if severe	Avoid **all** other antipsychotics including haloperidol, risperidone, olanzepine. Risk of neuroleptic malignant syndrome. Clozapine can only be prescribed by registered users, usually psychiatry team))
Dementia	Screen and monitor using Montreal Cognitive Assessment (MOCA) ideally (more weighted to cognitive defects encountered in PD). PD team or GP to refer to psychiatry for consideration of (ChE-I) if significant symptoms Consider advanced care planning while patient has capacity.	
Sleep disturbance	Full history including sleep initiation, maintenance and waking; limb movements, hallucinations, vivid dreams, acting out dreams, nocturia, anxiety. Advise good sleep hygiene Identify and manage restless legs syndrome Identify and manage REM sleep behaviour disorder	Consider whether sleep disturbance is causing excessive daytime sleepiness (see caution below)
Excessive daytime sleepiness (EDS)	Take sleep history as above and optimise night time sleep. Modafinil can be considered for EDS	Patients who have sudden onset of sleep or excessive daytime sleepiness should be advised not to drive and consider occupational hazards. Drug regime should be adjusted by PD team to minimise recurrence.
Pain	Consider whether pain is dystonic and may respond to dopaminergic medication (call PD team) Consider musculoskeletal causes of pain, often secondary to rigidity and bradykinesia e.g. frozen shoulder	Other types of pain in PD: -primary or central pain -neuropathic pain
Weight loss	Investigate for medical causes (e.g. malignancy, endocrine) Investigate swallow and refer to speech therapist (SLT) Review anti-PD drugs if prominent dyskinesia (contact PD team) Refer to dietician and consider supplements	
Dysphagia	Early referral to speech and language therapy – consider video fluoroscopy to exclude silent aspiration Consider enteral feeding if appropriate	
Constipation	Increase dietary fibre and fluid intake (> 8 glasses water per day) Increase exercise if possible Consider fibre supplements, stool softener (e.g. docusate), osmotic laxative (e.g. lactulose), polyethylene glycol solutions (macrogol) Enemas as required	Colonic dysmotility occurs in up to 30% of PD patients and anorectal dysfunction in up to 60%
Urinary dysfunction	Exclude UTI if abrupt change in voiding pattern Exclude diabetes if polyuria and frequency are prominent Consider anticholinergics if appropriate especially trospium chloride which does not cross the BBB	Occurs in up to 75% of PD patients Caution with anticholinergics crossing BBB (tolterodine, oxybutinin, propiverin) as can cause confusion and hallucinations
Sexual dysfunction	In cases of erectile dysfunction (ED), rule out comorbid conditions (e.g. check TFT, prolactin), depression, drug induced ED (alpha blockers) Consider sildenafil	Hypersexuality can be induced by all dopamine agonists and must be screened for and monitored along with other impulse control disorders (pathological gambling, binge eating and compulsive shopping).
Orthostatic hypotension	Eliminate or reduce antihypertensives and review PD medications Increase dietary salt and fluid, avoid alcohol, avoid caffeine at night Elevate head of bed by 30-40° Consider fludrocortisone (max 400 mcg/day) Consider midodrine (off licence, named patient basis – call PD specialist team)	Drop in systolic BP on standing by ≥20 mmHg or to less than 90 mmHg Refer for tilt testing if severe
Drooling	Refer to SLT for assessment of swallow Advice and trial of behavioural management Consider botulinum toxin injection to salivary glands (off licence)	Sublingual 1% atropine can be considered but beware of precipitating hallucinations/psychosis

Table 1. Managing the non-motor symptoms of PD. Abbreviations: SSRI Selective serotonin reuptake inhibitor; SE side effects; ChE-I cholinesterase inhibitors; REM rapid eye movement.

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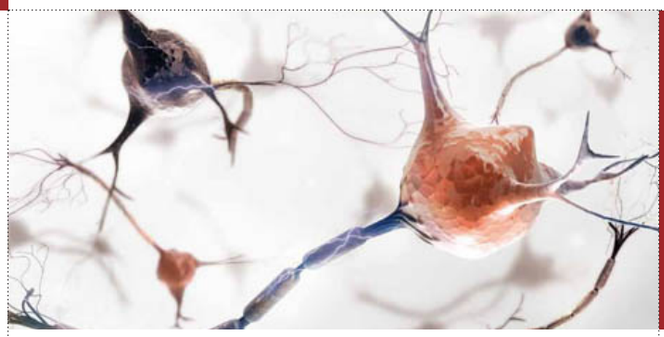
Author

A Lindahl

MOTOR NEURON DISEASE - WHAT DO YOU NEED TO KNOW?

TW Payne, CJ McDermott



Motor Neuron Disease - What do you need to know? Patient Management

Abstract

This article on good clinical care focuses on the presentation of Motor Neuron Disease (MND). Taking a thorough history and examination is crucial in both the diagnosis of MND, and the assessment of a patient's current disease state. This article aims to give foundation doctors the tools they need when assessing patients with MND, and an awareness of key investigations and principles in patient management.

An Example Scenario

Mr Smith is 72 year old retired teacher who has been electively admitted to the Care of the Elderly ward with a 6 month history of progressive lower limb weakness. He now states he has difficulty swallowing. Your consultant is concerned he may have Motor Neuron Disease and wants to investigate him further with respect to this. You are the F1 and have been asked to clerk him, what do you need to be aware of?

Background

Motor Neuron Disease (MND) is a devastating neurodegenerative disease characterised by progressive weakness and muscle wasting until death, which is most commonly due to paralysis of the respiratory muscles. Life expectancy is 2-3 years [1]. The typical variant is that of Amyotrophic Lateral Sclerosis (ALS), and is clinically characterised by a combination of upper and lower motor neuron signs. The two other variants are rare in comparison and can present as pure lower motor neuron disease (progressive muscular atrophy) or pure upper motor neuron disease (primary lateral sclerosis).

MND is not a common disease, with an incidence of approximately 2 per 100,000 in the UK and a prevalence of up to 7 per 100,000 [1]. It is, however, an important disease to be aware of due to the catastrophic nature of the diagnosis and the complex needs these patients often have.

