The Royal Society of Medicine

STUDENT SECTION

Neurology and Neurosurgery Specialty Educational Booklet

April 2022

CONTENTS

Note from the Editor

This edition of the specialty booklets is underpinned by collaboration.

Collaboration between the surgical and medical sides of the brain, as well as a combination of work from students in different universities and year groups. This collaboration aims to convey a perspective on neurosurgery and neurology, which is both interesting and unique.

We start this booklet with an insight into the student experience. Entering a surgical environment can be daunting but equally exciting; on page 3, Shivani Sekar captures the feeling of entering a neurosurgical theatre for the first time. On page 16, Shivani also explains the challenges in managing paediatric epilepsy. Honey Panchal introduces the phenomenon of cortical spreading depression and suggests practical solutions on how to apply this knowledge on page 5.

On page 8, you will find an excellent and comprehensive overview of post-haemorrhagic hydrocephalus provided by Matthew Kane. Tayyibah Patel highlights some emerging technologies in the field of neurology, on page 12 and on subsequent pages, you can find some facts on the history of these technologies.

Divanshi Trivedi, introduces us to some rare but important causes of strokes, which you may not have previously heard of- on page 19. Finally, we finish the booklet with a structured checklist covering the cranial nerve examination compiled by Annie Gheasuddin, which I am sure will be useful revision.

On behalf of the Student Section, I thank all of the students for their contributions. We hope you will enjoy reading through the range of articles and can learn something new, as I definitely did!

Faisa-Hamda Yusuf
Editor
RSM Student Section Academic Officer
Cardiff University

An Experience in Paediatric Neurosurgery

Shivani Sekar, The University of Cambridge

"We're ready to begin."

I watched with bated breath as the scalpel descended. It seemed to take only seconds before they could peel away skin to reveal pearly white, glistening bone. I had only ever seen the chalky, yellow-grey of skeletons before in anatomy. The skull in front of me was as shiny and perfect as a baby's milk tooth, the many layers we had learned about in lectures stripped back in one paper-thin sheath.

When my project supervisor suggested that I attend his next surgery,

> *I felt excitement and trepidation in equal measure*

at the prospect of seeing everything that I had learned about paediatric neurology 'in the flesh'. Seeing neurosurgery so early in my first clinical year seemed less like jumping into the deep end and more like cliff-diving. I had arrived at the theatre and spent most of my time on a swivel stool, watching the languorous preparations of the many scrub nurses and anaesthetists around the octopus-like cornucopia of tubes sprouting from the tiny patient's bed. My supervisor had strode through like a paper-cloaked T-rex, hands cocked in front, given a wide-berth by the others. He'd pointed out the strange plastic box suspended from the ceiling that created a pressure gradient, ensuring that air moves out of the room through a vent and preventing contaminated air from entering.

Now, watching the first incisions, I felt as though I could sense the oppressive weight of the room upon me. The smell of burning tissue fizzled in the air as they cut through bone with equal ease. I leaned in as close as I could whilst staying outside the red box marked on the floor to separate the scrubbed-in medical team from us, occasionally watching instead on a nearby screen. Folds of brain bulged out of the gap in the skull, clearly under high pressure, netted with dark purple vessels. It was the first time that I had seen a 'fresh' brain.

> *I somehow felt as though I should be able to see all the child's unformed thoughts – see ideas zipping between neurons like a current, new memories humming beneath the meninges.*

My supervisor stepped back to talk to me, allowing the registrar to begin the delicate process of separating the dura and identifying the precise location that would enable them to reach the surface of the tumour fastest. This involved holding something that resembled a knitting needle to positions millimetres apart and looking at the screen opposite to see which location this corresponded with on the MRI scans.

"Will they be able to put that piece of bone back?" I asked my supervisor. He explained that replacing that puzzle piece was usually done in a second surgery later and that titanium cranioplasty was often preferred nowadays. This was due to challenges with bone preservation. I was horrified to hear that in many countries today, the piece of bone was usually tucked into an incision made in the patient's abdomen, providing it with a 'mini womb' of nutrients to survive.

By this point, the surgeons had got through the outer grey matter and reached the inner layer of white matter, finally disclosing the tumour beneath – a red, vascular heart, throbbing and wine-dark. It was a choroid plexus tumour secreting increased levels of CSF, causing ventricular dilatation and high pressure within the child's skull. It was these symptoms that had caused the child to be admitted to the emergency department days before. This was easy to see now, as the brain and tumour both throbbed, turgid and taut with extra fluid.

I wish I could say that the entire thing was scooped out and plopped into a tray to be sent to histology. In reality, they began the arduous process of separating it from the surrounding normal tissue in an attempt to preserve normal brain function as much as possible. It surprised me that all the healthy brain that was cut through to reach the tumour would not just become redundant but had the plasticity necessary to maintain most function.

It turned out that the patient had been managed first by radiologists in the angiography suite, who had worked on embolising the blood vessels supplying the deep part of the tumour to allow the neurosurgeons to only contend with the superficial vessels, reducing the scope for massive haemorrhage. However, the tumour was still so heavily vascularised that the process of identifying vessels and meticulously cauterising them was painstaking work.

It was easy to lose a sense of perspective,

while watching the screen. The tools began looking like crowbars and hedge trimmers, and I would look back, startled to see the needle-like tools they were using. Pieces of what looked like wire mesh were added at intervals, and I was told that this would aid clotting and turn crusted and black. There was also a gritty, jelly-like substance squirted on areas bleeding particularly vigorously, along with an explosion of swabs. I remembered hearing that swabs were used in multiples of fives to ensure that none were left inside, and I could see a scrub nurse writing tallies on the whiteboard next to me. Each time the cavity was filled with blood, I expected a scene from a medical drama, with people shouting and machines beeping, but in reality, there was just the gentle ebb and hum of suctioning and flushing.

