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Independent learning program for GPs

Unit 497 August 2013

Neurology

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The five domains of general practice
Communication skills and the patient-doctor relationship
Applied professional knowledge and skills
Population health and the context of general practice
Professional and ethical role
Organisational and legal dimensions

RACGP

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This unit of *check* looks at some common and serious neurological problems that present in general practice. This unit includes clinical scenarios related to Parkinson disease, multiple sclerosis, facial pain, stroke, migraine in a child and the concerns related to pregnancy in a woman who has epilepsy.

We would like to thank the authors for providing a wealth of information about neurological problems for this unit of *check*.

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The learning objectives of this unit are to:

- list the differences between migraine in a child and an adult
- discuss the issues relevant to pregnancy in a person on epileptic medication for epilepsy
- compare the various treatment options for patients with multiple sclerosis
- explain the preventive measures to be taken by a patient with a transient ischaemic attack
- recognise and recall patients with risk factors such as hypertension to prevent stroke.

We hope this edition of *check* will help you to manage patients who present to your practice with a neurological problem.

Kind regards

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GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

AF	atrial fibrillation	MS	multiple sclerosis
BP	blood pressure	OR	odds ratio
CT	computerised tomography	PBS	Pharmaceutical Benefits Scheme
DBS	deep brain stimulation	RCTs	randomised controlled trials
INR	international normalised ratio	TIA	transient ischaemic attack
LP	lumbar puncture	TN	trigeminal neuralgia
MCQs	multiple choice questions	TTE	transthoracic echocardiogram
MRI	magnetic resonance imaging		

CASE 1

ANNE HAS PERSISTENT HEADACHES

Anne, aged 10 years, presents to you with her mother, Catherine. Anne has been having headaches for approximately 2 years. These occur up to 2–3 times per month, although she sometimes has headache-free periods lasting for up to 3–4 months. The headaches are located in the bilateral temporal regions and feel like 'a hammer banging on my head'. Sometimes the headaches also occur in the facial and maxillary areas. The headaches are accompanied by nausea and photophobia, but not phonophobia. There are no consistent triggers but headaches are sometimes precipitated by hunger or lack of sleep. Attacks are severe and Anne is unable to attend school when they occur. The episodes last 2–4 hours and are usually aborted by sleep.

In childhood, from age 5 to age 7 years, Anne had recurrent periods of non-colicky midline abdominal pain. An extensive gastrointestinal work-up revealed no abnormalities.

Anne has a history of motion sickness.

The psychosocial history is unremarkable.

Anne has a younger brother, Greg, and lives with both parents. Her mother, Catherine, has a history of headaches, and so does one of Catherine's two sisters.

You find no abnormalities on the physical and neurological examination of Anne.

QUESTION 1

What is the most likely diagnosis of Anne's headaches?

QUESTION 2

In what ways are migraines in children and adults different?

QUESTIONS 3

What neuroimaging is indicated for Anne?

QUESTION 4

What would be the recommended first-line acute treatment for Anne?

QUESTION 5

What preventive medications can be used for paediatric migraine?

QUESTION 6

Should Anne be offered preventive medication?

QUESTION 7

Anne's mother, Catherine, asks what she can do to help decrease the occurrence of Anne's headaches. What advice can you give her?

CASE 1 ANSWERS

ANSWER 1

The most likely diagnosis of Anne's headache is migraine. The severe intensity and presence of nausea and photophobia are characteristic of migraine. The history of motion sickness is also suggestive of migraine, and the prior history of recurrent abdominal pain with normal investigations likely represents abdominal migraine, a migraine variant that usually occurs in childhood. The normal neurological examination, the absence of focal neurological signs and symptoms, the 2-year history of stereotypical attacks, and the months-long intervals without headaches are all reassuring for the absence of a secondary headache disorder or structural abnormality.

Tension-type headache is mild or moderate in intensity and is generally not disabling.

Cluster headache is characterised by severe attacks of unilateral pain accompanied by autonomic features such as ptosis, lacrimation or conjunctival injection; it rarely occurs in children.

Acute sinusitis can cause headaches and facial pain, but is also associated with nasal discharge, nasal obstruction, night cough, decreased sense of smell, bad breath and/or fever. Recurrent headaches that occur in the maxillary regions, without any of these other features, are most likely migraines, with involvement of the second branch of the trigeminal nerve. A misdiagnosis of 'sinus headaches' is one of the most common causes of delay in migraine diagnosis and treatment.

ANSWER 2

While migraine in adults lasts for at least 4 hours by definition,[1] children are more likely to have attacks of shorter duration. Photophobia and phonophobia often do not develop until after 12 years of age.[2] Migraines in children are more likely to be bilateral, though younger children may not be able to report the location or quality of their headaches. The use of children's drawings can be both sensitive and specific in the diagnosis of childhood headaches.[3,4]

Although migraine has been shown to be comorbid with mood and/or anxiety disorders in adults, this does not appear to be the case in children. A recent large systematic review[5] of clinical studies assessing psychological functioning and/or psychiatric comorbidity in children with migraine showed that paediatric migraineurs do not have more psychological dysfunction or comorbid psychiatric diagnoses compared with healthy controls. However, if psychiatric comorbidity is present, mental health referral may result in improved migraine management.

ANSWER 3

Neuroimaging is not indicated in patients with recurrent headaches characterised by consistent features, absence of focal neurological signs and a normal neurological examination. Neuroimaging should be considered in patients with an abnormality on neurological

examination, a change in character or pattern of pre-existing headaches, new-onset severe headaches, seizures or other signs of neurological dysfunction, a history of neurocutaneous syndrome (e.g. neurofibromatosis, tuberous sclerosis or Sturge–Weber syndrome), or if the child is younger than 6 years of age. If the headache location is exclusively occipital, further assessment is also warranted.[6]

ANSWER 4

Non-steroidal anti-inflammatory drugs and paracetamol are first-line medications for the acute treatment of paediatric migraine, and these would be offered for Anne.