Approximately 5% of MND is familial, clinically it behaves the same as sporadic MND. The pathology of MND is not completely understood but some genetic factors form the basis of our current understanding. In familial ALS (FALS) about 10% of individuals have a genetic mutation in the copper/zinc superoxide dismutase gene (SOD1) which acts as a free radical scavenger, which prompted the theory that ALS is in part due to oxidative stress. However, SOD1 mutations only make up 2% of ALS overall, and key pathological features in sporadic ALS are not found in SOD1 related FALS.

Recently, the gene C9ORF72 has been identified which has been found both in apparent sporadic ALS and FALS. C9ORF72 FALS does show the common pathological finding of TDP-43 cytoplasmic inclusions within the motor neurons, which is also seen in sporadic ALS but not in SOD1 FALS. The identification of TDP-43 as the main constituent of inclusions in both ALS and fronto-temporal lobe dementia, prompted the theory of a TDP-43 proteinopathy being the underlying pathological process to both of these neurodegenerative diseases, which have a recognised clinical overlap [2] [3].

The History

When taking a history from a patient with suspected or confirmed MND it is important to note that there are three main patterns of presentation:

- *Limb onset MND: the most common presentation and typically presents with asymmetrical distal limb weakness. In the lower limbs this can present as foot drop and progressive difficulty mobilising, and more proximal weakness with difficulty rising from chairs. In the upper limbs this can present as clumsiness in the hands (dropping things), difficulty writing, gripping objects and more proximal weakness can show as difficulty reaching objects, showering and lifting objects.*

- *Bulbar onset MND: less common (roughly 20%) and carries a poorer prognosis. Presentation is with progressive dysarthria, dysphagia, choking episodes with or without aspiration and difficulty chewing food.*

- *Respiratory onset MND: rare in comparison and presents predominantly with dyspnoea and orthopnoea. Due to hypoventilation and respiratory muscle weakness when sleeping, these patients may present with symptoms similar to sleep apnoea. This is due to carbon dioxide retention and narcosis, manifesting as daytime somnolence, unrefreshing sleep and frequent waking from sleep.*

Eventually, patients may progress to have symptoms in all of the above domains and so when taking a history for MND remember to ask about all the above. Cramp is also a very common problem in MND which is troublesome for patients but easily treated (see later).

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In all patients with MND it is critical to assess their respiratory function and swallowing function, when taking a history remember to ask about daytime somnolence and morning headaches as this could herald the need for non-invasive ventilation (NIV). Also check for any recent episodes of choking, problems with handling theirs secretions and any features indicating potential aspiration.

Subtle cognitive changes and/or behavioural changes can develop in approximately a third of patients with MND, this generally first presents with features of emotional lability and outbursts of laughing or crying [3]. Rarely frank fronto-temporal dementia may occur.

It is also important to note that although patients may complain of sensory symptoms, the presence of prominent sensory symptoms and/or sensory signs should prompt the consideration of alternative diagnoses. Similarly, involvement of the extraocular muscles or prominent sphincter disturbance would not be expected in MND.

The Examination

When clerking a patient such as Mr Smith with suspected MND the key is to look for a mixture of both upper and lower motor neuron signs in the same affected area. A brisk or easily elicitable reflex in a weak and wasted limb would be a combination that indicates the possibility of MND.

Weakness is typically distal and asymmetrical, upper limb onset is more common than lower limb onset. The patient should be fully exposed to look for any fasciculations (small, localised involuntary muscle contractions in skeletal muscle-gives the appearance of muscles 'twitching') or evidence of muscle wasting in any limb and particular attention should be paid to the reflexes. Sensation and co-ordination should be intact (although the latter can be hard to assess due to weakness).

Muscle wasting can commonly be found in the dorsal interossei of the hands (most prominent in the first dorsal interossei), tibialis anterior and the tongue (Fig. 1). Quadriceps wasting is also common and usually easily noticed in lower limb onset MND. Fasciculations follow a similar pattern.

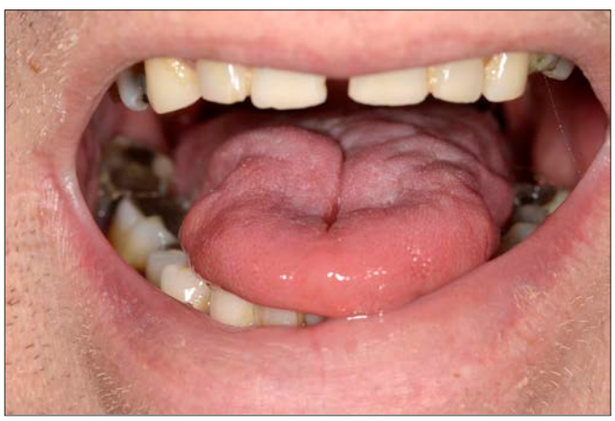

Figure 1: (a) Prominent wasting of the tongue, a common bulbar sign.

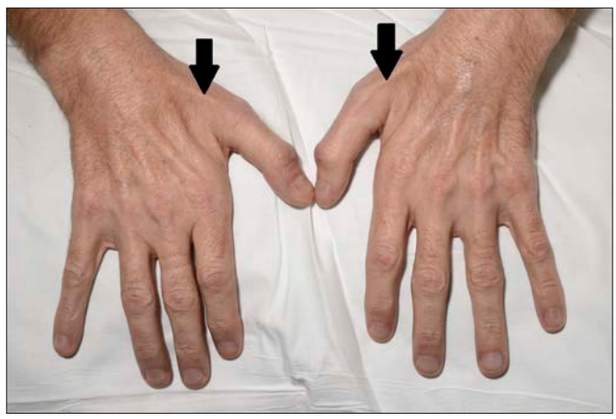

Figure 1: (b) Wasting of the dorsal interossei (arrows).

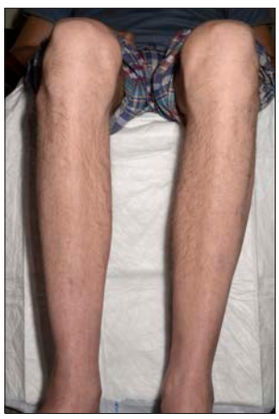

Figure 1: (c) Wasting of tibialis anterior, notice the asymmetry with the wasting being more pronounced in the left than the right.