"We've caught the tiger by the tail," my supervisor said at one point grimly. They had caught the tumour in a particularly risky way. The sky darkened outside, and the theatre was particularly quiet, ready for an intermission that did not seem to be coming. My supervisor came by wearily to tell me that it looked like the surgery would continue until late. Eventually, around 6 pm, I left. Later that night, I checked the patient's post-op notes to find that he was right – they had persisted until 10 pm. The tumour was more vascularised than they had anticipated, and they were losing too much blood and had to close up. I felt a pit in my stomach that night and checked the case every day until eventually, after two more revisions, the post-op notes finally indicated that they had removed the tumour. Despite the rush of relief, I felt at this, I knew it would be a long road ahead for recovery and was comforted by the idea that the surgeons were handing over the baton to an extensive team of neurologists, oncologists, physiotherapists, child psychologists, and nurses that would support the oncoming journey.
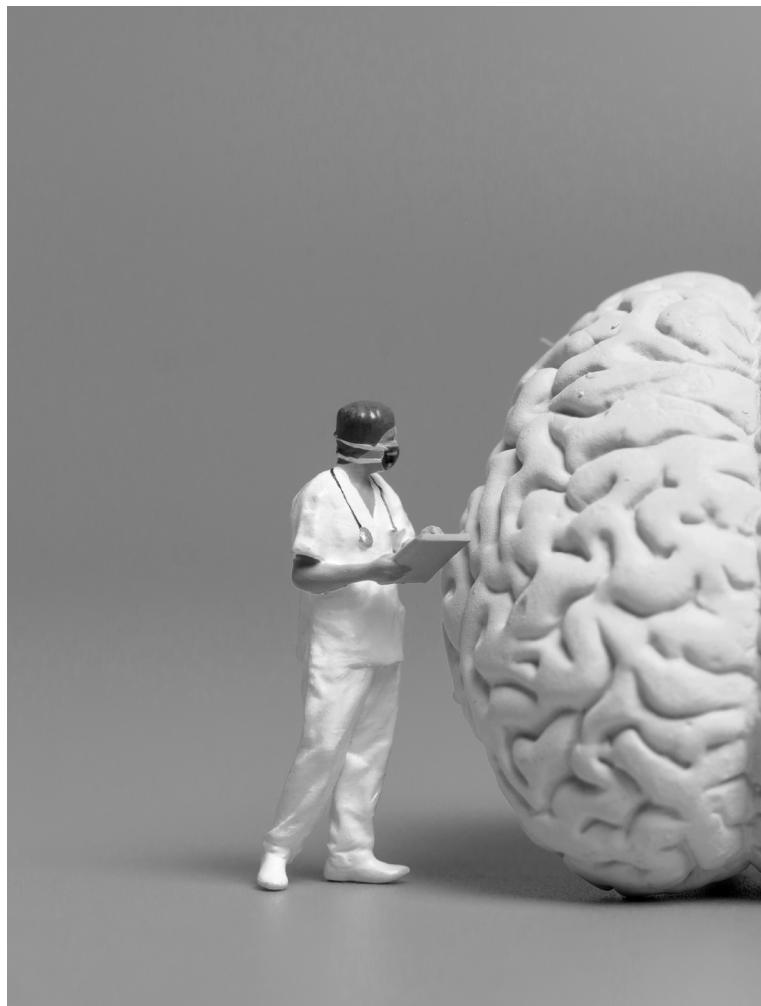
Delving Deep into Depolarisation:

What is CSD and how can we treat it?

Honey Panchal, University College London
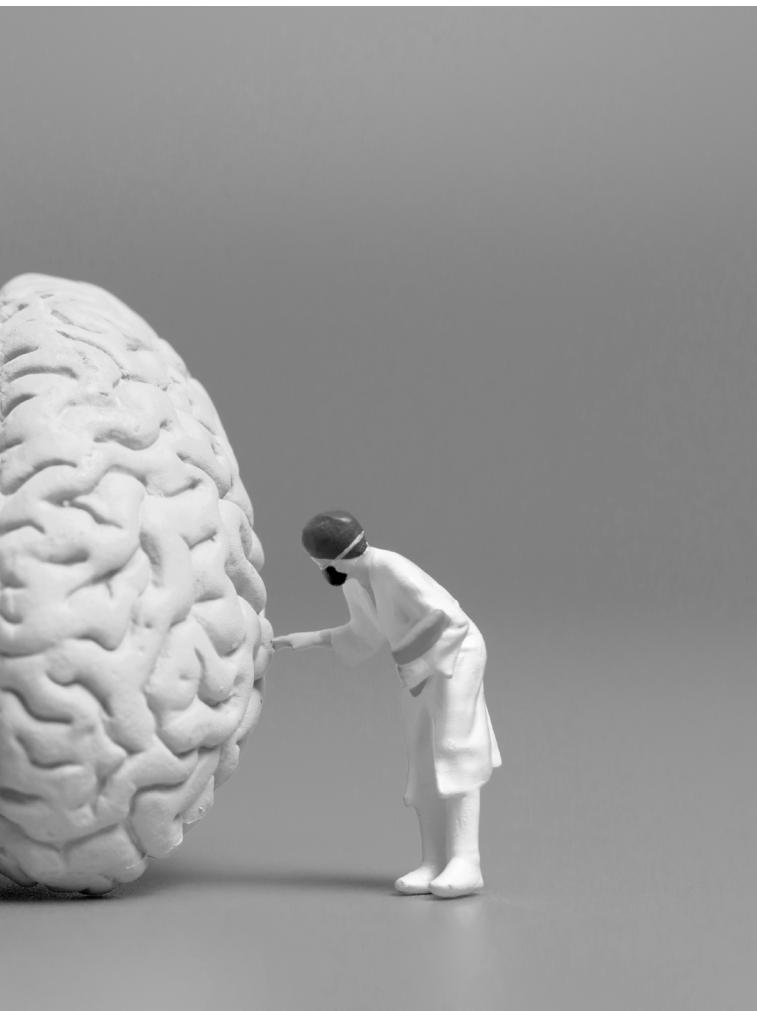
Cortical spreading depression (CSD) is a phenomenon that results in triphasic wave activity, consisting of transient neuronal hyperexcitability followed by depression.[1] Cortical refers to the cortex of the brain whilst spreading depression or depolarisation reflects the wave's movement through the brain. It can be a consequence of neurological trauma or injury, which result in hypoxia, ischemia or hypoglycaemia.[2]

CSD is found in a plethora of conditions, including epilepsy and migraines, enhancing the debilitating effects of both.[2] These conditions alter the cellular environment by changing the ionic gradient of cations, including K^+, Ca^{2+}, Na^+ and amino acids such as glutamate. Disruption of these homeostatic mechanisms can be stimulated artificially in vivo or in vitro, which allows us to understand the detrimental effects this can have on the brain.[2] Therefore, it is crucial to learn more about the pathophysiology of this propagating wave of brain activity as it brings us a step closer to new therapeutic targets.

Wave after wave: the pathological implications of CSD

Mechanism of CSD

Many factors can trigger CSD within the healthy brain, one of the most important is increased extracellular potassium ion concentration ($[K^+]_o$).[1] An accumulation

of K^+ in the interstitial space originating from hyperactive neurones causes depolarisation of the presynaptic bulbs, leading to the release of glutamate via Ca^{2+} dependent synaptic transmission. In contrast, the depolarisation of postsynaptic bulbs results in augmented extracellular K^+ release.

