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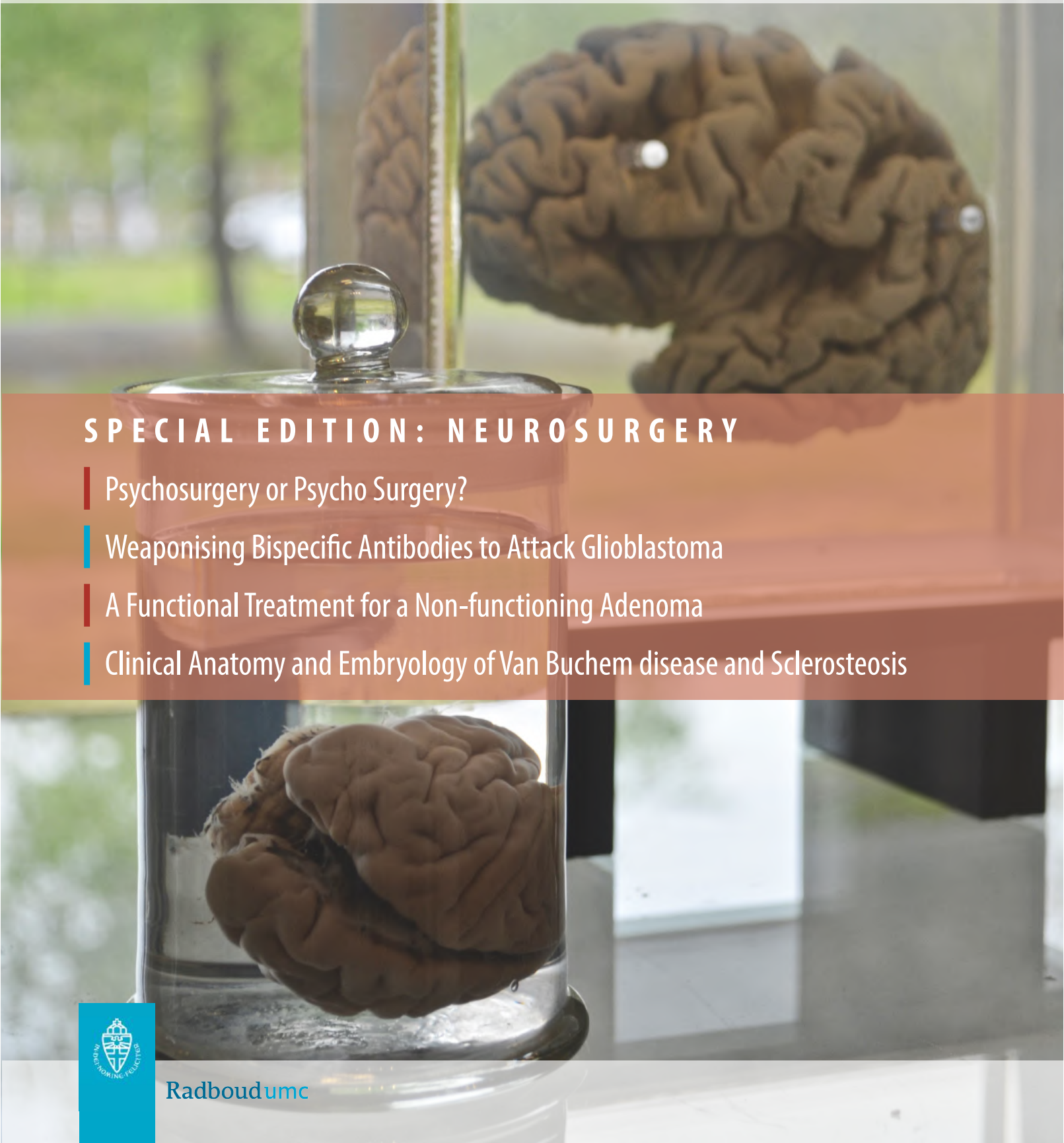

SPECIAL EDITION: NEUROSURGERY

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FROM THE EDITORIAL BOARD

Dear reader,

Our time as members of the editorial board has almost come to an end. It was fun, we learned a lot, we met amazing people and I think that we have successfully continued the work of our predecessors by improving and developing RAMS. This is the result: our special edition about Neurosurgery! However, not all we did for RAMS this year worked out the way we wanted it to. We did a lot, since we thought this was the right thing to do, not because it was evidence based editorial practice. No evidence is available on being an editor-in-chief for an upcoming journal made by and for students. Therefore we limited ourselves to best and common practice. These methods worked fine for running RAMS but are not very satisfying when you are a neurosurgeon. However, true evidence based practice, based on systematic reviews of randomised clinical trials, is not always available in the world of neurosurgery. On page 21 you will find the opinion of neurosurgeons on the evidence available and usable in the clinical practice of Neurosurgery.

Although we prefer to work with evidence based guidelines and the best prediction models, we need to start somewhere. This means that not everything is evidence based practice from the start. For example, a new therapy for glioblastomas or new treatment options for intracranial aneurysms cannot be evidence based from the beginning. It needs to surpass several stages before reaching that golden status of being evidence based.

Besides developing RAMS, we developed ourselves. We formed numerous new neural connections within our brain. Some of these connections are already lost, others are still there. We have no idea which connections remained and which disappeared. Our brain is still one of the most powerful computers in the world. Its functioning is like a black box: there is an input and output without any knowledge of the steps that are taken in between. It continuously adapts itself in order to generate a better outcome. What if we can mimic this self-learning property of our brain and use this trained 'neural network' as a prediction model? Imagine the possibilities in the field of medicine.

I hope that the interesting topics in this edition of RAMS will wire your brain differently in order to make you more interested in doing research in the field of neurosurgery

This special edition is part of our International Summer School. Students from all over the world are visiting our faculty to participate in the extensive educational, practical and social program. Hereby, I would like to thank the dedicated RAMS Summer School Committee for doing such a great job! "It's going to be great. It's going to be absolutely fantastic! You will love it, it's great!"

Yours faithfully,

Sebastian Arts
Scientific Editor-in-Chief

INDEX

PSYCHOSURGERY OR PSYCHO SURGERY?

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Introduction

Editorial

Whereas neurosurgery primarily deals with diseases of the central and peripheral nervous system, psychosurgery or 'functional surgery for psychiatric disease' aims to treat or alleviate mental illness. The latter discipline has a complex and controversial history, during which medical successes were alternated with fatal mistakes. Psychosurgery has definitely known some remarkable and obscure byways that are unimaginable nowadays.