Reflexes are commonly brisk in clinically affected limbs and can be brisk in subclinically affected muscle groups as well.

Bulbar signs are that of a weak, wasted, fasciculating and spastic tongue that is slow to move, and if seen this should always be considered MND until proven otherwise. Soft palate movement may also be poor. Always examine the jaw jerk in MND patients as it is commonly brisk and an important upper motor neurone sign to note. Patients can commonly be dysarthric, or if seen later in the disease course, completely anarthric. Especially important in patients with bulbar dysfunction is to auscultate the chest to check for any evidence of aspiration.

An assessment of cognitive function should be carried out in all patients as a significant proportion will have cognitive and behavioural changes which may impact on the disease management [3].

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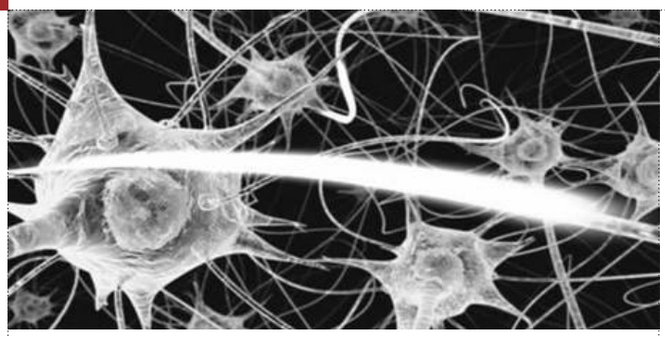

Investigations

The diagnosis of MND is largely made on the history and examination with the investigations being used mostly to exclude mimics. The principal investigations in MND are the electromyogram (EMG) and nerve conduction studies (NCS). In MND the EMG typically shows changes of acute and chronic denervation, whilst the nerve conduction studies would be largely normal [4].

MRI scans of both brain and spinal cord can show signal change in the corticospinal tracts and cerebral atrophy in MND but in most cases imaging is normal. However, imaging is useful to exclude differentials such as cervical radiculomyelopathy (Table 1) [5].

	Clinical features	Useful investigations
Cervical Radiculomyelopathy	Mixture of upper and lower motor neuron signs (upper motor neuron signs are not found above the level of lower motor neuron signs). No bulbar involvement. Pain and sensory disturbance.	MRI- can show multilevel cervical disc disease, cord compression with T2 signal change and/or foraminal stenosis.
Multifocal motor neuropathy with conduction block	Rare- generally unilateral distal arm weakness in young/middle aged patients.	EMG- key finding is the presence of motor conduction block.
Myasthenia Gravis	A common cause of bulbar and limb weakness. Crucially, the weakness is fatiguable and there is an absence of upper motor neuron signs.	EMG, acetyl choline receptor antibodies
Inclusion Body Myositis	Distal weakness (classically the long finger flexors) with no sensory symptoms.	EMG and histological diagnosis can be made on muscle biopsy
Benign Cramp Fasciculation Syndrome	Fasciculations or cramps commonly in larger muscles, which can be provoked by exercise. No weakness or wasting.	EMG

Table 1: Important Differentials when considering MND.

Pulmonary function tests and overnight transcutaneous carbon dioxide and oxygen monitoring (TOSCA ©) are important for assessing respiratory muscle weakness and the need for non-invasive ventilation.

Management

There is one proven drug treatment, riluzole, which can prolong life expectancy by 2-3 months [6]. Otherwise treatment is supportive, helping patients to live with MND and managing the various symptoms they encounter to maximise their quality of life (Table 2).

Symptom	Appropriate management
Cramps	Quinine sulphate, atropine, amitriptyline, physiotherapy.
Difficulty swallowing secretions	Hyoscine patches, amitriptyline and botulinum toxin injection of the salivary glands. Portable suction devices are also available.
Thick bronchial secretions	Mucolytics e.g. carbocisteine (250-750mg three times daily)
Spasticity and jaw spasm	Physiotherapy and baclofen are both effective. Other drugs you can use include dantrolene, tizanidine and clonazepam.
Emotional lability or depression	Amitriptyline or SSRI's such as citalopram
Urinary frequency	Amitriptyline, oxybutynin. Assess other contributing factors such as caffeine intake etc.
Constipation	Movicol, lactulose, docusate, senna. Assess nutritional intake and fibre intake.
Choking and respiratory distress	For short episodes- lorazepam (0.5-2.5mg) sublingually
	For repeated episodes- Morphine orally 2.5mg, four to six times daily
	For prolonged and severe episodes- subcutaneous morphine at 0.5mg/hr. Possible to titrate higher depending on severity of dyspnoea.

Table 2: Symptom Management in MND [8]

Recently the emphasis of treatment has moved to focus on the respiratory muscles, with the use of non-invasive ventilation (NIV) which improves quality of life and prolongs survival [7] [8]. Newer devices such as CoughAssist ©, a mechanical insufflator-exsufflator device, helps to clear secretions in patients with a poor cough due to bulbar dysfunction. Another recent advance is that of diaphragmatic pacing, where pacing wires are implanted to stimulate diaphragm movement. Originally developed for diaphragmatic paralysis in spinal injuries patients, this may be an alternative for the many patients who do not tolerate NIV well [9].

Nutrition is usually difficult, due to poor appetite in many patients and bulbar dysfunction. Many patients will eventually need parenteral nutrition in the form of percutaneous endoscopic gastrostomy (PEG), however in patients with poor respiratory function the anaesthesia is difficult and these patients my need to have a radiologically inserted gastrostomy (RIG) which is a procedure better tolerated by MND patients [8].

The MDT approach is a valuable asset in MND, physiotherapy is useful for advice on mobilisation, treating spasticity and jaw spasm. MND patients commonly have foot drop and physiotherapy can provide a variety of support devices to prevent the foot dropping when walking. Occupational therapists can advise on home adaptations to help both patients and their carers cope at home. Specialist nurses can be valuable in assessing patients and are a great source of emotional support and as a first point contact if patients run into any difficulties.