The triphasic wave consists of three phases: a negative wave of 5-20mV in the first 30-50s, a positive-going wave with a smaller amplitude that lasts longer than the previous, and finally, an inhibition of neuronal activity that accompanies the start of a negative slow voltage shift.[1] This wave activity that is characteristic of CSD is termed slow potential change. Astrocytes would normally buffer this rapid increase in $[K^+]$o through the Na^+/K^+ ATPase and other carrier-mediated channels. However, this regulation method is only successful until the $[K^+]$o exceeds a certain threshold. After this, astrocytes not only fail to ensure homeostasis but also act to propagate the CSD waves via glutamate release.

CSD in migraines

Migraine is one of the most common nervous system disorders, defined as a "chronic neurological disorder characterised by attacks of moderate or severe headache and reversible neurological and systemic symptoms".[3] Migraines are thought to have a genetic basis; hypothesised ionopathies lead to neurological manifestations.[4] An ionopathy is a defect in ion channels that may be genetically induced. A key part of the pathology for most individuals is migraine aura - a localised neurological disturbance resulting in visual, sensory or motor symptoms.[4]

One way that CSD may be implicated in migraines is via the genesis of visual auras. These begin in area 17 (primary visual cortex) and propagate throughout the cortical surface of the primary visual cortex.[2] This region has the lowest density of astrocytes, which is pertinent as it means that this region of the brain may be particularly vulnerable to CSD. Furthermore, visual aura formation has a rate of 2 to 6mm, which mirrors that of CSD spreading, suggesting it is a direct consequence of the CSD.[4]

Another similarity present in both migraines and CSD is regional alterations in cerebral blood flow (CBF).[3] Spreading oligaemia is a phenomenon that occurs in both instances, which consists of a "reduction in CBF without acute tissue damage" propagating it. This phenomenon leads to maintenance of focal

autoregulation, "CO_2 reactivity and the functional coupling between neuronal activity and CBF is attenuated."[5] These changes are noted to coincide with visual auras in the occipital cortex.[5]

CSD and epilepsy

Epilepsy is often an extremely debilitating condition characterised by the predisposition to epileptic seizures. Epileptic seizures are temporary symptoms resulting from abnormal excessive or synchronised neural activity within the cerebral cortex.[6]

The relationship between seizures and CSD is fascinating; despite numerous decades of research establishing a relationship between the two, the type, extent and implications of this link remain unknown. Seizures have been seen to occur before, during and after CSD.[7] They create a favourable and conducive environment for CSD to occur. Experimental evidence in rats has shown that CSD creates a state of neuronal activity similar to that which is seen preceding seizures. Another study showed that induced seizures in rats were halted upon the onset of CSD. These findings lead to the conclusion that both CSD and seizures exert a bidirectional influence upon each other.

Ionopathies present in familial hemiplegic migraine causes both epilepsy and migraines due to hyper-synchronisation of neuronal impulses. This suggests that CSD may be the bond that ties the two conditions.[7]

Treatments

CSD is a potential cause of many neurological disorders; therefore, treating CSD may be an appealing common therapeutic target. There are a variety of treatment options that can interfere with CSD activity, including: antiepileptic drugs, vagus nerve stimulation and repetitive Transcranial Magnetic Stimulation (rTSM).

Pharmacological therapies, including anti-epileptic drugs, can reduce CSD occurrence. For example, drugs that target GABA receptors, such as sec-butylpropylacetamide (valproic acid derivative) are important in CSD treatment. These reduce the activity of NMDA-R via GABA-mediated potentiation.[7] These receptors are highly active in

both epileptic activity and CSD, further emphasising the relationship between both.

The use of rTSM holds significant potential as a treatment method for CSD, and it is favourable as it provides a non-invasive intervention. This method uses an electromagnetic coil on the scalp to alter neuronal activity, CBF and metabolism[8,6] Changing the ionic gradients or reducing levels of intracellular Ca^{2+} can disrupt the propagation of CSD waves. This may be a potential mechanism for its neuroprotective efficacy. Rat studies have shown that rTMS can increase the overall volume of neurones within the stimulated region.[8]

Conclusion

Overall, CSD is prevalent in a range of conditions, whilst the mechanisms remain unknown, treatment methods such as rTMS hold significant potential within this field.

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Post-Haemorrhagic Hydrocephalus

Matthew John Kane, University of East Anglia

Introduction

Post-haemorrhagic hydrocephalus (PHH) represents the most common cause of hydrocephalus in developed nations [1], with approximately 34% requiring neurosurgical intervention.[2]

PHH arises in premature infants as a complication of germinal matrix haemorrhage intraventricular haemorrhage (GMH-IVH).[3] PHH can develop acutely following a large GMH-IVH, due to deposition of microthrombi throughout the ventricular system. These microthrombi obstruct the arachnoid villi channels, preventing cerebrospinal fluid (CSF) drainage from the subarachnoid space.[4] During the following weeks, extracellular matrix proteins are deposited throughout the ventricular system, resulting in permanent CSF outflow obstruction.[4]

Once established, PHH can induce white matter injury via direct brain parenchymal compression, cerebral hypoperfusion, and free radical injury.[4] Consequently, PHH is associated with substantial morbidity, including cognitive disability, cerebral palsy, and epilepsy.[5,6] These infants typically require long-term care, with economic impacts on families, healthcare, education, and the wider society.[7,8]

Investigations

The devastating impact of PHH necessitates early recognition and appropriate management, with white matter damage somewhat reversible by CSF drainage.[9]

The signs and symptoms of PHH are attributed to raised intracranial pressure (ICP). These include:

- rapidly increasing head circumference
- splaying of cranial sutures
- full anterior fontanelle apnoeas/bradycardias
- seizures
- 'sun-setting' eyes.[10]

Importantly, these signs develop late in the pathological process, as premature infants can accommodate greater ventricular dilatation relative to adults.[10]

Cranial ultrasound (CrUSS) provides a safe and readily available imaging modality, which enables direct visualisation of the ventricular system. CrUSS screening is routinely performed in all infants born at less than 32 weeks' gestation, facilitating the diagnosis and monitoring of GMH-IVH and PHH.[11,12]

The most common metric to quantify ventricle dilatation is the ventricular index (VI) (Figure 1). Normative reference ranges for VI have been established, which are used to guide the timing of neurosurgical intervention.[13] Other CrUSS measures include anterior horn width (AHW) and thalamo-occipital distance (TOD), which detect enlargement of the frontal and occipital horns, respectively.[14]