Sumatriptan and other triptans have been used in children as young as 6 years of age though there is no clear-cut evidence for efficacy in this age group. However, sumatriptan nasal spray is safe and effective in patients older than 12 years of age,[7] and zolmitriptan and rizatriptan have shown efficacy in adolescents.[8] The efficacy of dihydroergotamine in paediatric migraine is unclear.

ANSWER 5

When choosing a preventive medication for migraine, comorbid conditions such as depression, epilepsy or obesity should be taken into account, such that one medication may be used to treat two disorders.

Medications that have been used for paediatric migraine prevention include antidepressants (e.g. amitriptyline), antihypertensives (e.g. propranolol), antihistamines and antiserotonergics (e.g. cyproheptadine, pizotifen) and antiepileptics (e.g. valproic acid, topiramate). However, only topiramate has been shown to be statistically superior to placebo in randomised controlled trials (RCTs),[9,10] and may be particularly useful in overweight patients due to the potential side effect of weight loss. Flunarizine, a calcium-channel blocker, has also demonstrated efficacy in paediatric migraine,[11] but is not available in Australia. Amitriptyline is widely used and has been shown to be effective in open label studies.[12] Its once-daily dosing is appealing and may increase compliance. Cyproheptadine reduced headache frequency in a retrospective study[13] and may be used in younger children who are unable to swallow tablets. Although beta-blockers have also been used for paediatric migraine prevention, RCTs investigating their use in this context[14–16] have not demonstrated their efficacy over placebo, and the risks of hypotension, depression and exacerbation of asthma likely outweigh the potential benefits in many cases.

The use of nutraceuticals such as magnesium,[17] riboflavin,[18–20] and coenzyme Q10[21] in paediatric migraine prevention has been studied in a few small RCTs, but none has shown superiority over placebo. However, these may be considered in cases where traditional medications are not tolerated or where a more 'natural' approach is preferred.[22]

ANSWER 6

Preventive medication is indicated when headache frequency has reached an unacceptable level. Though preventive medication is certainly warranted if the patient has four or more severe attacks per month, it may be considered at lower frequencies if the child is missing school regularly or is unable to participate in social and family activities due to headaches. Preventive medication is not usually required over a long period. Once headache frequency has decreased and remained stable for several months, medication may be tapered, and many patients are able to cease preventive treatment without a recurrence of high-frequency attacks.[23]

The use of preventive medication should be discussed with Anne's mother, Catherine. Its use would depend on how much school Anne was missing and would probably be deferred until after other, non-drug approaches had been tried.

ANSWER 7

Lifestyle modifications can be very effective in reducing migraines and should be incorporated into Anne's daily routine. These include:[23]

- hydration – with at least eight glasses of non-caffeinated drinks daily. Although caffeine is often beneficial in the acute treatment of migraines, daily consumption of caffeinated beverages can result in the development of chronic daily headache
- sleep hygiene – including 8 hours of sleep at night. Bedtime and awakening should be at consistent times each evening and morning throughout the week, as lack of sleep and too much sleep can both trigger headaches
- exercise – incorporating 30–60 minutes of aerobic exercise, at least three times per week
- meals – making sure Anne consumes three daily meals, with mid-morning and mid-afternoon snacks, as hunger appears to trigger headaches in Anne. Meals should be relatively high in protein, vegetables and fibre, and low in fat and sugar. Highly processed foods or those with additives and preservatives are best avoided.

CASE 2

JILL WANTS ADVICE ABOUT EPILEPSY TREATMENT DURING PREGNANCY

Jill, 28 years of age, has well-controlled juvenile myoclonic epilepsy, for which she takes sodium valproate and lamotrigine. Jill was diagnosed 10 years ago on electro-clinical features. She comes to see you for family planning advice. Her last seizure was 3 years ago.

QUESTION 1

What factors influence seizures during pregnancy?

QUESTION 2

What are the known predictors of seizure frequency?

QUESTION 3

What are the risks associated with seizures during pregnancy?

QUESTION 4

What risks do antiepileptic drugs pose to the foetus?

QUESTION 5

Does prenatal antiepileptic drug exposure affect cognitive outcomes in children?

QUESTION 6

Are there any obstetrical risks associated with antiepileptic drugs?

QUESTION 7

Can pregnancy affect a mother's epilepsy?

QUESTION 8

How would you manage Jill?

CASE 2 ANSWERS

ANSWER 1

Seizures during pregnancy can be broadly influenced by metabolic and pharmacokinetic changes, and other factors such as sleep deprivation, malaise and vomiting. Although sex hormones may influence seizure frequency in those with catamenial epilepsy, there is insufficient evidence that changes in sex hormones during pregnancy affect seizure frequency.[24]

Pharmacokinetic effects of drugs in pregnancy are well described in the literature[25–27] and relate to decreased absorption and degree of protein binding, as well as to changes in the individual's volume of distribution, metabolism and excretion.[27] Patients on lamotrigine or oxcarbazepine are likely to have a significant decrease of plasma drug concentration during pregnancy with subsequent increase in seizure frequency.[28,29] This can be attributed to the pharmacokinetic effects of pregnancy. Oxcarbazepine is metabolised to an active metabolite that is rapidly eliminated in pregnancy and may also be influenced by pharmacogenetic variability.[29] Hence, levels of the active metabolite fall during pregnancy, leading to an increased risk of seizures.

Despite marked clearance changes with lamotrigine[25,30] that may lead to an increased risk of seizures, lamotrigine is still considered a safer alternative to valproate monotherapy[31] and has the lowest rate (2%) of congenital malformations with doses <300 mg/day.[32] Baseline pre-pregnancy lamotrigine levels along with regular monitoring and dose adjustments during pregnancy to maintain pre-pregnancy levels have resulted in improved efficacy.[30] Algorithms have been published for monitoring levels and titrating lamotrigine dose.[33] These algorithms also emphasise the increased risk of toxicity in the immediate post-partum period due to a rapid reduction in lamotrigine metabolism.