Conclusion

MND is a devastating disease for which there is no cure. It is important to be able to spot any warning signs that a patient may have MND, which requires a thorough and competent history and examination. MND patients have a variety of issues that as a Foundation Doctor you need to be aware of in order to treat them appropriately and maintain their quality of life.

MOTOR NEURON DISEASE - WHAT DO YOU NEED TO KNOW?

TW Payne, CJ McDermott

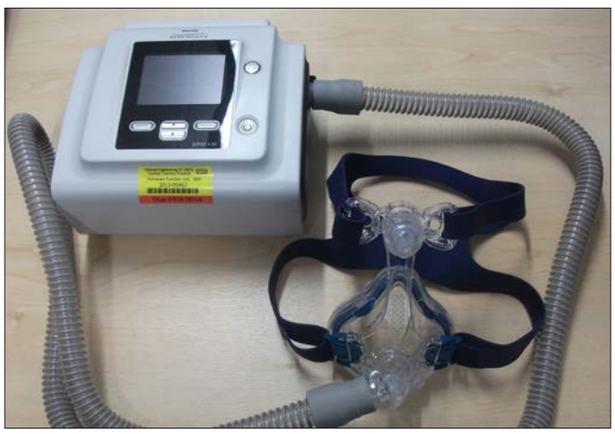

Figure 2: (a) Typical NIV box and face mask.

Figure 2: (b) A set of pacing equipment, showing the pacing machine, connection lead and pads for use.

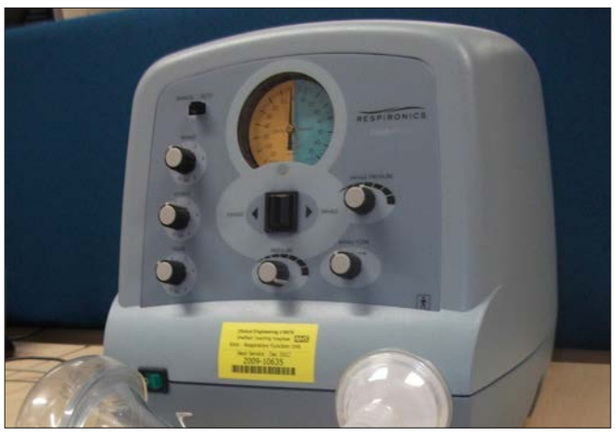

Figure 2: (c) A CoughAssist, a mechanical insufflator-exsufflator device and mask.

Test Yourself

1. Which group of muscles are not affected in MND?

a. Extraocular
b. Pharyngeal
c. Respiratory (intercostal muscles and the diaphragm)
d. Facial muscles
e. Tongue

2. Which intervention(s) have been shown to prolong survival in MND?

a. NIV only
b. Riluzole only
c. Both NIV and riluzole
d. NIV and physiotherapy
e. Riluzole and physiotherapy

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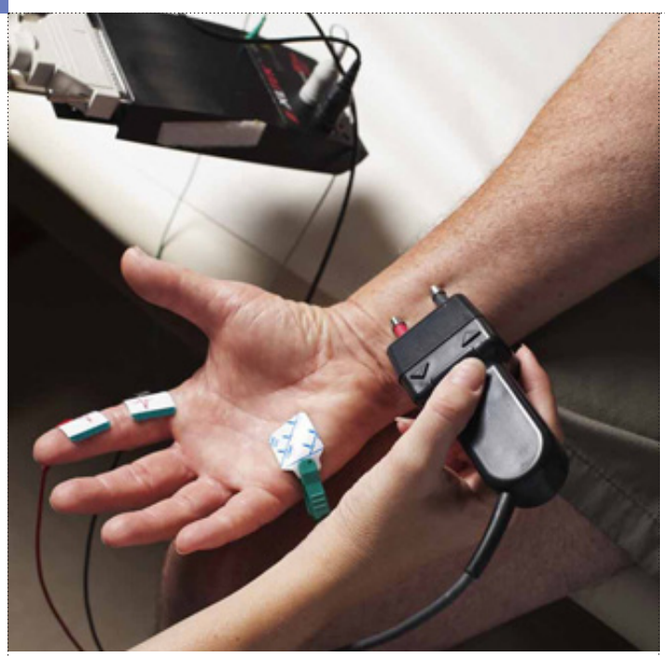
Authors

Thomas W Payne
The Medical School, University of Sheffield,
Beech Hill Road, Sheffield, S10 2RX

Christopher J McDermott
Sheffield Institute for Translational Neuroscience,
University of Sheffield, 385A Glossop Road, Sheffield, S10 2HQ

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

SA Yaacob, A Mallik



What is a nerve conduction study?

The terms nerve conduction study (NCS) and electromyography (EMG) are often used interchangeably but are separate parts of a neurophysiological examination. In the UK, medically qualified specialists called clinical neurophysiologists usually perform or supervise these tests. In this article, we give a brief introduction to the basic of NCS and EMG. A detailed account is beyond the scope of this paper but the reader is directed to the references for further information.

NCS test peripheral nerve function specifically the fastest and largest motor and sensory nerve fibres. A small electrical current is applied to the nerve to generate action potentials which then propagate along the nerve. The responses are recorded with surface electrodes. For motor studies, the recording electrodes are placed over the muscle innervated by the motor nerve. For sensory studies, recording electrodes are placed along the sensory nerve (See Figure 1). The time taken from the stimulus to the evoked response is known as latency. The amplitude crudely reflects the numbers of conducting fibers. The duration is a measure of synchrony of each individual muscle fibre action potentials or the summation of all individual sensory fibers. The conduction velocity is the speed of the fastest myelinated nerve fibers. For motor studies in adults this is normally greater than 50 meters/second in the upper limbs and 40 meters/second in the lower limbs