Figure 1:
Cranial ultrasound metrics in the (A) coronal plane
VI = ventricular index
**AHW** = anterior horn width
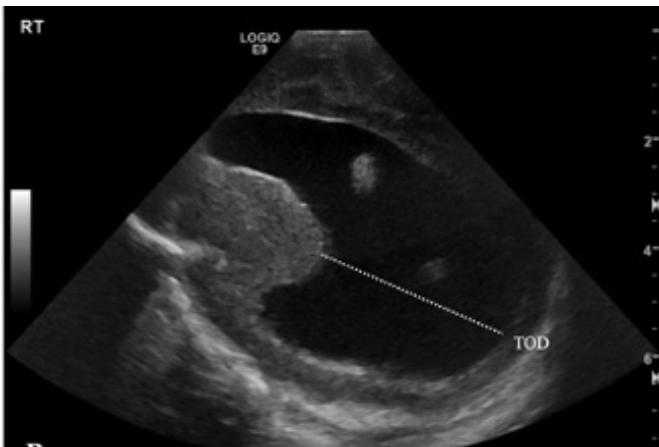
Figure 1:
Cranial ultrasound metrics in the (B) sagittal plane
TOD = thalamo-occipital distance

Management

Timing

Once PHH develops, treatment should be commenced based on radiological evidence of PHH, prior to signs of raised ICP. Most tertiary centres in the United Kingdom (UK) initiate treatment once the VI has exceeded 4mm above the 97th centile.[4]

Temporising Measures

Temporising measures are frequently used in PHH to provide initial CSF diversion. This delays the insertion of a definitive shunt, which is contraindicated in small premature infants due to clinical instability and high risk of surgical complications.[4,15] Moreover, PHH resolves in a proportion of infants following a temporising period, thus obviating the need for a lifelong shunt.[16]

Ventricular access device (VAD) and ventriculosubgaleal shunt (VSGS) (Figure 2) are the most common temporising devices used in PHH. No evidence has indicated superiority of one intervention over the other and current guidelines defer to the physician's preference.[17,18]

VAD comprises a ventricular catheter, which is connected to a subcutaneous reservoir at its distal end. This facilitates percutaneous CSF tapping to halt the progression of ventricular dilatation without the need for repeated trans-frontal ventricular taps.

A key disadvantage of VAD is the necessity to perform regular CSF taps, typically once per day, which carries a theoretical risk of infection. Additionally, periods of high ICP between VAD taps potentially cause further injury.[19] CSF removal also leads to hyponatraemia, which requires careful monitoring and replacement.[20]

VSGS comprises a ventricular catheter that drains CSF directly into the subgaleal space, which is expanded intra-operatively to form a large subgaleal pocket. Post-operatively, infants are positioned to avoid lying flat on the dissection site, thus encouraging CSF drainage via the subgaleal pocket and reducing the risk of re-adhesion.

The major benefit of VSGS is the formation of a closed system, reducing the need for CSF tapping and the theoretical risk of infection. The subgaleal space facilitates continuous CSF removal, avoids fluctuations in ICP, and prevents loss of electrolytes.[21] Consequently, VSGS is less labour-intensive and stabilised patients can be discharged home prior to definitive shunt insertion. VSGS survival is influenced by the absorptive capacity of the subgaleal space, the size of the subgaleal pocket, and VSGS tapping.[22] The longevity of VSGS is often sufficient, however extremely preterm infants may require VSGS revisions to maintain CSF drainage prior to definitive shunt insertion.[23]

Neuroendoscopic lavage (NEL) represents a novel approach, comprising irrigation of the ventricles and aspiration of large haematomas.[24] The clearance of blood products may improve surgical and neurodevelopmental outcomes in PHH.[25,26] The TROPHY registry will compare NEL with other temporising measures to inform treatment guidelines for this complex neurosurgical condition.[18]

Definitive Management

The majority of infants with PHH receiving a temporising device will require lifelong CSF diversion with a definitive shunt. The shunt comprises a ventricular catheter, reservoir, valve, and a distal catheter that drains CSF to the peritoneal cavity, atrium, or pleural cavity. Ventriculo-peritoneal shunt (VPS) (Figure 3) is the standard definitive shunt in hydrocephalus, due to an improved safety profile relative to atrial and pleural shunts.[27]

There is no agreed threshold for definitive shunt placement in PHH, therefore this remains a subjective decision by the treating neurosurgical team.[17] Tertiary
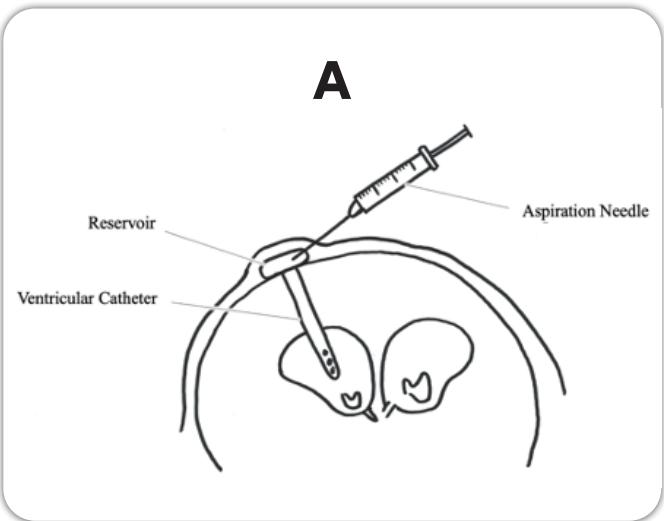
Figure 2:
Coronal view of
(A) ventricular access device and
(B) ventriculosubgaleal shunt
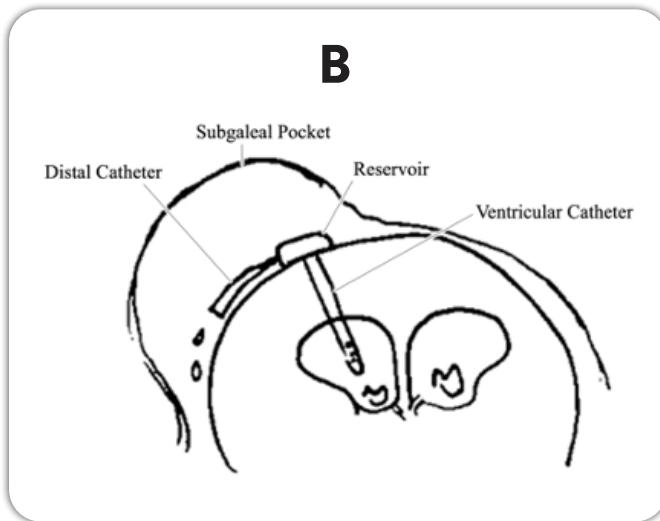
centres in the UK generally consider VPS insertion for infants with progressive hydrocephalus who are clinically stable, weigh greater than 2.5kg, and have CSF protein content less than 1.5g/L.[4]