Sleep deprivation – from nocturia, discomfort or anxiety – has been described.[34] Malaise and vomiting may theoretically lead to decreased drug absorption, but this is an uncommon cause of antiepileptic drug failure in pregnancy.[27]

ANSWER 2

Data from the Australian Pregnancy Registry, reported in 2009, suggested that the risk of a seizure during pregnancy for women who had been seizure-free during the year prior to pregnancy was 50–70% less than for women who had had one or more seizures during the preceding year.[35] The patients who had been seizure-free during the prior year tended to be those with primary generalised epilepsy rather than focal epilepsies. The American Academy of Neurology and the American Epilepsy Society guidelines in the same year concluded that 84–92% of those seizure-free for at least 9–12 months pre-conception remained seizure-free during pregnancy.[24] More recent studies have suggested the most important predictor of seizures during pregnancy is the history of a seizure in the month prior to pregnancy;[36] the next most important predictor is antiepileptic drug polytherapy. Timing of seizure exacerbations is also a factor, as focal seizures tend to have exacerbations in the second to the third and sixth month, whereas generalised seizures demonstrate seizure exacerbations in the third pregnancy month.[36] Interestingly, valproate monotherapy is associated with a significantly lower risk of seizure recurrence.[13] For reasons already discussed, lamotrigine and oxcarbazepine monotherapy have been demonstrated to be a predictor of recurrent seizures.[29]

ANSWER 3

Seizures during pregnancy are associated with small-for-gestational-age babies,[34] occurring at approximately twice the expected rate.[37] Low-birthweight infants and pre-term delivery have also been associated with seizures during pregnancy;[34] however, there has been no demonstrable association between epilepsy type or a first trimester generalised tonic–clonic seizure and risk of major congenital malformations.[32]

ANSWER 4

Teratogenicity is the major concern with antiepileptic drugs. Pre-conception folic acid supplementation (400 µg/day) is recommended to reduce the risk of major congenital malformations and should be continued throughout the pregnancy.[38] Consensus guidelines suggest that there is a probable increase in risk of major congenital malformations when antiepileptic drugs are taken during the first trimester but it is unclear whether this applies to all or some antiepileptic drugs.[37] A meta-analysis of pregnancy outcomes found valproate to have the highest incidence of major congenital malformations (10.73%).[39] In contrast, lamotrigine has a 2.91% risk of major congenital malformations.[39] The Australian Pregnancy Registry major congenital malformation rate for lamotrigine is 5.2%.[40] History of a major congenital malformation in a previous pregnancy has been suggested to be a predictor of future malformations, with an increased risk of congenital malformations in the second pregnancy if the mother is still on the same antiepileptic drugs.[41] Additionally, antiepileptic drug polytherapy is probably associated with increased risk of major congenital malformations, leading to the recommendation to avoid polytherapy in the first trimester of pregnancy.[37]

The effect of antiepileptic drugs on the foetus is dose-dependent. An increase in malformation rates has been observed with increasing antiepileptic drug doses, with initial findings of a significantly greater risk of foetal malformations with valproate ≤1.1 g/day (30.2%) compared with <1.1 g/day (3.2%).[42] The European Register of Antiepileptic Drugs in Pregnancy, which involves 42 countries, recently published their findings that support a dose-dependent risk of malformations.[32] The lowest rates of malformation occurred with <300 mg/day lamotrigine, and with <400 mg/day carbamazepine. Dose-dependent higher rates (compared with lamotrigine) were confirmed on multivariable logistic analysis with valproate, carbamazepine at greater than 400 mg/day, and phenobarbital.[32]

Newer antiepileptic agents may confer lower risk of malformations; however, further data is still required. Levetiracetam is promising, with malformation rates ranging from 0.7%[43] in a UK/Irish registry to 2.4% in a North American registry.[44] In the Australian Pregnancy Register, only 22 exposures to levetiracetam monotherapy have been recorded so far, with no known documented malformations.[40]

ANSWER 5

Children of mothers on polytherapy probably have reduced cognition compared with those of mothers on monotherapy, which has led to the recommendation to consider monotherapy to reduce this risk.[37] Valproate exposure in utero has been associated with an increased risk of language impairment,[45] reduced IQ (by 7–10 points), and worse verbal and memory abilities at age 6 compared with exposure in utero to carbamazepine, lamotrigine and phenytoin.[46] Valproate exposure in utero has also been associated with worse non-verbal and executive function compared with exposure in utero to lamotrigine.[46] A dose-dependent effect has been seen, as the outcomes for those exposed to <1 g/day of valproate did not differ from the results for those exposed to other antiepileptic drugs.

The effect of antiepileptic drugs on cognitive outcomes may also be influenced by periconceptional folate, which has a demonstrable benefit, with higher mean IQs in children exposed to periconceptional folate across all antiepileptic drugs.[46]

ANSWER 6

There is no conclusive evidence of a higher risk of obstetrical complications in pregnant women taking antiepileptic drugs.[37] The American Academy of Neurology and the American Epilepsy Society consensus guidelines suggest that the risk of caesarean delivery is probably not increased,[24] although subsequent studies suggest the risk of caesarean delivery may be increased.[47, 48] The two subsequent studies did not specify the circumstances surrounding the decision to undergo caesarean delivery and hence further evidence is required.

Not enough evidence exists for other complications such as pre-eclampsia, pregnancy-induced hypertension and spontaneous abortion.[1] The risk of premature contractions and premature labour and delivery is probably not moderately increased; however, there may be a substantially increased risk if the woman is a current smoker.[24] The risk of pregnancy-related bleeding complications is probably not substantially increased.[24]

ANSWER 7

Not enough evidence exists to prove seizure frequency and status epilepticus are increased in pregnant women with epilepsy.[24]

ANSWER 8

You should aim to switch Jill to lamotrigine monotherapy and commence folic acid. You should take pre-conception baseline lamotrigine levels, and check levels during pregnancy to maintain this pre-pregnancy level.

CASE 3

MARY PRESENTS WITH FACIAL PAIN

Mary, 39 years of age, comes to see you with a 5-day history of left-sided facial pain that has kept her away from work. Mary has only recently been attending the clinic and has no relevant past history; she is not taking any medications. She has a husband and one daughter.

QUESTION 1

What are the key features to elicit from Mary about the pain?