The history of psychosurgery goes back to prehistory and has been comprehensively described. The pioneers who played a key role in advancing the field all believed in the central idea that destruction or modification of the brain areas involved in emotional and cognitive aspects of mental illness could alleviate the symptoms observed [1]. The surgical procedures that are currently employed for psychiatric disease, are indicated for – often refractory – affective and anxiety disorders such as depression and OCD, rather than cognitive disorders (e.g. schizophrenia) [2]. Nowadays, the field is strictly regulated by ethical guidelines. This makes it hard to believe its controversial applications in the past, which sometimes crossed medical and scientific borders.

Between 1962 and 1979 in West Germany, surgical hypothalamotomies were carried out to treat 'sexually deviant patients', such as pedophiles and exhibitionists. Patients might, however, not be the proper description: half of the so-called patients of Roeder and colleagues [3], who performed stereotaxic ablation of the ventromedial hypothalamic nucleus, was homosexual. Homosexuality was considered a mental disorder until 1973. Nevertheless, the surgical procedure was successful in reducing sexual drive [4]. These observations were corroborated by Schmidt and Schorsch, who evaluated the results of 75 patients who had received ventromedial hypothalamotomy. These subjects were imprisoned after having been accused of sex offense and most of them were male. The theoretical foundation of the surgical procedure, however, was questionable and the effects were not properly reported, especially on the long term [5]. Subsequently, psychosurgery of sex offenders became a big political issue in Germany. It was heavily criticized and finally abandoned [4]. Long-term follow-up studies on the satisfaction of the operated subjects were conducted in later times (1989 [6] and 2003 [7]), which reported surprisingly positive outcomes. However,these publications were never formally peer-reviewed.

Another remarkable story in the history of psychosurgery was an experiment by Jose Delgado in 1965, who implanted a stimoceiver – a remotely controllable brain electrode invented by Delgado himself – in the caudate nucleus of a bull's brain. He stepped in the Cordoba bull ring and managed to stop the charging bull. The caudate nucleus is involved in controlling voluntary movements and using the stimoceiver, Delgado claimed to have tempered the bull's aggressive instinct. The Spanish physician experimented with electrical stimulation on cats, monkeys and patients and promoted the idea of psychocivilizing society using psychosurgery, as illustrated in his book Physical Control of the Mind: Toward a Psychocivilized Society [8]. In the same era, Mark and Ervin published a book called Violence and the brain, in which they suggested the use of neurosurgical procedures as a method to suppress the violent behaviour observed in society [9]. This idea was almost realized in the case of one prisoner whom was offered an experimental operation on his brain that would reduce his aggression. The surgical procedure was prevented and rejected in the end, because voluntary consent of the patient was virtually impossible in this setting [10]. The aforementioned events eventually led to an ethical evaluation of psychosurgical procedures by the National Commission for the Protection of Human Subjects of Biomedical Behavioral Research [11]. Against public expectations, psychosurgery was not fully banned and its use as a treatment of last resort – but not for application in minors, prisoners or individuals incapable of giving informed consent – was encouraged [12].

Obviously, the seemingly barbaric events discussed above should be viewed in their historical context, in which pharmacological therapies did not seem efficacious, detailed knowledge on brain function was limited and non-invasive alternatives had not yet been developed. Nowadays, less invasive and more targeted strategies, such as transcranial magnetic stimulation, vagal nerve and deep brain stimulation, gene therapy and stem cell therapy are promising alternatives. Furthermore, the clinical use of neurosurgical procedures for psychiatric disease is strictly regulated. For instance, it is only meant for patients who do not respond to pharmacologic, psychotherapeutic or electroconvulsive therapies and should be supported by both the patient's psychiatrist and the patient's family [2]. Conclusively, the psychosurgery will always remain a controversial subject. It might keep pushing the boundaries of what is acceptable and what is not in a direction that will be shaped by the passing of time as well as the available technologies.

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during the bachelor! The right answers can be found further on in this journal.

We challenge you!

Question 1

A 35 year old motorcyclist crashes on the highway. Eventually he is admitted to the intensive care. His EMV score is E1, M1, V1. After a while, he is able to display a conscious reaction. It seems this is a case of the so-called locked-in syndrome.

What conscious reaction can a patient with locked-in syndrome give?
A. blinking
B. move eyes up and down
C. move eyes left and right
D. move tongue

Question 2

What brain structure is affected in a patient with locked-in syndrome?
A. frontal cortex
B. hypothalamus
C. pons
D. thalamus

The answers to these questions can be found on page 25 in this journal.

WEAPONISING BISPECIFIC ANTIBODIES TO TACKLE GLIOBLASTOMA

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Abstract

Mini review

BACKGROUND: Glioblastoma is amongst the most common and most aggressive types of brain cancers. The tumour cells are highly malignant and often recur after treatment. Due to its location, it is out of reach for most therapies, rendering it virtually resistant. It is currently impossible to cure patients. With the standard treatment, less than 3-5% of patients survive longer than five years.
OBJECTIVE AND METHODS: By evaluating the current developments in tumor immunology, a targeted therapy that is specifically aimed at tumour cells, ideally with no collateral damage, is discussed.
RESULTS: In glioblastomas, multiple mutations are known. Unfortunately, driver mutations specific for all types of glioblastoma have yet to be identified. Receptor tyrosine kinases, like EGFR, VEGFR and PDGFR, seem to be promising targets for therapy. Nevertheless, any drug against glioblastoma needs to be able to cross the blood-brain barrier (BBB).
CONCLUSION: A bispecific antibody with two active sites could be developed, which independently aid in crossing the BBB and targeting glioblastoma cells. In addition, a toxic compound, attached to the bispecific antibody, could be employed to tackle tumour cells upon binding. With this strategy, future glioblastoma patients can possibly be cured.

WHAT'S KNOWN: It is possible for bispecific antibodies to cross the BBB. Furthermore, targeting glioblastoma cells specifically by binding to their characteristic membrane molecules is possible, e.g. overexpressed or mutated EGFR.

WHAT'S NEW: Bispecific antibodies that can both cross the BBB and specifically target tumour cells in glioblastoma, bear the promise of giving patients a longer life expectancy and better prognosis.

KEYWORDS: blood-brain barrier, targeted therapies, brain cancer, targeted drug delivery, tumor immunology

Glioblastoma

Glioblastoma is the most common and aggressive cancer that commences in the brain. The incidence increases with age, affecting more men than women. Glioblastomas are highly malignant and often recur after treatment [1]. Radiotherapy and surgical resection are therapies that are difficult to apply in glioblastoma because of its diffuse, infiltrative growth into the surrounding brain tissue. Currently, standard treatment consists of radiotherapy followed by a daily dose of the cytostaticum temozolomide [2]. Using this therapy, however, less than 3-5% of patients survive over five years. For the time being, curing patients is impossible [1].