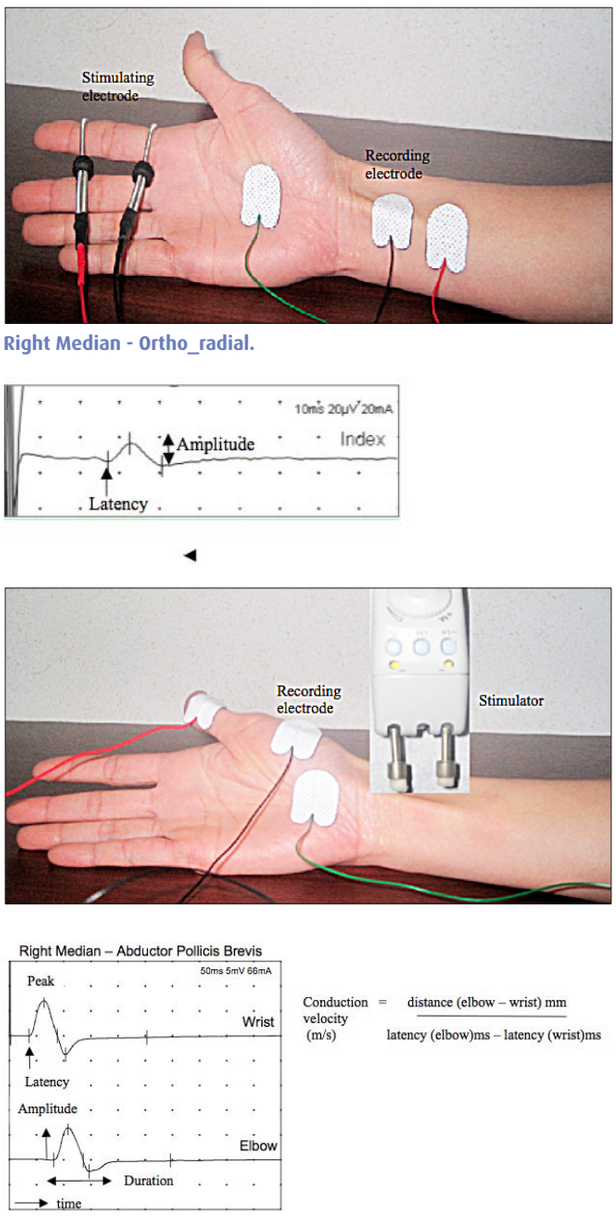


Figure 1: Showed an example of median sensory nerve conduction study (top picture) and median motor nerve conduction study (bottom picture) recording over the right abductor pollicis brevis muscle. The diagram demonstrates the CMAP responses following stimulation at the wrist and at the elbow. The CMAP responses should be almost the same when stimulating the nerve at the distal or at more proximal sites. It also shows how the conduction velocity is measured.

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

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EMG is usually performed together with NCS to record the electrical activity in the muscle. This involved using a fine needle, almost like one used for acupuncture, which has a recording electrode. The needle is inserted into the muscle to be studied and motor unit potentials are recorded. EMG may help diagnose whether the problem is neurogenic (motor nerve axon problem) or myopathic (muscle problem). See Figure 10.

Thinking about the patient

Most patients are seen in the out patient clinic setting. Therefore for inpatients it is important to check that the patient is well enough to come for the test which may take between 30 minutes to an hour. Patients who are acutely unwell may need to have portable studies at the bedside but not all departments provide this service. It may be more time consuming and technically difficult to do portable studies therefore good communication with your clinical neurophysiologist is important. The clinical neurophysiologist takes a history from the patient and performs a focused neurological examination. A differential diagnosis is formulated. The tests and the reasons for doing them are explained to the patient. It is important to think of the tests as an extension of the clinical examination. A good clinical neurophysiologist will have a flexible strategy tailoring tests to the differential diagnosis under consideration and if there are unexpected findings be prepared to look for other conditions. It is crucial that the referring doctor provides adequate history and examination findings so that the relevant clinical questions can be answered.

Most patients are able to tolerate the tests well but it is important to be aware that the tests are uncomfortable. Most patients are understandably anxious before they attend but a calm empathic clinical neurophysiologist will usually be able to put them at ease and get the necessary information. A small number of patients cannot tolerate the tests at all and they have to be abandoned. Most neurophysiology departments send patients in advance written information about what to expect which can be helpful. Information about the tests is best given by those performing them to avoid causing undue patient alarm. I know of several instances when referring doctors have told patients how "horrible the tests are". After the tests, the neurophysiologist may tell the patient the results but this depends on the individual doctor and the diagnosis being considered. For example it is not usually appropriate to give a diagnosis of motor neurone disease at this point.

Indications for NCS/EMG

NCS/EMG detect lesions in the peripheral nervous system and help localize the site of lesion to the following:

- *Anterior horn cell e.g. motor neurone disease*
- *Nerve roots*
- *Plexus*
- *Peripheral nerve (motor and sensory)*
- *Neuromuscular junction e.g. myasthenia gravis*
- *Muscle*

NCS can determine whether a peripheral neuropathy is axonal or demyelinating (See table 1). This can be very important in deciding further investigation and management. Common neurological condition and neurophysiological findings are described in table 2.

	Axonal	Demyelination
Sensory study	SNAP† small or absent	Normal SNAP or Absent
Motor study	Small CMAP‡ amplitude, normal or slightly delayed conduction velocity. No conduction block or temporal dispersion	Delayed distal motor latency, conduction slowing with conduction block or temporal dispersion
F wave minimal latencies	Normal or slightly prolonged	Significantly prolonged or absent

†SNAP; sensory nerve action potential, ‡CMAP; compound motor action potential

Table 1: Nerve conduction study features in axonal degeneration and demyelination.