FURTHER INFORMATION

Mary describes episodes of lancinating pain in the distribution of her left cheek and jaw that last only a few seconds. The episodes are always the same. She has no associated visual disturbance, scalp tenderness or jaw claudication. There is no past history of facial shingles.

On examination she is very reluctant to let you make contact with her chin, as she is concerned that this will precipitate an episode of her facial pain. Other than this concern of Mary's, examination of her face is unremarkable in that there is no rash, bitemporal pulses are present and the arteries are not thickened and there is no motor or sensory deficit other than reported sensitivity to light touch and pin prick in the distribution of the second and third branches of the left trigeminal nerve (cranial nerve V). Visual acuity and fields to confrontation are normal. Additionally, the region of the temporomandibular joints and sinuses are non-tender.

QUESTION 2

What are the differential diagnoses of Mary's hemi-facial pain?

QUESTION 3

What are the common clinical features of trigeminal neuralgia (TN)?

QUESTION 4

What is the natural history of TN?

QUESTION 5

How is TN generally diagnosed?

QUESTION 6

Is imaging necessary?

QUESTION 7

What treatment would you suggest to Mary?

CASE 3 ANSWERS

ANSWER 1

You need to ask focused questions about the pain, including:

- type
- distribution
- duration
- associated features (visual disturbance, tenderness).

You also need to ask about a past history of facial pain or shingles, and whether she has any dental problems.

ANSWER 2

Differential diagnoses to consider for Mary are:

- TN
- primary headache (which includes migraine)
- dental pathology
- temporomandibular joint dysfunction
- maxillary sinus disease
- temporal arteritis.

ANSWER 3

Epidemiologically, the ratio of women to men affected with TN approaches 2:1. The incidence gradually increases with age and is rare below the age of 40 years.[49] Common features include sudden onset, paroxysmal, stereotypical episodes of intense, sharp or stabbing pain in the distribution of one or more branches of the trigeminal nerve (see *Figure 1*). In one study, 29% of patients had only one episode of pain, 19% had two episodes, 24% had three episodes, and 28% had four to 11 episodes.[49]

Classical TN generally involves the second (maxillary) or third (mandibular) divisions of the trigeminal nerve. The first division is affected in less than 5% of cases.[50] There may be trigger zones in the distribution of the affected nerve, which are often located near the midline, and, if present, are often activated by superficial contact such as light touch, shaving, washing, tooth brushing or cold air. (You will recall that Mary was very hesitant about you examining her chin for fear of precipitating her facial pain.)

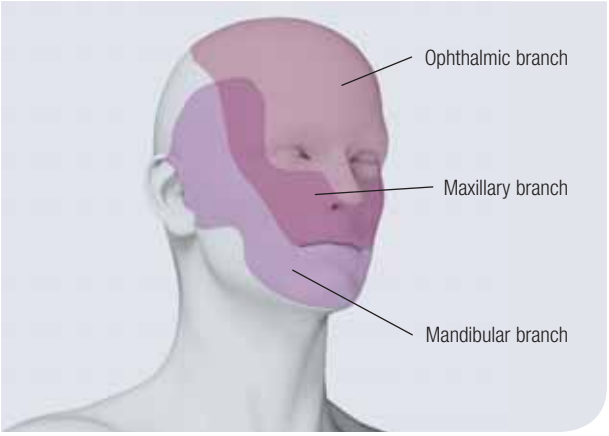

Figure 1. Distribution of the trigeminal nerve (cranial nerve V)

ANSWER 4

The course of TN is variable; episodes may last weeks or months and are generally punctuated by pain-free intervals. It is common for symptoms to recur, with continuous pain being the exception. Most often, the condition tends to fluctuate in severity and frequency of painful exacerbations.[51]

ANSWER 5

TN is principally a clinical diagnosis and is based upon the characteristic clinical features described above, particularly paroxysms of pain in the distribution of the trigeminal nerve.

The International Headache Society diagnostic criteria for classic TN are shown in *Table 1*.[50]

Table 1. Diagnostic criteria for classic trigeminal neuralgia

A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C.
B. Pain has at least one of the following characteristics:
1. intense, sharp, superficial or stabbing
2. precipitated from trigger areas or by trigger factors.
C. Attacks are stereotyped in the individual patient.
D. There is no clinically evident neurological deficit.
E. Not attributed to another disorder.

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ANSWER 6

It is believed that the vast majority of cases of TN are caused by vascular compression of the trigeminal nerve root.[52] An evidence-based practice parameter found that the pooled literature on head computerised tomography (CT) or magnetic resonance imaging (MRI) identified a secondary cause of TN (other than vascular compression) in 15% of patients and found insufficient evidence to support or refute using MRI to identify neurovascular compression in classic TN.[53] However, considering the causes of secondary TN include tumours, multiple sclerosis (MS) and skull base abnormalities, some practitioners adopt the stance that a low threshold for performing an MRI should exist.[54]

ANSWER 7

TN is generally refractory to commonly used analgesics.

Carbamazepine is the most thoroughly studied treatment for classic TN and is established as effective.[52,53,55] Side effects are generally manageable, particularly if low doses are prescribed initially with gradual up-titration. Initial dosing is usually 100–200 mg once or twice daily, and the dose can be increased gradually in increments of 100–200 mg every 3 days as tolerated until sufficient pain relief is attained. A dose of 600–800 mg daily, given in two divided doses, is generally ample, with a maxmum suggested total daily dose of 1200 mg.

There should be periodic attempts to gradually withdraw the drug if Mary's pain has been adequately controlled. If Mary does not respond to carbamazepine, consider referrring her to a neurologist.

CASE 4

KAREN HAS A NUMB FOOT

Karen, aged 34 years, is a mother of two who presents 3 months after giving birth to her second daughter. She has noticed a patch of altered sensation that feels a bit like a dentist's anaesthetic injection on her right foot. The odd feeling started a few days earlier, but has since spread up the leg to her thigh. There is no significant past history, except for an episode of visual loss in her left eye 10 years earlier that spontaneously resolved. Karen ceased breastfeeding 2 weeks after childbirth due to difficulties feeding. The only medication she is taking is the contraceptive pill, and she has no allergies.