Glioblastoma cells are often supported by an extensive network of blood vessels, allowing them to proliferate rapidly [1]. Glioblastoma cells originate from astrocytes. The exact function of astrocytes is not yet fully identified, but it is known that they only appear in the central nervous system and are essential for the brain to function [3]. Astrocytes are often referred to as the support of neural cells in the brain, but researchers suggest that astrocytes also play an important role in potassium buffering, pH control mechanisms, cell signaling, glutamate and GABA uptake, control of cerebral blood flow, water transport, lactate shuttling, antioxidant functions and perisynaptic processes [4].

Targeted Therapy

The development of cancers is a complicated, multistep process. The first step of this process entails the accumulation of mutations in the DNA of some cells, eventually turning them into cancerous cells. However, not all acquired mutations contribute to the development of cancer. Mutations that do not lead to phenotypic changes are merely present due to faulty gene repair and are termed 'passenger mutations'. On the other hand, the mutations that drive the transition from a healthy cell towards a tumour cell are aptly named 'driver mutations' [5]. Passenger mutations have no prognostic value, even though they are abundant in rapidly proliferating tumour cells. Driver mutations are more rare in tumours, but are compelling targets for therapies [5].

To deal with glioblastoma in patients, it is important to develop a therapy that is specifically targeted at the tumour cells, yet causes little to no harm to the surrounding healthy brain tissue. Such a therapy could be aimed at specific genes, pathways, or cell surface receptors that are abnormally expressed on glioblastoma cells. Several mutations in glioblastomas are known. Unfortunately, a driver mutation that is both specific to and present in all types of glioblastomas, has not yet been discovered [1]. Nonetheless, a couple of genes and pathways with considerable impact on the development of glioblastomas have been identified. Receptor tyrosine kinases, like EGFR, VEGFR and PDGFR could be used to specifically target the glioblastoma cells [6]. Moreover, IDH1, an enzyme part of the TCA cycle in glucose, is often mutated in glioblastoma and expressed in MHC class I on the cell surface. While also present in normal brain cells, EGF receptors and IDH1 are mutated in 70% and 90% of primary and secondary glioblastoma patients, respectively [7, 8]. Therefore, they offer the possibility to distinguish between tumour cells and normal cells.

Blood-brain Barrier

Any drug targeting glioblastoma needs to be able to cross the blood-brain barrier (BBB), since direct injection in the brain is not preferred due to safety concerns, such as risk of infection and the vulnerability of the brain. The blood-brain barrier is the barrier that prevents compounds from the blood circulation to go straight into the brain. The BBB con-

Figure 1: *Schematic depiction of the blood-brain barrier. The upper part of the figure shows the blood vessel and the lower part shows the brain area, the middle part shows the barrier. Route A shows how substances can go through the barrier by using transporters on the cell membrane of the epithelial cells. Route B shows that some very small compounds are able to pass the barrier by passing the tight junctions.*

Figure 2: *Schematic depiction of a bispecific antibody that could be used to treat glioblastoma. The bispecific antibody consist of two regular antibodies attached to each other via a connective molecule. The part responsible for transportation over the BBB is depicted in red, the part that recognises the tumour cells in blue. Shown in black is the connective structure keeping the two antibodies together. The orange sphere represents the toxic agent, responsible for killing the tumour cells.*

sists of three main cellular elements: endothelial cells, astrocyte endfeet and pericytes (figure 1). Tight junctions between the endothelial cells prevent compounds, especially hydrophilic molecules, from entering the brain directly. The basal lamina of the endothelial cells is also important for the BBB, since it forms yet another physical barrier between the blood and the brain [9].

There are, however, mechanisms to make specific compounds able to cross the BBB. For example, the brain needs nutrients such as glucose, iron and amino acids for numerous cellular activities. These nutrients are not able to cross the BBB spontaneously. To facilitate the transportation of these nutrients, specific transporters are present on the cell surface of the cerebral endothelial cells. Whereas small lipophilic compounds, such as O2 and CO2, are able to diffuse freely across the BBB to driven by their concentration gradient [9]. Of course, transportation is not limited to the molecules listed here, as others are indispensable to normal brain functioning as well. Given this restrictive nature of the BBB, it is hard but not impossible to target diseases that are located in the brain with drugs [9].

Bispecific antibody

Bispecific antibodies are artificially made antibodies that are able to specifically bind to two distinct targets. This is possible because of their two different variable antigen-binding sites (Figure 2) [10]. By binding two different targets, it should be possible to make a compound that can bind a receptor on the BBB in order to reach the brain (similar to route A in figure 1). The other binding site of the antibody could, once it has passed the BBB, bind to the tumour cells. Moreover, a specific toxic sphere could be added that kills the tumour cells after the bispecific antibody has reached its target. This technique could be used to develop a drug that is able to specifically target the glioblastoma cells.

Discussion

Patients diagnosed with glioblastoma have a poor prognosis, because the current treatment is unable to successfully target the tumour cells located in the brain. The main problem in treating glioblastomas is the inability of effector molecules to pass the BBB in order to reach the tumour cells. This renders almost all commonly used anticancer drugs useless for treatment of glioblastomas. A medicine mimicking glucose, iron or certain amino acids, could be carried over the BBB using transporters on the cell membrane of the epithelial cells that make up the BBB. Another difficulty when developing an innovative therapy for glioblastoma, is finding a specific molecule to target the tumour cells. EGF receptors and IDH1 could be suitable targets to differentiate between tumour cells and normal cells. A targeted therapy aimed at such molecules can reduce the damage to tissue surrounding the tumour and thereby reduce complications resulting from the treatment.

The ultimate goal is to find a medicine that is able to cross the BBB and selectively tackle the glioblastoma cells at the same time. Bispecific antibodies that specifically recognise both the tumour cells and a receptor that facilitates its transportation over the BBB appear to be promising to achieve this. A cytotoxic agent could be attached to the bispecific antibody, which should only be activated upon tumour cell recognition and binding. Using this approach, it could be possible to cure glioblastoma patients in the future.

Acknowledgements

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FUTURE PERSPECTIVES
PREVENTING ALZHEIMER'S DISEASE WHILE SLEEPING

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ABSTRACT

Short Perspective

BACKGROUND: Alzheimer´s disease is an incurable neurodegenerative disease where the brain is clogged with amyloid beta plaques. Patients have to cope with memory loss and problems with praxis and visual recognition. Two forms of Alzheimer's disease, early onset and late onset, are caused by genetic factors and several risk factors respectively. Since there is no medicine to cure Alzheimer disease, insight into risk factors which can contribute to effective prevention is crucial. It is thought that sleep might play an important role in the development of late onset Alzheimer's. Sleep is regulated by orexin molecules and their receptors. A high number of orexin receptors induces insomnia and disrupts sleep. When sleep is disturbed, the brain is not given enough time to clear the accumulated amyloid beta plaques, leading to increased wakefulness and an increased risk of developing Alzheimer´s disease. Nowadays orexin antagonists are used to treat insomnia and they might therefore also have potential to prevent Alzheimer disease. Studies in which mice were treated with orexin antagonists have shown promising results. Therefore we suggest to design a clinical trial to explore if the use of this medicine has an effect on the sleep-wake cycle leading to a better removal of amyloid beta and thereby decreasing the risk for Alzheimer´s disease.