VPS insertion is the most commonly performed procedure in paediatric neurosurgery, however complications remain prevalent.[17] PHH has the poorest VPS survival relative to all causes of infant hydrocephalus, with an estimated failure rate of 41% at one year and 63% at five years.[6,28] Although antibiotic-impregnated catheters have reduced VPS infection rates[29], further work is needed to optimise long-term surgical outcomes for these vulnerable infants.
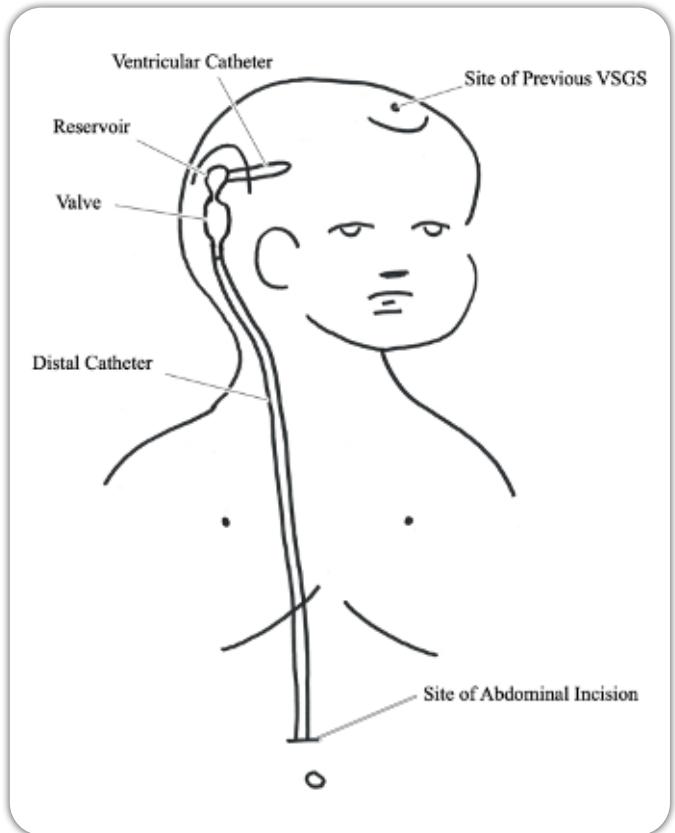

Figure 3:
Ventriculoperitoneal shunt (VPS)

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Light, Sound or Electricity:

Advances in Neuromodulation Technologies
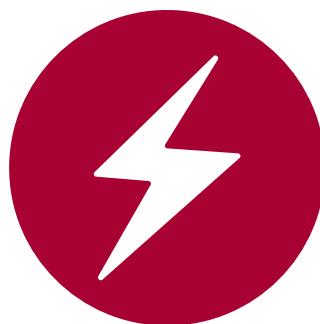
Tayyibah Patel, University College London

Neuromodulation is a technique to alter neuronal firing, either centrally or peripherally, to treat disease.[1] Traditional methods involve electrical deep brain stimulation (DBS), or targeting ion channels using pharmaceutical agents. More recently, biomedical engineers, physicists and neurosurgeons have been combining their expertise to develop novel techniques, such as exploiting light in optogenetics and ultrasound in sonothermogenetics.

Contemporary Neuromodulation Practices

As mentioned above, DBS has been the primary method of controlling neural activity for the past few decades, relying on electricity to interrupt normal signalling. The reversible nature of this technique meant that it quickly replaced standard stereotactic lesioning in the late 20th century.[2] Despite requiring invasive surgery to implant the electrodes, this procedure has several advantages over pharmaceutical therapies: it targets specific brain regions and produces more rapid effects. As a result, DBS has been widely successful in treating certain neurological diseases, including Parkinson's, epilepsy and psychiatric conditions such as depression and schizophrenia. Similar practices have also been attempted using magnetic stimulation.

There are drawbacks associated with these techniques; despite being localised to a specific region, it is not possible to select for a single type of neurone, giving neurosurgeons limited control over the volume of activated tissue. Furthermore, there are instances of unintentional external electromagnetic interference, which can damage the DBS electrodes or even cause harm to cortical tissue.[3] Newer technologies aim to keep the rapid and reversible nature of DBS while increasing the precision of stimulation and reducing possible complications.[4]

DID YOU KNOW?

In 1979, Francis Crick actually posed the idea of using light to target and control specific neurones in real time. Unfortunately, the technological limitations of that time meant scientists were unable to incorporate photosensitive proteins into human cells, leaving Crick's hypothesis as a simple thought experiment.[6]

Optogenetic Opsins:
Shining Light on a Possible Route

Optogenetics is a highly cell-selective method of neuronal stimulation. Its mechanism is based on channelrhodopsins (ChRs), which are naturally-occurring ion channels (termed 'opsins') that open in response to specific wavelengths of light. For example, when blue light is shone on ChR_2, trans-retinal channels will undergo a conformational change, permitting cation entry and subsequent cell depolarisation.[3] These are found in various organisms; as well as allowing green algae to photosynthesise, opsins are present in human cone photoreceptor cells to enable our detection of red, green and blue.[5] Artificially incorporating ChR proteins into selected human neurones (which do not otherwise express them) will allow cation influx and impulse transmission under light stimulation, mimicking the effects of DBS.

A viral vector incorporates genes encoding the opsin into a host cell's genome. Given that each cell type expresses a different set of promotor genes, the viral vector can be manipulated to insert the ChR gene downstream of a given cell-specific promotor, ensuring the ion channel is only expressed by that cell type. An optic fibre cable is then surgically implanted within the brain, directing light of a particular wavelength to the target area.[6] For example, stimulation of afferent axons projecting to the subthalamic nucleus could be therapeutic in alleviating motor symptoms of Parkinson's disease.[7] Note that despite the entire region receiving light, only those cells expressing ChR will be stimulated by it, giving optogenetic technology increased precision over electrical DBS. Further selectivity can be generated by changing source properties such as orientation, colour and polarisation.

Another advantage can be seen in neurostimulation regimes, which rely on sensing physiological signals to trigger the source to transmit an impulse.[3] However, in DBS, these small signals can be disturbed by the large artificial electrical stimulation itself, rendering the feedback system useless. Optogenetic activation has the benefit of not interfering with small physiological recordings.

Nevertheless, this new technology is not flawless. Channel density is the major limiting factor to stimulation, along with optic characteristics of intervening tissues (although low electrical conductivity of these tissues also poses a problem in DBS). Natural light-sensing pathways occurring in surrounding neurones could be stimulated, producing unwanted effects. Furthermore, the heating effect of repeated light emission can potentially alter neuronal function, limiting the power that can be safely used. Placing the optic fibre cable further away from the target source can reduce this effect, although it would likely attenuate opsin response.[3]

Successfully injecting a viral vector into a precise location within a patient's brain, ideally on the first attempt, is undoubtedly a challenge. Placement of electrodes is also an invasive neurosurgical procedure, and both of these carry the risk of infections and foreign body reactions. Finally, it is important to consider the long-term effects; plasticity of neurones could result in modified behaviour over time, for example, via long term potentiation or a reduced response to normal stimulation. Sufficient time has not yet passed for any long-term changes to be observed in humans.[3]

Recent Success of Optogenetics in Humans

In 2021, Sahel et al.[8] showed the potential for optogenetic technology to restore partial vision in a patient with retinitis pigmentosa. They injected an adenovirus vector encoding ChrimsonR (a ChR protein) intraocularly, targeting retinal ganglion cells. Light stimulation was administered via engineered goggles, removing the need for a surgical procedure to insert optic fibre cables. Responses with these goggles were compared before and after opsins were administered, testing the patient's ability to locate, touch, count and reach for the object, together with EEG monitoring. Results from all tasks suggest that light successfully

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DID YOU KNOW?