QUESTION 1

What is the most likely diagnosis?

QUESTION 2

What further history taking and examination would you undertake?

FURTHER INFORMATION

On further questioning, Karen states that her mother had MS, but she has not thought to mention it before now. This increases Karen's risk 20–40-fold. She also admits to intermittent urinary incontinence, but has put this down to an aftermath of the pregnancy.

Examination reveals altered, but not absent, sensation in the right leg extending to an area around the perineum. Karen's visual acuity is normal and she has no mobility disturbance.

QUESTION 3

What investigations are appropriate? Can a diagnosis of MS be confirmed at this first presentation?

FURTHER INFORMATION

An MRI establishes the diagnosis of MS, with evidence of multiple brain and spinal cord lesions, including two gadolinium-enhancing lesions, one at T10, indicative of recent onset and probably responsible for her presenting symptoms.

QUESTION 4

Should you commence treatment for Karen? What are her options?

QUESTION 5

Given that MS is familial, is there an opportunity for primary prevention in close family members?

CASE 4 ANSWERS

ANSWER 1

While increasing neurological deficit can be caused by a number of illnesses, in a young adult woman, one should consider a diagnosis of MS. MS is the most common neurological illness in young adults and is more common in women. In this case a past history of visual loss that resolved suggests an earlier attack in optic neuritis, a common first presentation of MS that was not diagnosed. Relapses or flare-ups of MS are more common after childbirth, although breastfeeding offers some protection.

ANSWER 2

MS is familial, so it is important to take a family history. However, the great majority of people with MS have a negative family history. Further history should focus on any other neurological symptoms, particularly bladder issues and mobility. It is not unusual for people with MS to have evidence of existing neurological lesions at first presentation. Similarly, examination should look for evidence of other neurological disturbance. Visual acuity should be tested.

ANSWER 3

An MRI is the most definitive test to establish the diagnosis of MS, and can rule out other pathologies as well. Many neurologists today will not proceed to lumbar puncture (LP), depending on positive MRI findings, as the findings on LP are relatively non-specific. On MRI, evidence of typically located old lesions as well as new gadolinium-enhancing lesions indicates separate attacks, confirming MS, according to the McDonald Criteria 2010,[56] without needing to wait for follow-up scans or relapses. Recent evidence suggests that hypovitaminosis D is more common in people with MS than others[57] and is a common trigger for MS presentation and relapse, and the addition of vitamin D supplementation to standard therapy improves outcome in MS.[58] Vitamin D levels should be obtained; there is considerable evidence that people with MS should maintain high normal levels of vitamin D for optimal outcome, and that such levels are safe.[59] For people with low vitamin D levels at presentation (<75 nmol/L), a one-off megadose of 150 000 IU to 500 000 IU, depending on how low the level is, is safe and brings serum levels up rapidly.[60]

ANSWER 4

Disease-modifying therapies such as the interferons and glatiramer reduce the rate of relapses, but there are conflicting results on the rate of progression to disability.[61] However, as Karen has had only one previous documented attack, which was more than 2 years ago, this therapy would not be subsidised by the Pharmaceutical Benefits Scheme (PBS) in her case.

A secondary prevention approach, with modification of adverse risk factors, can provide significant benefits, with studies showing improvements in quality of life with a comprehensive risk factor modification approach.[62] Risk factors implicated include dairy and saturated fat consumption, stress, and lack of omega 3s, sun exposure and vitamin D.[63] Given the frequency of depression in MS, the GP should proactively focus Karen on attending to life pressures, stress and other risks for depression. Mindfulness-based meditation has been shown in a randomised trial to improve quality of life and depression.[64] Consideration may be given to referral for a residential educational workshop to assist in risk-factor modification (see *Resources*).

The interferons (interferon beta-1a and interferon beta-1b) produce a flu-like syndrome in around half the people who take them, which can have a significantly negative effect on quality of life. They are also associated with more significant toxicity including thyroid, hepatic and bone marrow problems. Glatiramer is relatively free of side effects, and just as effective, although it does require daily injection. New medications are more potent, but tend to have more side effects, although oral agents such as fingolimod are now available and these may be more acceptable to many people. Careful consideration of side effects is necessary.

Karen should be offered immediate treatment with intravenous methylprednisolone for her relapse while long-term prevention strategies can be discussed at a subsequent consultation.

ANSWER 5

The risk of developing MS for close family members is substantial. There is now considerable evidence that vitamin D supplementation reduces the risk of developing MS in susceptible individuals by up to 70%.[65–67] Doses of the order of 5000 IU daily of vitamin D should be taken by adult relatives, suitably adjusted for children. There is no danger of toxicity at that dose[68] so blood testing is unnecessary. Such supplements are available from compounding chemists or from reputable suppliers. Commonly available vitamin D supplements of 1000 IU a day are insufficient to affect vitamin D levels significantly.

CASE 5

MARTIN HAS INVOLUNTARY MOVEMENTS

Martin, 57 years of age, has had Parkinson disease for 6 years. He comes in to see you with his wife, Lorraine. He sits wriggling and squirming in the chair with choreiform movements more marked in his right limbs. He has facial grimacing movements and says that he has been having difficulty coping with the hot weather when his involuntary movements are even more troublesome. Lorraine starts crying and says that she can't take it any more. Martin has been a secondary school teacher for 30 years and says that he is still coping with work. At times his voice is soft and his gait is slower with a tendency to freeze.

He is on a combination of levodopa 150 mg/carbidopa 37.5 mg/entacapone 200 mg and he takes this combination in six tablets a day at intervals of 3 hours from 6 am. He also takes pramipexole extended release 4.5 mg once daily and rasagiline 1 mg mane.

QUESTION 1

What is the most likely cause of Martin's involuntary movements? What action might be taken to reduce them?

QUESTION 2

Lorraine is visibly distressed. What questions would you ask Lorraine?

FURTHER INFORMATION

Given the presence of impulse control symptoms, you decide to remove the pramipexole from his medication list.