WHAT'S KNOWN: Studies in mouse models have demonstrated that there is an association between extracellular accumulations of amyloid beta, wakefulness and orexin. The administration of orexin in mice models showed that both wakefulness and amyloid beta levels increased significantly. After the treatment with an orexin receptor antagonist, the amyloid beta deposition decreased. Another recent study showed that infusion of an orexin antagonist led to a decrease in amyloid beta level in the interstitial fluid. It is known that amyloid beta dynamics in mice are comparable to the dynamics in humans. Furthermore, the same relationship between sleep and amyloid beta as seen in mice is present in humans as well.

WHAT'S NEW: Although orexin antagonists are used as a treatment for sleeping disorder, to the best of our knowledge, so far no study has been published investigating the effects of orexin antagonist treatment in humans on the deposition of amyloid beta. Investigation of this effect can be a crucial step forward in the prevention of Alzheimer's disease.

KEY WORDS: sleep, Alzheimer's disease, orexin, amyloid bèta

Introduction

Alzheimer´s disease is an age-related neurodegenerative disease [1]. In the Netherlands, around 250.000 people suffer from this disease [2]. The number of patients is certain to rise in the coming decades because more people reach a higher age. In the beginning patients suffer from progressive memory loss, which later develops into dementia [1]. They have a reduced sense of orientation in space and time, language problems, problems with praxis and with visual recognition [2]. The memory loss is caused by atrophy of the hippocampus. This brain structure is involved in the storage of new information.

Alzheimer´s disease is mainly caused by the emergence of amyloid plaques in the limbic cortex and neocortex, which consist of the protein amyloid beta [3]. According to the amyloid cascade hypothesis, increasing concentrations of plaques in the cortex lead to the magnitude of cognitive decline [3,4]. Another neuroanatomical change of Alzheimer´s disease is the emergence of neurofibrillary tangles in the neocortex and the limbic cortex caused by tau protein [3].

Although different treatments are available to slow down the process of disease, there is currently no medicine for curing Alzheimer´s disease [3].

Besides searching for treatment strategies, scientists are also searching for potential causes of the disease, including personal lifestyle. A recent point of interest is the relation between sleep and the development of Alzheimer's disease. During sleep amyloid beta plaques are thought to be cleared. Therefore people suffering from sleeping disorders might have a reduced clearance of these plaques, resulting in a higher risk of developing Alzheimer's disease. Since insomnia is a common condition, with an estimated prevalence of 14% in the Netherlands [5], this potential cause is worth further exploration. In this article, we will discuss what is currently known about the relationship between sleep and Alzheimer's disease and suggest future research directions.

Pathophysiology

Amyloid beta protein (Aβ) is part of the Amyloid precursor protein (APP) [4]. Normally the APP is cleaved by alpha- and gamma-secretase. In Alzheimer's disease APP is cleaved by beta and gamma-secretase, leading to three cleavage products: sAPPβ, Amyloid β and C99 [2]. Aβ has different isoforms, the most important for Alzheimer´s disease is Aβ-42 [6]. Aβ-42 can aggregate fast to form plaques and is the most toxic one, leading to vascular damage and dementia. Scientists suggest that the formation of Aβ-42 leads to the hyper-phosphorylated form of tau [2]. Normally, tau is a protein that binds to microtubule and stabilizes them. In patients with Alzheimer's disease tau is hyperphosphorylated by kinases. This leads to a collapse of the microtubules and essential metabolites cannot be transported. In a later stadium it causes neuronal loss.

Causes for Alzheimer's disease

Mainly, two forms of Alzheimer's disease exist. Early onset Alzheimer's, which is caused by genetic factors and late onset Alzheimer's, caused by several risk factors. Early onset familial Alzheimer´s disease is associated with mutations in the amyloid precursor protein (APP) [6]. This gene is encoded on chromosome 21 [2]. There could be mutations on the N- or C-terminal of Aβ increasing Aβ and Aβ42 production. Mutations in the Aβ sequence itself affect Aβ aggregation and cause vascular variants of Alzheimer´s disease. There can also be different presenilin mutations, which lead to Alzheimer disease. Presenilin protein is part of the γ-secretase complex. Mutations in presenilin-1 increase the ratio Aβ42/Aβ40 or total amount of Aβ.

Late onset Alzheimer´s disease, also called sporadic form of Alzheimer´s disease, is caused by many non-genetic risk factors. Since there is no effective treatment against Alzheimer's disease yet, prevention is crucial. Mapping of risk factors is therefore important. Several known risk factors are age, alcoholism, atherosclerosis, chronic stress, diabetes, eating disorders, high cholesterol, hypertension, apolipoprotein E4 gene, obesity and smoking [7].

Sleep

One other risk factor that has only been discovered recently is sleep deprivation. Several theories about this relation have been developed. The clearance of Amyloid-beta(Aß) happens during sleep [8]. The sleep-wake cycle has been disrupted in patients with Alzheimer's disease (AD) [9]. The quality and quantity of sleep is observed to be decreased in humans with preclinical evidence of AD. The relationship between sleep and AD is however still poorly understood. It is known that hormones are involved in the initiation and the maintenance of wakefulness. These hormones are orexins. They play an important role in arousal and regulation of sleep [10]. The current theory is that the orexins act as excitatory neurotransmitters [11]. on the orexin receptors found on the orexins neurons. Orexin neurons are specifically found in the hypothalamus. Individuals with a high percentage of orexin receptors are found to suffer from insomnia while individuals with a low percentage of receptors are found to suffer from narcolepsy [12,13]. It is thought that orexins are not directly involved in the development of Alzheimer's disease, but indirectly through the maintenance of wakefulness and the decreased Aß clearance during wakefulness. A study performed in mice where the orexin gene was knocked out showed a decrease in the amount of Aß found in the brain with an increase in sleep time. It was also shown that the rescue of hypocretin neurons in APP/PS1 mice which lacked the neurons, Aß was increased in the brain. According to this research it seems that hypocretins and their effects on sleep modulate the Aß pathology in the brain [14]. Moreover, a study including 298 women without dementia showed that the 105 women with sleeping disorder had an OR 1.85 of developing cognitive impairment or dementia [15].

Although the relationship between sleep and Alzheimer's disease might seem clear, it is more complicated. The relationship is bidirectional [16]. Sleep deprivation can lead to Alzheimer's, but at the same time, Alzheimer's leads to sleeping problems. This relation involves the same mechanism. The deposition of Aβ in the brain causes wakefulness and less sleep. This consequence starts to develop when Aβ plaques accumulate in the hippocampus and the cortex. Increased wakefulness is a heavy burden for patient as well as caregivers, since patients start wandering around during the night [17]. This dangerous consequence of Alzheimer's disease is often a cause of institutionalization.