Electrical stimulation has been used as early as the Roman times; in the text "Compositiones medicamentorum" (46 AD), Largo suggested the use of electrical rays – fish which discharge electricity – to treat headaches. Electrical fish were exploited in therapies for depression and seizures until the 18th century.[10]

induced visual perception, and this was stable over the course of 5 months. EEG activity also confirmed variations in occipital lobe activity when the object was present. These findings are preliminary, particularly considering that the retina is easier to target than deep-brain regions. However, it shows strong promise for the future of optogenetics.

Next steps: Limiting Invasion with Sonothermogenetics

Even more recently, focused ultrasound (FUS) has been used to evoke movement in mice, without the need for surgically-placed energy sources.[9] This technique (termed 'sonothermogenetics') has a similar mechanism to optogenetics, but viral vectors instead encode thermosensitive ion channels such as TRPV1. Ultrasound is applied externally, creating heat within the target region to induce stimulation. Eliminating the need for surgery reduces the opportunity for tissue damage and infection, thereby increasing survival. The majority of current evidence is limited to non-human models, but there is hope that with further research, this technology can move to clinical trials.

It is therefore clear that advances in neuromodulation are marking new territory for less-invasive treatments of neurological disorders, with the potential to benefit a great number of patients in the future.

DID YOU KNOW?

Opsins can be generally classified into two types: microbial (type I) and human (type II). Microbial opsins include ion channels and pumps, while animal opsins are commonly coupled to G-proteins. This makes type 1 opsins (such as ChRs) the method of choice for optogenetic research, due to their simplicity, relative ease in genomic manipulation and faster kinetics.[6]

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Considering the Challenges of Paediatric Epilepsy

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Epilepsy is complex to diagnose and manage, and patients often require long-term support. Understanding the additional nuances of managing paediatric epilepsy can help to improve the quality of care for patients and their families.

Causes

Seizures may have a varied aetiology, including:

● traumatic brain injury

● stroke

● intracranial haemorrhage

● space-occupying lesions and other causes of raised intracranial pressure

● infective causes e.g. meningitis, cerebral abscess

● alcohol or benzodiazepine withdrawal

● drug use

● metabolic or electrolyte imbalances (hypoglycaemia, uraemia, hyponatraemia etc.)

● congenital causes e.g. Dravet syndrome, tuberous sclerosis

● idiopathic.[1]

As part of the differential diagnosis for a paediatric patient it's important to evaluate potential congenital conditions, as genetic analyses in recent years have uncovered many associated genes, (particularly so-called 'channelopathies') that alter the balance of excitatory and inhibitory neurotransmission in the brain.[2] A key example of this is the SCN1A gene mutation seen in Dravet Syndrome, which impairs the function of neuronal voltage-gated sodium channels. In other cases, paediatric seizures may have a much more benign aetiology, and can occur due to a systemic infection – so called 'febrile seizures'.[3] It is key to distinguish these childhood seizures from a diagnosis of epilepsy, which involves repeated seizures as part of chronic neurological dysfunction.

Presentation

A detailed history is often indispensable in order to diagnose epilepsy, as it allows for seizures to be better characterised (e.g. as tonic-clonic, myoclonic etc.) and to be distinguished from syncope (fainting).

Paediatric seizures are frequently absence seizures (also referred to as 'petit mal'), in which the child stares blankly into space. It's often challenging for parents to identify this as abnormal, and particularly so in very young infants as the episode may only last for seconds, and may or may not include automatisms such as lip smacking, nor post-ictal confusion or tiredness.[1]

Red flag signs include sudden onset, perhaps in the middle of activity or a sentence, and the child may be unresponsive to their name being called or stimuli such as touch. Even tonic seizures may present clinically in a more subtle way than seen in adult patients, and so it may be prudent to be more suspicious in paediatric patients and thoroughly follow-up such cases with blood tests, MRI and EEG investigations. Video evidence of suspected seizures may be requested for diagnosis and parents should be encouraged to provide teachers with permission to video record children with suspected seizures in the event that they occur during school. This can be highly informative and important in characterising the nature of seizures and the potential risks to the child.[4]

Once a diagnosis of epilepsy is made, there are a variety of options for management. Anti-epileptic drugs (AEDs) are often effective, and newer AEDs

such as levetiracetam (also known as Keppra) with a better safety profile may be preferable and better tolerated than older options such as sodium valproate. Certain AEDs such as valproate are considered teratogenic and so this should also be evaluated when initiating therapy. In many patients AED monotherapy is sufficient to manage ongoing seizures, with benzodiazepines such as midazolam used short-term to terminate serious epileptic attacks (status epilepticus).[5] It is often found that treatment with multiple AEDs concurrently rarely provides additional benefit, and so is infrequently used. An exception to this is seen in epilepsy with a congenital aetiology, in which many patients can be refractory to treatment.[6]

A ketogenic diet (high fat, low carbohydrate) is often an effective alternative for this cohort and has long been described as an adjunctive method for managing children with GLUT1 deficiency.[7] The mechanism by which this diet is effective is still unclear, but it has been postulated that it may work by altering electrolyte levels in the patient's tissues, including sodium and potassium balance. However, this diet may not be well tolerated by parents, as various studies have noted that parents find it challenging to enforce in young children.[8] Surgical intervention is also an option for patients with intractable epilepsy, and options range from more conservative approaches such as vagal nerve stimulation to stereotactic laser ablation and even corpus callosotomy or resection.[3] Whilst corpus callosotomy appears to be a radical choice, it prevents a seizure initiated at a particular epileptogenic focus from involving both hemispheres (a generalised seizure), reducing severity and frequency of seizures for sufferers.

When discussing a treatment plan with families it's essential to appreciate the impact of epilepsy on patients. The spectrum of severity ranges from infrequent recurrent seizures, to over 50 attacks per day.[1] It is undeniable that this can have a profound impact on a patient, affecting educational attainment and social activities and thereby causing long-term psychological distress.