Martin and Lorraine attend again a week later. Martin's appearance has changed and he is now free of the wriggling movements, but appears slow and shuffly with a dejected expression. Lorraine once again appears tearful. Martin has been sleeping poorly and complains of restlessness in his legs and reduced energy. He has been unable to concentrate when taking classes and he requests some time off work.

QUESTION 3

What factors could contribute to Martin's difficulty in coping with work?

QUESTION 4

What might be done for his insomnia and restless legs syndrome?

FURTHER INFORMATION

Martin returns the following week and says that he has been able to sleep 5 hours per night. He still has some discomfort in his legs in the early hours of the morning and his energy levels remain poor. His off-phases are troublesome and he is concerned that he will not be able to return to work.

QUESTION 5

What other treatments might be considered?

CASE 5 ANSWERS

ANSWER 1

Martin's involuntary movements are most likely drug induced. Drug-induced dyskinesia can produce writhing or wriggling movements, which can be mild and confined to a distal limb or may be worse on the side more affected by the Parkinson disease. This type of dyskinesia may also involve cervical and truncal rocking movements and facial grimacing. Sometimes there is a dystonic component with a tendency to hold the neck tilted or turned or to invert a foot or hold an arm in an unusual posture.

The levodopa preparations, rasagiline and pramipexole (a dopamine agonist), can all contribute to dyskinesia. When there is a sudden worsening it may relate to a change in the patient's medication. In Martin's case, rasagiline[69] was added soon after it was listed on the PBS in August 2012, and the dyskinesia, which had been mild prior to that, had become quite troublesome. Martin had been advised to reduce the levodopa (by reducing the combination tablet) if dyskinesia occurred, but he preferred to stay on the higher dose.

The use of dopaminergic medication that is disproportionate to the degree of immobility experienced in the off-phase of Parkinson disease is now recognised as an iatrogenic disorder called 'dopamine dysregulation syndrome'. In dopamine dysregulation syndrome,[70] patients often adjust their medication upwards themselves. They are tolerant of dyskinesia with accompanying euphoria in their on-phases and dysphoria in their off-phases. This craving or addiction to dopaminergic replacement can also manifest with impulse control problems and may be resistant to downward adjustment of their medication. Impulse control disorders[71] can express themselves as pathological gambling, hypersexuality, excessive shopping and punding (pointless obsessional behaviour such as the repetition of complex motor behaviors [e.g. collecting or arranging objects]).

The most immediate benefit might be obtained from reducing the number of levodopa combination tablets per day. Pramipexole may also contribute to dyskinesia and impulse control problems. Consider reducing the dose of pramipexole first if there are behavioural problems and mental side effects associated with the dyskinesia.

ANSWER 2

Carer stress associated with Parkinson disease is often exacerbated by impulse control problems. The long-term difficulties of reduced ability to work, income insecurity and reduced shared household work are compounded by social withdrawal, mood change and lack of motivation from the Parkinson disease. When there is a crisis in a marital relationship, secrecy associated with the patient's gambling or problems related to hypersexuality are commonly found. Ask Lorraine specific questions about gambling behaviour, punding and hypersexuality. In this case, Lorraine had found a credit card deficit and, when she checked the history of their internet usage, found extensive use of pornographic websites.

ANSWER 3

The impact of parkinsonian motor features depends on the person's social and occupational situation. A mild dysarthria with reduction in gesture and facial expression will have significant impact for a teacher. The presence of dyskinesia can be disabling in social situations. Similarly, subtle cognitive changes, such as word-finding difficulty, difficulty changing mental set and distractibility, will be significant problems for somebody with intellectually demanding work. Other non-motor features of parkinsonism, including depression and an increased tendency to anxiety, may lead to difficulty coping with stress. Fatigue and apathy may also reduce working hours.

ANSWER 4

The sudden withdrawal of pramipexole may lead to exacerbation of parkinsonian motor features, increased fatigue, the recurrence or exacerbation of restless legs syndrome, low mood and sleep disturbance. Sometimes it is necessary to resume the dopamine agonist at a lower dose, but this carries a significant risk of recurrence of the impulse control problems such as gambling and hypersexuality. Sometimes a compromise can be reached. Practical measures to help control them include counselling for financial and gambling-related problems as well as marital counselling.

A low dose of amitriptyline can be useful for middle and late insomnia associated with Parkinson disease. While there is a risk of developing serotonin syndrome in using antidepressant agents with rasagiline (a monoamine oxidase type B inhibitor), small doses of amitriptyline may be tolerated.

ANSWER 5

Deep brain stimulation (DBS)[72] should be considered for the treatment of patients with Parkinson disease who are having significant motor fluctuations that are difficult to control with drug therapy. This may be because of a tendency to dyskinesia in the on-phases or the unpredictability of the off-phases. At other times, difficulties in tolerating drug treatment because of behavioural side effects might also favour this treatment modality as it may allow a reduction in dose of parkinsonian drugs, in particular dopamine agonists.

DBS should not be considered if there are other major health risks such as major depression or significant cognitive impairment. If gait changes and freezing improve significantly with drug therapy they will often respond quite well to DBS surgery, but severe balance problems and 'freezing', regardless of drug treatment, are more resistant.

DBS is often a favoured option in the treatment of patients with early-onset Parkinson disease who, after several years of responding quite well to drug treatment, are having increasing difficulties that threaten their social and working life.

CASE 6

PETER HAS HIGH BLOOD PRESSURE

Peter, 72 years of age, comes to see you for a check-up and a repeat prescription of perindopril. He is divorced and lives alone on a small property 20 km outside Bendigo in regional Victoria. He drives a car and works 2 half days as a bookkeeper in Bendigo. He is a right-handed ex-smoker who quit 6 years ago after he had a heart attack. This is documented in his past history as a 'non-ST elevation myocardial infarction'. He also has a past history of hypertension and hypercholesterolaemia. He previously smoked 5 cigarettes per day for 30 years (8PY) before quitting.

Peter has no family history of stroke or of cardiovascular disease. He has osteoarthritis of both knees, but is otherwise well. Recent blood tests showed a normal fasting glucose as well as a normal fasting cholesterol profile. His current medications are aspirin 100 mg, perindopril 5 mg, metoprolol 25 mg and pravastatin 20 mg every day.