Future research directions

Nowadays orexin antagonists can be used as a treatment for insomnia. These orexin antagonists might have a potential to prevent Alzheimer´s disease as well. Studies in mouse models have demonstrated that there is an association between extracellular accumulations of Aß, wakefulness, and orexin. Administration of orexin in mice models showed that both wakefulness and Aß levels increased significantly [15]. After treatment with an orexin receptor antagonist, the Aß deposition decreased. To the best of our knowledge, so far no study has been published investigating the effects of orexin treatment in humans on the deposition of Aß. It is known that Aß dynamics in mice are comparable to the dynamics in humans. Prospective studies show the same relationship in humans between sleep and Aß as seen in mice. If it is proven that the orexin antagonist could improve sleep quality and also reduce Aß concentrations in patients, it will be possible to provide preventive care for people with high risk for Alzheimer's disease.

A possible approach to investigate the effect of Suvorexant (an orexin antagonist) on amyloid bèta levels in cerebrospinal fluid is to design a clinical trial including patients with insomnia (figure 1). Participants will be asked to stay in a sleeping centre for three nights. All participants are randomly split into two groups. One group will receive Suvorexant. The control group will receive a placebo. Treatment will be given before the third night. The two groups will be compared with regard to the Aß concentration in cerebrospinal fluid. Possible secondary outcome measures are: orexin concentration, tau protein concentration, sleep quality.

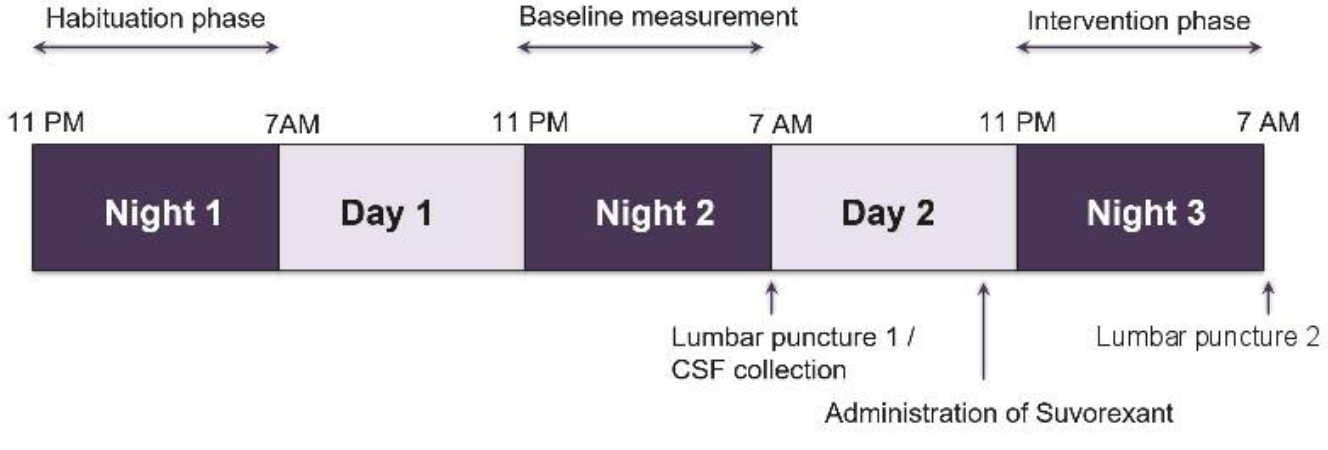

Figure 1: *Workplan of the clinical trial including patients with insomnia. CSF = Cerebrospinal fluid.*

Discussion and conclusion

The main cause of Alzheimer's disease is the presence of plaques of the amyloid beta protein. Aggregation of this protein leads to hyperphosphorylation of the tau protein which ultimately leads to neuronal loss causing Alzheimer's symptoms. Sleep deprivation is a recently discovered risk factor, leading to an increase of Aβ concentration and accumulation. In turn, Alzheimer's disease causes sleeping problems as well. This bidirectional relationship indicates the importance of sleep for the prevention of Alzheimer's disease. Treatment with Suvorexant might proof to be usable in the prevention and/or curation of Alzheimer's disease. If Suvorexant can improve sleep quality and thus also improve the clearance of Aβ during sleep, Suvorexant can be used as a prevention therapy. It might also be worthwhile investigating the effects of suvorexant on patients with Alzheimer's disease or even other forms of dementia. If sleep quality improves in patients with AD and Aβ aggregates diminish, Suvorexant might be used for curing patients with AD as well. When these studies show positive results, large trials can help the clinicians decide on whether to implement these treatments or not.

It should, however, first be proven that a lack of sleep does in fact greatly increase the chance of Alzheimer's disease. It might be possible that the observed relationship is actually pointing in the wrong direction. Patients with sleeping disorders might have a preclinical stage of Alzheimer's disease. That would mean the disease is causing sleeping problems, instead of the other way around. This doubt can be taken away by following people who sleep irregularly or hardly sleep at all due to their occupation (instead of sleeping disorders). If they show an increased risk of developing Alzheimer's disease, the existence of the relationship becomes highly likely.

It is definitely worthwhile exploring the relationship between sleep and Alzheimer's disease in order to be able to prevent or even contribute to curing this devastating disease.

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NOVELTIES IN NEUROLOGY AND NEUROSURGERY

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Editorial

Did you know that the first human head transplantation is scheduled for the near future?

This remarkable event is planned to take place in December this year and will be the first human head transplant in history [1]. The operation will be performed by the Italian neuroscientist Dr. Sergio Canavero on a Russian volunteer who suffers from Werdnig-Hoffmann Disease; a rare and often fatal genetic disorder that breaks down muscles and destroys motoric nerve cells in the brain and spinal cord. If his head is grafted onto a new body and the spinal cords fused, the owner of the head might enjoy the functional use of the body. However, these plans have already caused huge controversy in the scientific world. Besides the ethical debates [2], the scientific data to support Canavero's claims has also been widely criticised. Almost all head transplants on animals have had limited success to say the least, resulting in inability to move and certain death within a week after the operation. Canavero's response was that the transplant- which requires at least 80 surgeons and costs 10 million dollars- would still be possible with the recent development of fusogens to help refuse the spinal cord within weeks [3]. If so, this could be a massive breakthrough in science and medicine wherein the success of the operation will lead to infinite possibilities. Whatever the outcome may be, this will be an exciting Christmas!

Did you know that the U.S. presidential candidate Ben Carson was the first to successfully separate conjoined twins?