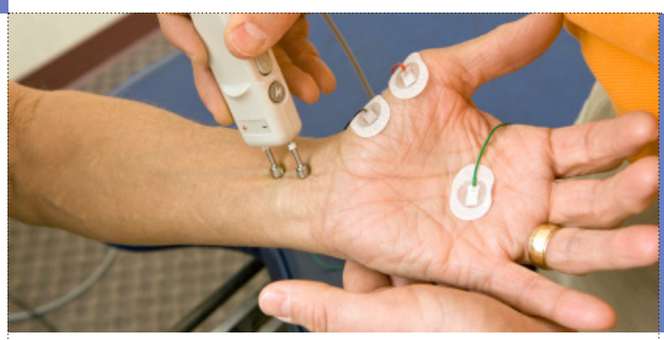
Site of lesion and symptoms	Conditions	NCS/EMG Findings
Muscle -muscle pain, proximal muscle weakness,	Myopathy, myositis,	EMG shows small myopathic motor units, spontaneous actvity in active myositis
Neuromuscular junction - diplopia, slurred speech, fatiguable weakness	Myasthenia Gravis	Repetitive nerve stimulation shows significant decrement pattern. Single Fibre EMG shows increased jitter
Peripheral Nerve - sensory disturbance, motor weakness (depends on site of lesions or more widespread symptoms in polyneuropathy)	Entrapment neuropathy: - Carpal tunnel syndrome - Ulnar neuropathy - Common peroneal neuropathy at fibular head Polyneuropathy: - Acquired (toxic, metabolic, infection, inflammatory, autoimmune) - Inherited (HNPP†),	Conduction slowing at site of entrapment. Small responses in axonal neuropathy, delayed conduction velocity with conduction block in demyelinating neuropathy
Plexus - shoulder pain, back pain	Brachial plexopathy (brachial neuritis). Lumbar plexopathy	Widespread small sensory and motor responses in the limb affected
Root - neck pain, lower back pain, weakness in upper or lower limb	Cervical radiculopathy, lumbosacral radiculopathy	Normal sensory studies. EMG shows neurogenic motor units with reduced recruitment pattern.
Anterior Horn Cell - progressive limb weakness without sensory symptoms, bulbar weakness, muscle fasciculation and muscle wasting	Motor Neurone Disease	Normal sensory study. Motor responses can be small. EMG showed florid dennervation (spontaneous activity) in at least 3 body regions with underlying reinnervation process

†HNPP; hereditary neuropathy liability to pressure palsy

Table 2: The common neurological conditions according to the site of the lesions and neurophysiological findings.

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

SA Yaacob, A Mallik



Does my patient need nerve conduction studies?
Teaching & Training

Information to include in a referral for NCS/EMG

1. Relevant history and examination findings.

2. Clear questions you wish answered. For example, "Does the patient have an ulnar neuropathy at the elbow or the wrist?"

3. Potential difficulties with the patient cooperation such as confusion, learning disabilities, needle phobia or if an interpreter is required.

4. Patient is taking anticoagulants like warfarin which may limit the needle EMG.

5. Pacemakers or implantable defibrillators are also important to know about as may limit electrical nerve conduction studies – check with your clinical neurophysiologist.

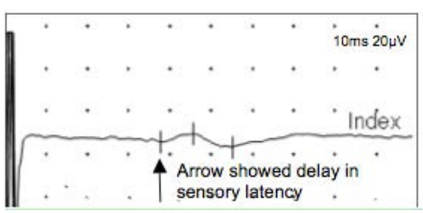
6. The patient is too unwell to come to the department and requires portable studies such as the ventilated patient in the intensive care unit. Remember this is challenging to do and may provide limited information only.

Below are 4 illustrative short cases commonly seen in neurophysiology clinic:

Case 1

A 46 year old lady with a history of type 2 diabetes complained of tingling in her right hand. This was worse during the night wakening her from sleep. Symptoms were exacerbated by manual tasks such as holding a book or driving. On examination there was some wasting of the right abductor pollicis brevis and thumb abduction was weak. There was reduced pin prick sensation at the tip of thumb, index and middle finger. The rest of the examination was normal. NCS of the right hand are summarised in figures 2 and 3.

Right Median – stimulating index finger



Right Ulnar – stimulating little finger

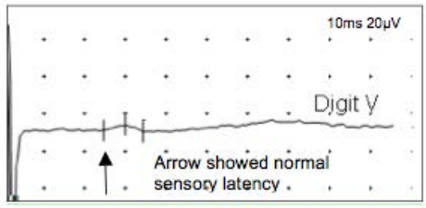
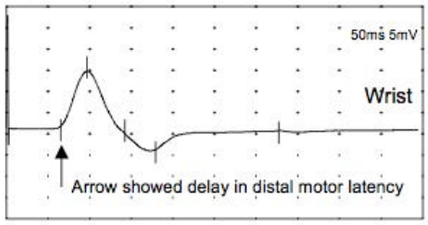


Figure 2: The right median sensory nerve conduction study showed delay in sensory latency compared with the right ulnar sensory study which is normal.

Right Median – Abductor Pollicis Brevis



Right Ulnar Right Ulnar– Abductor Digiti Minimi

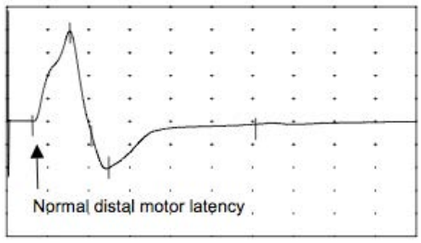


Figure 3: The right median motor nerve conduction study recording over the abductor pollicis brevis and the right ulnar motor nerve conduction study recording over the right abductor digiti minimi. The median nerve distal motor latency is delayed compared with the ulnar nerve motor response.

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

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Discussion

The patient has carpal tunnel syndrome which is caused by median nerve compression at the wrist. It is a very common cause for hand tingling or numbness. The classical distribution of sensory symptoms caused by carpal tunnel syndrome is shown in figure 4. However it is important to realise that patients often describe more widespread sensory symptoms affecting the whole hand sometimes extending up to the elbow. In mild cases only individual median innervated digits (thumb, index or middle finger) may be affected. The key points in the history are of intermittent tingling, nocturnal symptoms and exacerbation with manual tasks. Sensory symptoms are the first sign of carpal tunnel syndrome and may become more painful or constant with increasing severity. Motor weakness and thenar wasting are confined to severe cases. Hand weakness without sensory symptoms is not compatible with a diagnosis of carpal tunnel syndrome. The patient has diabetes which is a risk factor for carpal tunnel syndrome. The main differential diagnosis in this patient is a generalised diabetic peripheral neuropathy. The patient may benefit from carpal tunnel surgery.