On examination today his pulse rate is irregularly irregular and his blood pressure (BP) is 155/100 mmHg seated. An electrocardiogram confirms newly diagnosed atrial fibrillation (AF) at 66 beats per minute (bpm). Peter denies any symptoms consistent with transient ischaemic attack (TIA) or stroke.

QUESTION 1

What factors need to be addressed to reduce Peter's risk of stroke?

QUESTION 2

What further investigations, if any, would you order?

QUESTION 3

What medication would you prescribe, if any?

FURTHER INFORMATION

Peter refuses any further testing or medication change, as he feels well and is about to leave for a month's holiday in Thailand. Six months later he returns for a check-up and reports having had an episode of 2 hours non-fluent speech disturbance while at work about a month previously. His employer was away and he coped by not answering the phone at work that day. He was unable to process any numbers or figures during this time, but he is confident that he had no other symptoms. The speech disturbance recovered completely after 2 hours. He feels that he has now fully recovered. His BP today is 160/95 mmHg seated and he is in AF at 72 bpm. Examination is otherwise normal.

QUESTION 4

What is your diagnosis?

QUESTION 5

What investigation needs to be done now?

QUESTION 6

What medication changes would you recommend now?

QUESTION 7

What advice would you give Peter with respect to driving?

CASE 6 ANSWERS

ANSWER 1

The two risk factors that need to be addressed in Peter's situation to reduce the risk of stroke are hypertension and AF. The most prevalent reversible risk factor for stroke is hypertension.[73] Normalisation of hypertension significantly reduces stroke risk and the BP target in non-diabetic patients is 130/80 mmHg. Hypertension increases stroke risk in patients with other risk factors such as carotid stenosis.

Anticoagulation is recommended in Peter's situation to prevent an atrial thrombus forming in the presence of AF.[74] He has no previous history of stroke and there are no contraindications for him to commence on anticoagulant therapy. The overall risk of ischaemic stroke rises with age and over 70 years of age the prospective risk generally exceeds the annualised risk of haemorrhagic complications from anticoagulation.

ANSWER 2

Strictly speaking, no further tests are necessary. However it is prudent to order a transthoracic echocardiogram (TTE) in someone with newly diagnosed AF to check for mural dyskinesia or an occult valve lesion. Mural thrombi are seldom visible on TTE, but their absence will not affect the decision to commence anticoagulation treatment.

ANSWER 3

There is no particular drug needed to control hypertension in rate-controlled AF.

Standard stroke prophylaxis in Peter's case would be to commence warfarin. If warfarin is commenced then aspirin is stopped. Once started on warfarin his international normalised ratio (INR) needs to be kept between 2.0 and 3.0.

ANSWER 4

Peter has most likely had a minor cortical stroke or TIA, most likely in the middle cerebral artery distribution.

ANSWER 5

Carotid ultrasound is the investigation of choice in acute presentations of suspected TIA. High-grade stenosis (>70%) in the carotid artery poses significant stroke risk in males even in non-symptomatic patients. Endarterectomy[75] significantly reduces this risk. Peter does not have an excessive surgical or anaesthetic risk and his life expectancy is greater than 5 years. The complication rate is for endarterectomy is 3–4%. The risk of developing a stroke with a high-grade stenosis is estimated at 6% in 2 years. The main complication of endarterectomy is perioperative stroke. The benefit of surgery declines 2 weeks post stroke or TIA, but surgery may still be indicated in this case.

Non-contrast brain CT[76] is useful prior to anticoagulation to exclude small or occult infarcts, as well as prior small intracerebral haemorrhages, which may have been unreported or asymptomatic. These may indicate amyloid angiopathy in someone aged over 70 years and makes anticoagulation more of a risk.

As well as imaging, it will be important to monitor Peter's serum glucose and lipid levels.

ANSWER 6

Peter now has an increased risk of developing a stroke and treatment is highly recommended. The treatment target for secondary prevention of stroke is still similar to primary prevention, but as his future stroke risk is higher, treatment is more strongly indicated.

A recent study suggested a very small relative benefit with combined perindopril and indapamide;[77] however, there is no compelling reason not to use another agent if Peter is intolerant of these drugs.

Warfarinisation reduces stroke risk overall by an odds ratio (OR) of about 0.65. Aspirin up to 150 mg a day alone is inadequate, as it only reduces the OR by 0.20–0.35, but is better than no treatment where warfarin is contraindicated. There is no strong evidence as to whether clopidogrel monotherapy, aspirin and clopidogrel, or a combination of aspirin/dipyridamole is of greater benefit in preventing stroke in AF. However, all these options are more effective than aspirin. Newer antiplatelet agents such as prasugrel have not been evaluated in high-quality studies with regards to preventing ischaemic stroke.

Newer anticoagulants that do not require INR testing are now becoming available. Rivaroxaban, apixaban and dabigatran are available in Australia although not all of them are currently subsidised by the PBS. They are expensive, and cannot be quickly reversed in case of catastrophic haemorrhage or emergency surgery, but they may have a slightly lower haemorrhage risk.

ANSWER 7

You need to advise Peter about current AustRoads[78] guidelines. These recommend not driving a private car for 2 weeks post TIA and 4 weeks post stroke. Neurological assessment is usually required for holders of heavy vehicle licences. Notification to the relevant road authority of a new medical condition like a stroke is a statutory requirement of the driver. Doctors are not compelled to report drivers, but consideration needs to be given if a non-compliant patient puts the community at risk by driving against this restriction. Drivers remaining unfit beyond these periods must remain off the road until fit to resume driving.

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RESOURCES FOR DOCTORS

Paediatric headache

- The American Academy of Neurology (www.aan.com/practice/) has published practice guidelines that can be accessed by non-members.
- The American Headache Society (www.americanheadachesociety.org) has information for both doctors and patients.