Ben Carson, one of the Republican nominees in the 2016 presidential election in the United States and also a very talented neurosurgeon, was the first to successfully separate conjoined twins who were attached at the back of the head (occipital craniopagus twins). In 1987, in a 22-hour-long operation, he led a surgical team of 70 people to complete this groundbreaking procedure. For this operation to succeed, Carson used a radical approach during which the twins' body temperatures were lowered to the point of circulatory arrest. Carson also optimized hemispherectomy, in which half of the brain is removed to prevent seizures in people with severe epilepsy. At the moment, Dr. Carson is the U.S. Secretary of Housing and Urban Development in the Trump administration [4].

Did you know that when you're training your hand for a certain task, your foot is simultaneously being trained for the same task?

Johns Hopkins researchers have discovered that training tasks with your hand also stimulates the areas of the motor cortex that control your foot. This so called motor learning is therefore transferred from one part of the body to another by the cerebellum, which means that practicing a newly learned task involving the hand can also improve a person's ability to perform the same task with the foot and vice versa. Thanks to the brain stimulation technique named 'Cerebellar inhibition', which shows how connections in the brain alter when people learn new motor skills, this study gives new insight into the cerebellum's role in the learning process to accurately coordinate and time movements. Hopefully, in the future, this newly gained knowledge can be used for the rehabilitation of patients who have lost functions in certain parts of their body [5].

Did you know that the new manual EEG device can detect brain bleeding after an injury faster and cheaper than a CT-scan?

In September 2016, the FDA approved a hand-held EEG device that can quickly and with 97% accuracy rule out brain bleeding in a person with an injury to the head. This clinical trial was conducted in 11 hospitals by researchers from the John Hopkins School of Medicine who discovered that the device did not cause any type of sensation or risk in contrast to the radiation exposure of a CT-scan. Most of the patients with suspected head injury receive a CT-scan which costs about $1,200 per scan in the United States and approximately 130,- in the Netherlands [6]. Although the exact costs have not yet been determined by Brainscope, the manufacturer of the instrument, the company states it will be a mere fraction of the CT-scan costs and that it will be significantly faster [7].

Did you know that the brain center of creativity may be situated in the cerebellum?

In a revolutionary discovery, new research from Stanford University reports that the cerebellum may be the seat of creativity in the brain. Traditionally, the cerebellum is only viewed as the centre of muscle movement and coordination, which means this could be a great turning point in Neuroscience research putting the cerebellum in the spotlight. In the predominant 'left-brain-right-brain model', creativity is believed to be in the right hemisphere. However, the Stanford study shows that activation of the brain's executive-control centres in the cerebrum actually impairs creative task performance. In other words: the more you think about it, the more you mess it up. Interestingly, high creativity scores were associated with lower activity in the left hemisphere combined with higher activation in the cerebellum, but not necessarily in the right hemisphere. According to the senior author Allan Reiss MD, professor of radiology and of psychiatry and behavioral sciences, it is likely that the cerebellum is the coordination centre of the brain, allowing other regions to be more efficient as well. Since the cerebellum holds 50% of the brain's total neurons even though it is just 10% of the total brain volume, the results could suggest that the functions that are executed by the cerebellum may be underestimated [8].

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CLINICAL ANATOMY AND EMBRYOLOGY OF VAN BUCHEM DISEASE AND SCLEROSTEOSIS: A REVIEW OF THE LITERATURE

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Review

ABSTRACT

BACKGROUND: Van Buchem Disease (VBD) is a rare condition present in parts of the Netherlands in which consanguineous marriage was common and causes sclerosing bone dysplasia. Its significantly worse equivalent, Sclerosteosis, is present in Afrikaners from Dutch descent and can be found mainly in South Africa. Both diseases, characterized by excessive formation of bone, have appalling consequences caused by the entrapment of nerves and blood vessels that pass through the foramina of the skull base.
OBJECTIVE: The aim of this study is to present an overview of the pathophysiology of VBD and to review the complicated embryology of the skull base and the four most involved cranial nerves: the trigeminal, facial, vestibulocochlear and vagal nerve.
METHODS: An extensive literature search on VBD and Sclerosteosis was conducted using various databases, including PubMed, Medline, EMBASE and the Cochrane Library. To create insights in the anatomy of the orofacial region, a mini-review was conducted.
RESULTS: VBD is recognized by neurological symptoms caused by compression of different cranial nerves (V, VII, VIII and X), high bone mineral density, craniofacial anomalies and increased intracranial pressure all caused by excessive growth of bone, so-called osteosclerosis. Sclerosteosis can be recognized by the aforementioned symptoms accompanied by syndactyly or other digital malformations. Both disorders are caused by a lacking regulatory element of the SOST-gene resulting in a deficit in the production of slerostin-protein.
CONCLUSION: VBD shows to be a disease with a fascinating pathophysiology. The symptoms from compression of the cranial nerves are a great vehicle to review the intricate embryology of the cranial base.

WHAT'S KNOWN: Rare bone deformation disorders, such as Van Buchem Disease (VBD), can provide insights in bone cell processes that may be involved in common diseases such as osteoporosis. Complex symptomatology in VBD can be explained using anatomical and embryological knowledge.

WHAT'S NEW: A comprehensive overview, ranging from embryological development and anatomical relations of involved structures to clinical features, is presented.

KEYWORDS: anatomy, cranial nerve, osteosclerosis, SOST-gene, Van Buchem Disease

Introduction

Urk used to be a small isle in the Zuiderzee, isolated from the rest of The Netherlands. For this reason, centuries have passed in which consanguineous marriages were frequent. The genome of this population contains different defects and the chance of genetic disorders has increased over the years. One of the typical disorders that only exist on Urk is Van Buchem Disease (VBD). VBD is a sclerosing bone dysplasia, first described in 1955 by Van Buchem and colleagues as hyperostosis corticalis generalisata familiaris [1]. In 1968, Fosmoe et al. introduced the eponym Van Buchem Disease for the first time [2]. When suffering from VBD, patients can endure a wide range of neurological symptoms including deafness, blindness and a form of peripheral facial paralysis (Bell's palsy) [3]. Sclerosteosis, a significantly worse type of VBD, has been mainly diagnosed among Afrikaners of Dutch descent, mainly habitants of South Africa [4].

Skeletal manifestations of VBD and Sclerosteosis are the result of endosteal hyperostosis and are characterized by progressive generalized osteosclerosis. The clinical result is enlargement of the jaw and facial bones leading to facial distortion, increased intracranial pressure and entrapment of cranial nerves, mainly CN V, VII, VIII and X. This phenotype is more severe in patients diagnosed with Sclerosteosis, compared to patients with VBD [5].

In this paper an overview of the pathophysiology of VBD and a review of the complicated embryology and anatomy of the skull base and CN V, VII, VIII and X is presented.