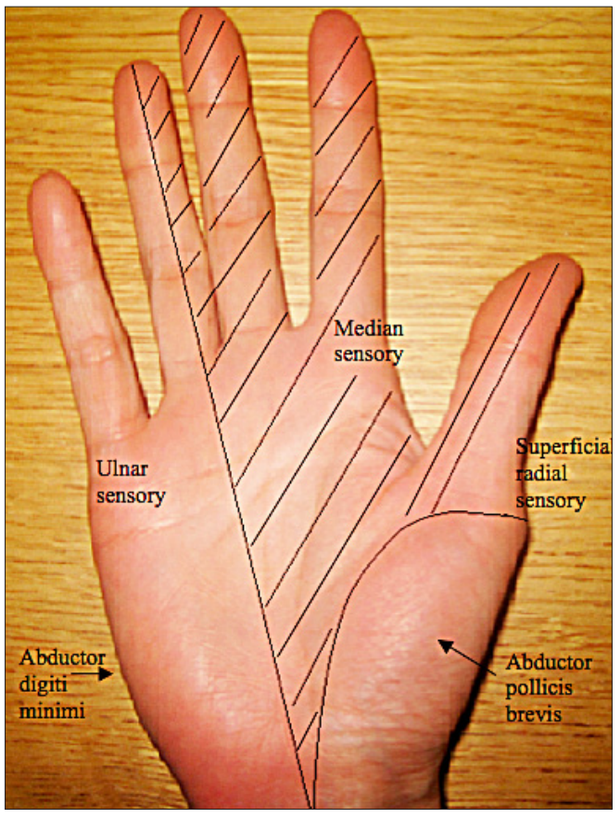


Figure 4: Shaded area showed median sensory distribution on palmar hand. Noted sparing of the area over the thenar eminence.

Peripheral nerve entrapment such as in carpal tunnel syndrome causes focal demyelination. In this case of moderately severe compression, there is slowing of median sensory and motor nerve conduction across the wrist as described in figure 2 & 3. In mild cases only sensory fibres would be affected.

Case 2

A 45 year old builder gave a 6 month history of tingling in his right little finger. This was worse when he leant on his elbow. He was otherwise well. On examination, there was marked wasting of his right first dorsal interosseous muscle (Figure 5). Finger abduction was weak. There was reduced pin prick sensation over the right little finger and half of the medial aspect of his ring finger. His reflexes were preserved.

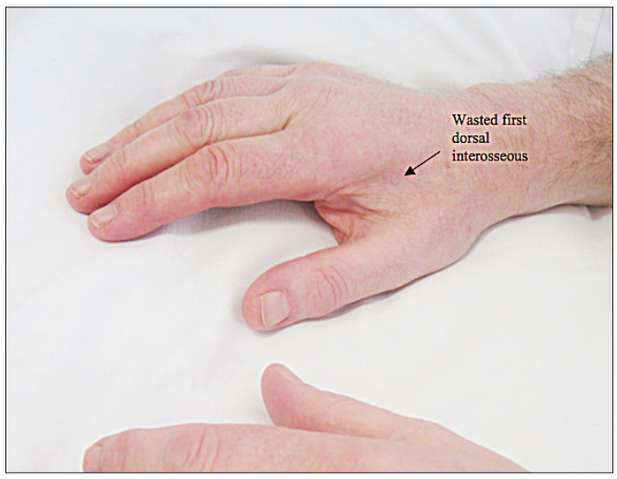


Figure 5: Showed wasting of the right first dorsal interosseous muscle.

The NCS showed absent right ulnar sensory responses (Figure 6). The right ulnar motor nerve conduction study showed normal compound motor action potentials when stimulating at the wrist and below the elbow but with a reduction in amplitude when stimulating above the elbow (Figure 7). There was ulnar motor conduction slowing across the elbow.

Right Ulnar – Stimulating little finger and ring finger.

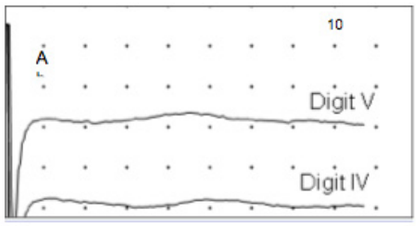
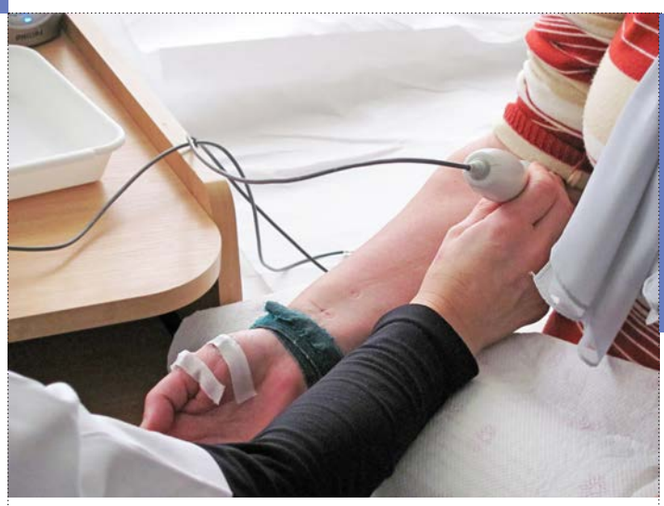


Figure 6: The right ulnar sensory nerve conduction study showed absent responses.

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

SA Yaacob, A Mallik



Right Ulnar – Abductor Digiti Minimi.

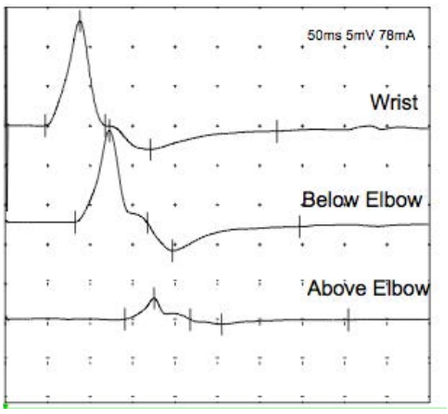


Figure 7: The right ulnar motor nerve conduction study recording over the right abductor digiti minimi showed conduction block when stimulating above the elbow ie: smaller amplitude response.