Multiple sclerosis

- The National Institute for Health and Care Excellence (UK) (http://guidance.nice.org.uk/CG8) provides guidance for doctors based on the best available evidence, including the management of MS.
- The Mayo Clinic (US) has information on MS (www.mayoclinic.com/health/multiple-sclerosis/DS00188).
- Prof George Jelinek, an experienced medical clinician and researcher, who has MS, recommends a range of well-researched options in his book *Overcoming multiple sclerosis: an evidence-based guide to recovery*, Sydney: Allen and Unwin; 2010 (www.overcomingmultiplesclerosis.org/book/).

RESOURCES FOR PATIENTS

Paediatric headache

- The American Headache Society (www.americanheadachesociety.org) has information for both doctors and patients.
- Information and support for migraine sufferers is provided by the Migraine Research Foundation (www.migraineresearchfoundation.org).

Facial pain

- The Better Health Channel website has good information on neuralgia (www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Neuralgia_explained).
- The Trigeminal Neuralgia Association Australia is a resource for patients (www.tnasydney.freeservers.com).

Epilepsy in pregnancy

- The Australian Epilepsy Pregnancy Register is a voluntary, nationwide study that is enrolling women with epilepsy/taking antiepileptic mediation who are currently pregnant or who have recently given birth (infants up to 6–9 months of age) (www.neuroscience.org.au/apr).
- Epilepsy Australia is a useful website for patients (www.epilepsyaustralia.net). Each of the states has a website. See under 'Epilepsy Australia Affiliates'.

Multiple sclerosis

- The Mayo Clinic (US) has information on MS (www.mayoclinic.com/health/multiple-sclerosis/DS00188).
- Prof George Jelinek, an experienced medical clinician and researcher, who has MS, recommends a range of well-researched options in his book *Overcoming multiple sclerosis: an evidence-based guide to recovery*, Sydney: Allen and Unwin; 2010 (www.overcomingmultiplesclerosis.org/book).
- An evidence-based website for patients diagnosed with MS is available (www.overcomingmultiplesclerosis.org).
- The Gawler Foundation offers a residential lifestyle program for patients diagnosed with MS (http://gawler.org/retreats/multiple-sclerosis).

Neurology

In order to qualify for six Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at www.gplearning.com.au, and
- log onto the *gplearning* website at www.gplearning.com.au and answer the following 10 multiple choice questions (MCQs) online, and
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at www.gplearning.com.au.

If you have any queries or technical issues accessing the test online, please contact the *gplearning* helpdesk on 1800 284 789.

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

John, 8 years of age, has been seeing you for review of his migraines. John has been having migraines for over 12 months. The headaches are throbbing, lasting 3–5 hours and are often in the right frontal area. They are worse with physical activity. His mother also gets migraines.

Which of the following statements is true regarding similarities and differences between paediatric and adult migraine?

A. Paediatric migraine is more likely to be unilateral in location than in adults.

B. Photophobia is more prominent in paediatric migraine.

C. Phonophobia is more prominent in paediatric migraine.

D. Paediatric migraine is often of shorter duration than adult migraine.

E. The association between migraine and mood disorders, as seen in adults, has also been demonstrated in children.

QUESTION 2

What neuroimaging is indicated for John for the diagnosis of migraine?

A. CT brain

B. MRI brain

C. MR angiography brain

D. CT sinuses

E. None of the above.

QUESTION 3

Which of the following medications is recommended for first-line acute treatment in this patient?

A. Dihydroergotamine

B. Ibuprofen

C. Sumatriptan

D. Amitriptyline

E. Topiramate.

QUESTION 4

Which of the following statements best characterises the use of preventive medications in the paediatric migraine population?

A. Preventive medication is not indicated if the patient has fewer than four headaches per month.

B. Once started, preventive medication is usually continued for several years.

C. The efficacy of nutraceuticals such as magnesium, riboflavin and coenzyme Q10 in paediatric migraine prophylaxis is supported by randomised controlled trials (RCTs).

D. The efficacy of amitriptyline and cyproheptadine in paediatric migraine prophylaxis is supported by RCTs.

E. Comorbid conditions can guide the choice of preventive medication.

QUESTION 5

Bob, 65 years of age, presents at your surgery with episodes of pain in the left side of his face. The episodes are brief and shock-like, and last from several seconds to nearly a minute. They occur around the left cheek and are triggered by washing the area and by shaving. There are no associated neurological features. Last year Bob had shingles on the right side of his face. What is the most likely cause of his pain?

A. TN

B. Post-herpetic pain

C. Cluster headaches

D. Sinus pain

E. Migraine.

QUESTION 6

What would be the first-line treatment for Bob?

A. Lamotrigine

B. Baclofen

C. Carbamazepine

D. Amoxicillin

E. Paracetamol.

QUESTION 7

Which of the following is true of TN?

A. Imaging is required to establish a diagnosis.

B. Blood tests are required to establish a diagnosis.

C. It is more common in men than women.

D. It usually affects the ophthalmic branch of the trigeminal nerve.

E. It usually affects the maxilllary or mandibulor divisions of the trigeminal nerve.

QUESTION 8

Bernadette, 35 years of age, is a mother of two. She has a 3-year history of MS. Bernadette presented initially with optic neuritis. She has been well since that time. She woke this morning with numbness in her left hand. This is her first relapse of MS. What is an effective treatment for a relapse of MS?

A. Methylprednisolone

B. Interferon b

C. Glatiramer

D. Vitamin D 100 000 IU

E. Fingolimod.

QUESTION 9

Athol, 61 years of age, has had Parkinson disease for 7 years. He currently takes levodopa, a dopamine agonist and an irreversible MAO inhibitor. The dose of his levodopa was recently increased from four to six times per day by a colleague. He presents with choreiform movements and truncal rocking. What is the most likely cause of his involuntary movements?

A. Stroke

B. Space-occupying lesion

C. Drug-induced dyskinesia

D. Multiple sclerosis

E. Lewy body dementia.

QUESTION 10

Tim, an accountant 63 years of age, has a 10-year history of hypertension. His blood pressure today is 170/90 mmHg. He has come in for a repeat prescription of irbesartan 150 mg, which he has not taken for a month or so because he ran out. One of his work colleagues recently had a stroke.

What is the most prevalent reversible risk factor for stroke?

A. Smoking

B. High cholesterol

C. AF

D. Carotid stenosis

E. Hypertension.