Material and Methods

A literature search on VBD and Sclerosteosis was conducted using PubMed, Medline, EMBASE and the Cochrane Library. The search strategy contained the following key words: Van Buchem Disease; Sclerosteosis; Osteochondrodysplasias; Sclerosing bone dysplasia. To enrich the results, Medical Subject Headings were incorporated within the search. Additional articles were included by cross-referencing.

With regard to the anatomy and embryology of the base of the skull or the cranial nerves in the oro-cervico-facial region, a mini-review was performed using various databases, including PubMed, Medline, EMBASE and the Cochrane Library and textbooks such as anatomical atlases.

Results

Embryological development of the base of the skull

The cranial base forms an important skeletal structure that provides protection and support of the brain [6]. Proper development of the base of the skull is paramount in the unimpeded passage of nerves and blood vessels through the skull base foramina. The development of the cranial base is regulated by several genes, including the Indian hedgehog-, Sonic hedgehog- (Shh-), Matrix metallopeptidase 9-genes and genes from the Dickkopf family [7-11].

The aforementioned genes and their appurtenant pathways among others, contribute to endochondral ossification of the skull base, which is a highly precise orchestration of cellular and molecular events [12-14]. Early in human development, the cranial base appears to be a sheet of undifferentiated mesenchymal cells. Endochondral bone formation starts with the formation of a cartilage template from condensed mesenchymal cells within this sheet. Chondrocytes in the center of the cartilage template undergo hypertrophic changes and subsequently undergo apoptosis. The vacant spaces within the cartilage template, called the primary ossification centers, undergo invasion of osteoblasts.

Both the cranial base and the long bones undergo this proces of endochondral ossification. However, in comparison to the chondrogenesis of the axial skeleton, the skull base develops cartilage in a later stadium. The postponed chondrogenesis of the skull base seems to be due to its insensitivity to Shh signaling [11]. The mesenchymal sheet forms the chondrocranium after condensation, chondrification and fusion of numerous individual cartilages [15].

The cranial base contains multiple growth centers to drive cranial and upper facial development. The growth centers of the prechondral, hypophyseal and parachondral cartilaginous plates form the central region of the cranial base [16]. These plates shape an uninterrupted cartillaginous structure spanning from the foramen magnum to the interorbital region. As development advances, ossification centers outline the ethmoidalFb; prespheoid; basisphenoid; and occipital bones [12,16]. Because development of cartilage through mesenchymal condensation occurs after the formation of organs, nerves and blood vessels, foramina develop on their specific locations [17].

Anatomy of the trigeminal nerve (CN V)

The trigeminal nerve forms the sensory supply of the orofacial region and provides motor innervation of the mastication muscles. From the peripheral orofacial region, multiple branches of the trigeminal nerve can be recognized. All these branches can be categorized into the three main branches of the trigeminal nerve that course towards the trigeminal ganglion: n. V1, V2 and V3, the ophthalmic, maxillary and mandibular nerve, respectively. The ophthalmic nerve has three peripheral branches, the lacrimal, frontal and nasociliar nerve. It courses through the superior orbital fissure after which it sprouts of the meningeal recurrent nerve. The sensory root of the pterygopalatine ganglion and the zygomatic and infraorbital nerves are the terminal nerves of the maxillary nerve. The zygomatic and the infraorbital nerve exit the orbital cavity via the inferior orbital fissure. The aforementioned three maxillary nerves fuse within the pterygopalatine fossa after they passed through the foramen rotundum. The mandibular nerve consist of four terminal branches: the lingual-, inferior alveolar-, auriculotemporal- and masticator nerves. The mandibular nerve emerges from the lateral part from the trigeminal ganglion, exits the cranial cavity through the foramen ovale and immediately passes between the tensor veli palatine muscle (medial border) and the lateral pterygoid muscle (lateral border). After exiting the skull, the meningeal branch and the medial pterygoid nerve are given off. The nerve then divides into two parts: a small anterior and large posterior trunk. The anterior division innvervates the mastication muscles, whereas the buccal nerve provides sensory to the cheek. From the posterior division three main sensory branches sprout, the auriculotemporal, lingual and inferior alveolar nerves. Furthermore, the motor fibers of the mandibular nerve supply the mylohyoid muscle and the anterior belly of the digastric muscle [18-23].

From the trigeminal ganglion, a motor and sensory rootlet course towards the lateral part of the pons where they enter the brainstem. The trigeminal tract runs in a dorsomedial direction, penetrates the middle cerebellar peduncle and then spreads over the central trigeminal nuclei 1) the mesencephalic nucleus; 2) the principal sensory nucleus; 3) the motor nucleus and; 4) the spinal trigeminal nucleus [24]. The mesencephalic nucleus is responsible for adjusting the bite by conveying proprioceptive fibers from the masticatory muscles, teeth, periodontium, hard palate and the temporomandibular joint. It also plays a prominent role in the function of the extraocular muscles [25]. The principal sensory nucleus is arranged in a dorsoventral organization; the mandibular division terminates most dorsal, the maxillary division intermediate and the ophthalmic division ventral. The principal sensory nucleus conduct both vital and gnostic sensory information of the orfacial region. The fibers of this principal sensory nucleus are both crossed and uncrossed and end in the ventral posteromedial nucleus of the thalamus. The trigeminothalamic tract is formed by the crossed fibers that originate from the ventral part of the principal sensory nucleus which ascend together with the controlateral medial lemniscus. The uncrossed fibers, originating from the dorsomedial part of the nucleus, ascend near the periaquaductal gray. The motor nucleus is located more medial from the principal sensory nucleus. Axons of the mesencephalic nucleus form a reflex arc in the modulation of the force of the bite together with the motor nucleus. The spinal trigeminal nucleus transmits pain and temperature. It extends from the midpons to the level of C2-C4 of the spinal cord and is located anterolateral to the fourth ventricle. It consists of three parts: an oral, interpolar and caudal part. The oral part receives sensory information of structures inside the nose and mouth. The interpolar part is related to the skin of the orofacial region whereas the caudal part represents the sensory information of the forehead, cheek and jaw [24].

Anatomy of the facial nerve (CN VII)

The course of the facial nerve can be subdivided into the intracranial segment, the segment in the facial canal and the extracranial segment where it pierces the parotid gland. In the cerebellopontine angle, in the caudal part of the tegmentum of the pons, the motor part of the facial nerve originates between the oliva and pons. Together with the vestibulocochlear nerve, the facial nerve runs through the internal acoustic pore. The facial nerve then courses through the petrous part of the temporal bone (pyramid) via the internal auditory meatus and canal into the facial canal. In this canal the nerve gives off the nerve to the stapedius. The motor part of the facial nerve runs through the stylomastoid foramen, posterior to the temporal styloid process, and forms an intraparotid plexus. Its peripheral motor branches, the temporal, zygomatic, buccal, marginal mandibular and cervical branch, can be found at the anterior edge of the parotid gland. Small communicating branches between other nerves and intercommunicating branches are discussed by others previously21. The facial nerve, however, does also contain visceromotor and parasympathic fibres. The parasympathic fibres, responsible for the correct action of the salvitory glands, run in the chorda tympani nerve. This nerve also provides taste in the anterior two-thirds of the tongue. When the fibers exit the glands and tongue they converge and run along

the lingual nerve (n. V3). This peripheral part runs towards the chorda tympani nerve and joins the facial nerve deep in the pyramid [21, 26-29].