Discussion

The patient had a right ulnar neuropathy at the elbow which after carpal tunnel syndrome is the second most common site for peripheral nerve entrapment. The clues were the sensory symptoms in the ulnar innervated digits (little and ring finger) and the weakness in ulnar innervated hand muscles with sparing of others.

The differential diagnosis includes a C8/T1 radiculopathy, brachial plexopathy or an ulnar nerve entrapment. The ulnar nerve is most commonly trapped at the elbow but the wrist is an alternative site. Clinical diagnosis can be difficult and nerve conduction studies are very helpful to localize the site of lesion. In this case NCS showed absent ulnar sensory response. The drop in motor response when stimulating above the elbow compared with below is termed conduction block and indicates focal demyelination of the ulnar nerve at the elbow. This patient was severely symptomatic and he was offered surgery to decompress the ulnar nerve at the elbow.

Does my patient need nerve conduction studies?
Teaching & Training

Case 3

A 23 year old gentleman was admitted with acute onset pins and needles in his feet and hands. A day later he developed progressive ascending weakness. A few weeks prior to this, he had a diarrhoeal illness. On examination he was weak in the upper and lower limbs. He was globally areflexic. There was reduced pin prick sensation at the tip of his toes and fingers. A selection of his nerve conduction studies are shown in figures 8 and 9.

Right Sural – stimulating behind the calf.

Right Median and Right Thumb Superficial Radial.

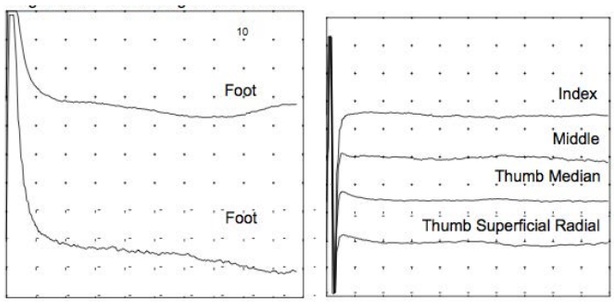


Figure 8: Absent sensory responses in the lower and upper limb.

Left Median – Abductor Pollicis Brevis.

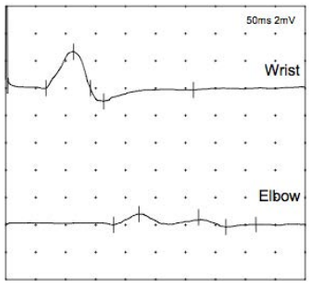


Figure 9: The left median motor nerve conduction study showed significantly drop in compound motor action potential amplitude and increased duration of the response when stimulating at the elbow compared with at the wrist. This is an example of focal demyelination.

DOES MY PATIENT NEED NERVE CONDUCTION STUDIES?

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Discussion

The patient presented with acute sensory disturbance and progressive paralysis without wasting. This is a typical of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a type of Guillain-Barré Syndrome.

The NCS show abnormal sensory responses in keeping with a neuropathy. Motor studies show features of focal demyelination of the median nerve in the mid-forearm segment which is not a common entrapment site (contrast with focal demyelination of the median nerve at the wrist in carpal tunnel syndrome. Further investigations such as lumbar puncture and antiganglioside antibodies should be initiated. Guillain Barré syndrome may progress rapidly with respiratory and bulbar problems. Therefore, early discussion with a neurologist regarding further management may be appropriate.

Case 4

A 54 year old gentleman complained of progressive lower limb weakness over the last 2 years. He had no sensory symptoms. He was previously diagnosed with sciatica. On examination there were widespread fasciculations seen in upper and lower limb muscles. There was a right foot drop. Power in the right lower limb was weaker compared to the left. Upper and lower limb reflexes were brisk. The right plantar responses were extensor.

NCS showed normal sensory studies. In contrast motor responses were of reduced amplitude. Needle EMG in normal muscles should show electrical silence at rest. In this patient EMG showed abnormal spontaneous activity at rest in various upper and lower limb muscles indicating motor axonal pathology or dennervation. Motor unit potentials were recorded with the needle left in the contracting muscle. Motor units were of higher amplitude and longer duration than normal indicating previous motor axon pathology with reinnervation. Figure 10 shows schematic diagram of neurogenic and myopathic motor unit.

Figure 10: Schematic representation of normal, neurogenic and myopathic motor unit action potential. Neuropathic motor unit is of long duration, high amplitude and complex shape (polyphasic). Myopathic motor unit is of short duration, small amplitude and polyphasic.

Discussion

The patient was diagnosed with motor neurone disease (MND). Fasciculations are a feature of MND but may be seen in healthy individuals (benign fasciculations). However, in this case there are other concerning features. The patient is weak and is progressing. There are a mixture of upper (brisk reflexes and extensor plantars) and lower motor neurone signs (wasting). NCS and EMG may provide support for a diagnosis of MND and are important to exclude other conditions which may mimic MND. Some MND mimics such as multifocal motor neuropathy are treatable. MND is a devastating fatal condition with no known cure. A diagnosis of MND should be carefully made and other mimics of motor neurone disorder should have been excluded.

Conclusion

Nerve conduction studies and electromyography are a useful diagnostic tool when used in an appropriate clinical setting. It is important to remember the tests have to be interpreted in the clinical context and do not replace a good history and a comprehensive neurological examination. If you are unsure whether a patient will benefit from these tests it may be worthwhile discussing with your local clinical neurophysiologist. We are generally very approachable and it can be satisfying when you get the right test to complete the diagnostic puzzle.

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Authors

Dr Siti Aisyah Yaacob
Specialty Training Registrar in Clinical Neurophysiology

Dr Arup Mallik
Consultant Clinical Neurophysiologist

Correspondence

Dr Siti Aisyah Yaacob
Specialty Training Registrar in Clinical Neurophysiology
Neurophysiology Department, Southern General Hospital
1345 Govan Road, Glasgow, G51 4TF
Tel: +44 141 201 2480
Email: Siti.Yaacob@ggc.scot.nhs.uk

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