Seizures in early life can affect development, and epilepsy is associated with a many neurobehavioural comorbidities such as ADHD, autism spectrum disorder, and developmental delay.[9,10] Screening for this and performing neurocognitive profiling routinely in follow-up for patients with epilepsy can help to provide better support for them during schooling and improve academic prospects. It is often seen that children present with these changes even before their first seizure and therefore it's possible that an underlying aetiology may be causative of both the cognitive deficits and epilepsy as opposed to the seizures themselves affecting development.[10] However, repeated seizures can have a direct causative impact on physical health as well, as there is an increased risk of SUDEP (Sudden Unexpected Death in Epilepsy), dying in status epilepticus, secondary brain injury, and fractures during seizures.[4] Therefore, managing epilepsy effectively can be essential for improving patients' quality of life, and long-term outcomes for children.

Summary

A holistic approach to treating patients with epilepsy and considering the ways in which a paediatric patient's seizures or treatment plan uniquely affect them, is integral for effective patient care. Considering the additional challenges posed at every stage from diagnosis to treatment can be of additional assistance to healthcare professionals.

Key areas for further research include an improved understanding of epilepsy that is refractory to treatment, a deeper understanding of the developmental impacts of seizures, and an improved model for identifying which therapeutic options are most appropriate for different patients.

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Strokes: Unusual Aetiology

A brief insight into rare causes of cerebrovascular events

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Over 100,000 people in the UK suffer from a stroke every year, thus making it a leading cause of death and disability.[1] Risk factors such as hypertension, atrial fibrillation, hypercholesterolaemia and diabetes are well researched in their contribution to the development of a stroke. However, there are many rare causes of both ischaemic and haemorrhagic cerebrovascular events that add to the overall disease burden of stroke in the UK; some of these are explored below.

Vasculitis:

Vasculitides represent a collection of disorders characterised by inflammation and destruction of the blood vessel wall.[2] They can be categorised based on the size of the blood vessel affected- ranging from small vessel vasculitis (e.g., granulomatosis with polyangiitis) to medium (polyarteritis nodosa) and large vessel vasculitis (giant cell arteritis). Primary angiitis of the central nervous system (PACNS) involves small and medium vessels of the brain parenchyma and meninges. Symptoms of PACNS include headaches, stroke, cranial nerve palsies and seizures. These can present gradually over weeks with a fluctuating and progressive course. The key factor in a diagnosis of PACNS is an absence of systemic vasculitis.

Diagnosis can be incredibly challenging; angiography is used to showcase bilateral vessel stenosis or occlusions- a ''beads on a string'' appearance- however, many patients with histologically proven PACNS (through a brain and leptomeningeal biopsy) have an entirely normal angiogram.[2] It is important to consider other causes that may mimic PACNS before initiating treatment, these causes may include:

- infections – such as neurosyphilis and HIV,
- migraines
- drugs
- hypertension.

Treatment is comprised mostly of a steroid and cyclophosphamide-based regimen.[3]

Genetic Causes of Stroke:

CADASIL – Cerebral autosomal dominant arteriopathy with subcortical ischaemic leukoencephalopathy

CADASIL is a genetic disorder responsible for causing strokes in younger people. It affects those in the third to fifth decade of life, with the mean age of stroke at 50.7 years.[4] This familial condition is caused by a cysteine altering mutation in the NOTCH3 gene on chromosome 19. The disease entity is characterised by prominent migraines with aura, multiple lacunar infarcts and extensive white matter abnormalities. The effect of recurrent strokes leads to progressive gait disorders, cognitive decline, dementia and urinary incontinence. In addition to this, CADASIL can also present with mood disturbances- specifically, severe depression.[5]

MRI findings of T2 hyperintensity involving the white matter (known as leukoaraiosis) as well as a progressive or relapsing-remitting course has historically led to a diagnostic challenge- with difficulties in differentiating between multiple sclerosis and CADASIL.[6] However, potentially distinguishing features of CADASIL include ischaemic leukoaraiosis, characteristically affecting the anterior temporal and frontal lobes, combined with a family history of strokes or migraines with aura and a lack of response to MS treatment.[7] While there is no known cure for CADASIL, patients are managed on a symptomatic bases – controlling migraines, mood disturbances and other vascular risk factors such as hypertension and diabetes.[8] Antiplatelet treatment with aspirin (75-300mg) is used for secondary prevention of further ischaemic strokes.
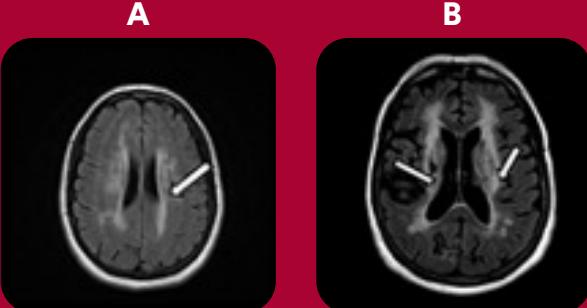
Axial MRI showcasing T2 hyperintensity in a patient diagnosed with multiple sclerosis. Image B, taken 10 years later, shows worsening white matter disease after this patient had undertaken several immunomodulating drugs as treatment for MS. The diagnosis was subsequently changed to CADASIL after genetic testing.[6]

Homocystinuria

Homocystinuria is an autosomal recessive metabolic disorder. Classically, it is caused by the deficiency of cystathionine β-synthase (CBS), encoded by chromosome 21. CBS is required to breakdown homocysteine (arising from the metabolism of methionine) into its metabolites – cystathionine and, eventually, cysteine.[5] This reaction is catalysed with vitamin B6 (pyridoxine) as a co-factor. Homocystinuria is thus characterised by elevated levels of plasma homocysteine and methionine. Affected individuals have multisystem involvement, including a Marfan-like habitus, ectopia Lentis (with bilateral inferior/nasal lens dislocation), skeletal abnormalities, intellectual disability as well as early atherosclerosis.

Elevated levels of homocysteine causing endothelial dysfunction and decreased bioavailability of vasodilators such as nitric oxide have been theorised to play key roles in the pathogenesis of thromboembolic events in homocystinuria.[9] Strokes and myocardial infarctions can occur before 30 years of age.[5] Homocystinuria is one of the inherited metabolic diseases tested for under the Newborn heel prick test (Guthrie Test). Management involves supplementation with vitamin B6, B12 and B9, avoiding methionine in the diet (excluding high protein foods such as meat, fish and cheese as well as specialised formula milk for infants), primary prevention of cardiovascular disease with statins and referral to specialists (ophthalmology) for a multifaceted treatment approach.[10]

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Reported to occur largely in women, specifically around the puerperium state[5], RCVS is characterised by recurrent thunderclap headaches, seizures, strokes and non-aneurysmal subarachnoid haemorrhages caused by segmental constriction of cerebral arteries. While the cause of RCVS is unclear, researchers hypothesize that it is caused by a transient dysregulation of cerebral vascular tone- which is influenced by fluctuations in hormones.

The most common presentation of a thunderclap headache- peak in intensity over seconds to minutes, often accompanied with nausea, vomiting and photophobia mimics the presentation of a ruptured cerebral aneurysm however, symptoms resolve quickly. On average, patients can have 4 such severe headaches over month. Focal neurological deficits (typically visual) and seizures have also been reported. Brain imaging shows vasogenic oedema, convexity subarachnoid haemorrhage (bleeding around the brain convexity without involvement of the adjacent parenchyma or ventricles) and focal intracerebral haemorrhage.[11]

Angiograms are required for a definitive diagnosis – showcasing segmental vasoconstriction of the cerebral arteries. Treatment involves the management of hypertension with calcium channel blockers such as nimodipine as well as possible endovascular interventions with balloon angioplasty and direct intra-arterial vasodilator administration.[12]

Moyamoya Disease

Moyamoya disease is chronic, progressive, steno-occlusive arteriopathy of unclear aetiology that mainly affects the intracranial internal carotid artery (ICA). Stenosis begins at the distal ICA, which undergoes tapering, becoming tortuous and occlusive. Pathological changes of the ICA demonstrate proliferation of smooth muscle cells.[13] Collateral vessels from the anterior and middle cerebral arteries develop anastomosing channels around this occlusion and appear as a "puff of smoke" on cerebral angiography. While the cause is unknown, research shows polymorphisms of the Ring finger 213 (RNF213) gene on chromosome 17 to be linked with an increased probability of developing this condition.[5]

Childhood-onset moyamoya disease has is seen more frequently in girls. Children present with symptoms corresponding to a reduced blood supply- which can be triggered by manoeuvres such as crying or exercise (thus leading to hyperventilation and consequently cerebral vasoconstriction).[14] Headaches and transient neurologic deficits– such as hemiparesis, aphasia, and visual disturbance are common.[15] Adults can also be diagnosed with moyamoya disease; however, they are more likely to suffer from deep brain haemorrhages secondary to the inability of small calibre anastomotic vessels to accommodate for higher blood pressures.[16] Treatment is surgical and angiography after revascularisation shows improved collateral blood flow.[5]

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Cranial Nerve Exam Checklist

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The cranial nerve exam is one of the commonest exams performed in the emergency department. But with 12 cranial nerves, it can feel like a very long and arduous examination to carry out. So here are the most important parts that shouldn't be missed out.

You will need:
- Pen torch
- Cotton wool
- Tendon hammer
- Neuro-tip
- Tuning fork

WIPER QQ
Every exam should start with:

- [ ] **W**ash your hands,
- [ ] **I**ntroduce yourself,
- [ ] seek **P**ermission (consent),
- [ ] **E**xpose (head & neck) the patient adequately,
- [ ] **R**eposition (sitting up with the examiner sitting at the same level as the patient),

and 2 important questions;

- [ ] **Q**: are you in any pain?
- [ ] **Q**: are you comfortable?

Look around the patient's bed for any signs of walking aids, hearing or visual aids or anything else that might provide you with any clues!

Start off with a general inspection of the head & neck, looking for obvious signs such as asymmetry or drooping of the face, problems of the eyes, eyelids and pupils.

CN I:
- [ ] Ask the patient "Have you noticed any change in your sense of smell recently?".
- [ ] If the patient reports a considerable change, ask the patient to smell some smelling salts.

CN II: AFRO-C:
- [ ] **A**cuity: Ask the patient to read a Snellen chart for near and distance vision.
- [ ] **F**ields: Start with both you and the patient covering their L eye. With the patient sitting directly across from you, ask them "Stare at my nose", wiggle your fingers in all four quadrants and ask the patient to say "yes" when they see your fingers in the peripheries of their vision. Repeat with the right eye.
- [ ] **R**eflexes: There are 4 reflexes that should be tested: direct, consensual, swinging light test for RAPD and accommodation.
- [ ] **O**phthalmoscopy: examine the retina with an ophthalmoscope.
- [ ] **C**olour: test with Ishihara plates

CN III, IV, VI:
- [ ] With the patient sitting across from you, ask them to keep their head still and follow your finger with their eyes only. Use your index finger to create an "H" shape to assess the function of their extra-ocular muscles.
- [ ] Remember to ask the patient to let you know if they feel any pain or experience any double vision during this one!

CN V:
- [ ] Ask the patient to close their eyes. Using a piece of cotton wool, gently touch in each of the divisions of the trigeminal nerve on both sides of the face. Ask the patient to say "yes" each time they feel the cotton wool. Ask the patient "does it feel the same on both sides?". Remember not to press too hard as you want to assess the light touch sensation rather than pressure!
- [ ] Repeat with a neuro-tip to assess pain sensation.
- [ ] While palpating the temporomandibular joints on both sides, ask the patient to clench their jaw to feel for the masseter muscles. Repeat at the temples for the temporalis muscles.

- The trigeminal nerve also plays a part in the corneal reflex & the jaw jerk reflex, these aren't usually done in practice as they are quite unpleasant for patients.

CN VII:

- Ask the patient to perform a series of facial expressions against resistance: "raise your eyebrows… scrunch your eyes shut… puff out your cheeks… purse your lips… smile as wide as you can showing me your teeth".

CN VIII:

- Weber's test: Vibrate a 512Hz tuning fork and place it in the centre of the patient's forehead. Ask the patient "Do you hear the vibration louder on the L or the R or is it the same on both sides?"

- Rinne's test: Place the vibrating tuning fork on the mastoid process behind the patient's ear. Ask the patient to say "start" when they start feeling the vibration and "stop" when they feel it stop. Once they feel it stop, move the tuning fork to the front of their ear. Ask "Can you still hear the vibration here". In a patient with no hearing loss, air conduction is better than bone conduction so the patient will answer yes here.

- Romberg's test: Ask the patient to stand with their arms crossed over their chest. Tell them to close their eyes and assess their balance.

CN IX, X:

- These are often grouped together: ask the patient to cough and swallow a sip of water. You can offer the gag reflex with a tongue depressor, but this is unpleasant for the patient and isn't often done in a clinical setting.

- At this point you can also ask the patient "Have you noticed any change in your sense of taste recently?"

CN XI:

- Ask the patient to shrug their shoulders and turn their head to either side against resistance to test the trapezius and sternocleidomastoid muscles, respectively.

CN XII:

- Ask the patient to stick their tongue out. Is there any deviation of the tongue? Place two fingers on the patient's cheek and ask them to push their tongue against your fingers. Repeat on the other side.

- Top tip: It is important to be very specific with your instructions. Practicing with your medical student peers is different to conducting the exam on patients as students often know what to expect and will co-operate much better!

NOTES:

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