Anatomy of the vestibulocochlear nerve (CN VIII)

The eighth cranial nerve consists of two different parts: a cochlear and vestibular part. The cochlear nerve originates as the organ of Corti (spiral organ) on the basal membrane of the cochlear membrane and sensors the orientation of the head in relation to the body. The axons of the cochlear nerve in the spiral organ are grouped together on the cochlea. The neuronal fibres of the peripheral neurons are connected to the cilia cells on the spiral lamina. The vestibular nerve arises from the junction of the superior and inferior vestibular nerves in the vestibular ganglion and has a sensor function in the balance and . Together with the cochlear nerve it runs through the temporal bone in the internal auditory canal and enters the cranial fossa through the internal acoustic pore [25-27]. The cochlear nerve lies posterolaterally to the vestibular nerve and together with the facial nerve it fills up the internal auditory canal [27]. The vestibulocochlear nerve crosses the cerebellopontine angle in the sagittal plane and enters the brainstem near the flocculus of the cerebellum in the cerebellopontine angle. The ampullary fibres join the superior (Bechterew nucleus), lateral (Deiters nucleus), medial (triangular) and inferior nuclei, which together form the four vestibular nuclei and can be found in the brainstems' rhomboid fossa. The saccular fibres terminate in the inferior vestibular nucleus and the utricle fibres end in the inferior and medial nuclei [30,31].

Anatomy of the vagal nerve (CN X)

The nucleus of the vagus nerve is shared with the glossopharyngeal nerve because they share sensory and motor function. Together with the accessory nerve and the glossopharyngeus nerve, the vagus nerve courses through the jugular foramen [25]. After exiting the skull, the vagus nerve has an extensive course through the human body, which is not considered to be within the scope of this review.

Pathogenesis of VBD and sclerosteosis

In order to understand the several clinical features of VBD, it is essential to comprehend that the compression of the cranial nerves, caused by the excessive formation of bone, is the common origin of the different symptoms. VBD as well as Sclerosteosis is caused by the lack of a regulatory element of the SOST gene (17q12-21), which encodes for sclerostin,

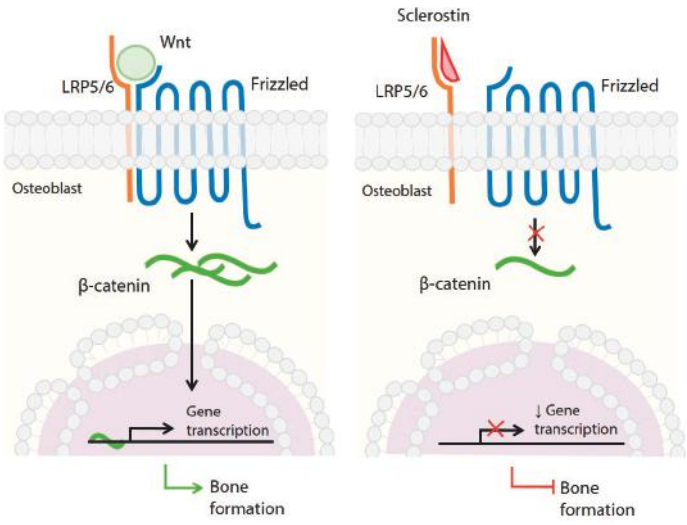

Figure 2: *Schematic model of antagonized canonical Wnt signaling. Canonical Wnt signaling involves formation of complexes of Wnts with Frizzled receptors and LRP5/6 co-receptors, resulting in the accumulation of β-catenin in the cytoplasm and translocation into the nucleus. The antagonist sclerostin inhibits canonical Wnt signaling by binding to probably the first β-propeller of LRP5/6. Whether sclerostin requires a cofactor like Kremen for Dkk1 to exert its antagonistic effect remains to be established.*

an osteocyte-derived protein that inhibits the formation of bone. In VBD a 52 kilobytes deletion can be found, 35kb downstream of the SOST-gene [32,33]. In Sclerosteosis, multiple SOST mutations have been reported thus far: three distinct stop mutations in families of Afrikaner, Brazilian, and mixed descent (northern European/Native American/African American) [34,35], a splicing mutation in an individual of African heritage from Senegal, and a missense mutation in siblings of Turkish stock [36].

SOST mRNA is expressed in many tissues during the embryonic development. Most postnatal tissues on the other hand, do not show these amounts of the sclerostin-protein. Terminally differentiated cells embed-

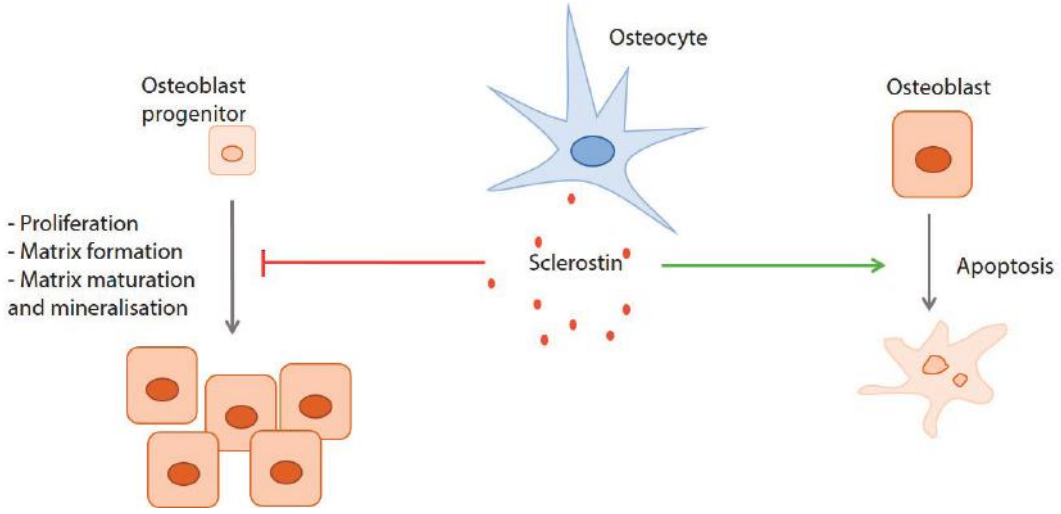

Figure 1: *Schematic model of the regulation of sclerostin on osteoblast development and survival. Sclerostin produced and secreted by osteocytes inhibits the formation of bone by inhibiting osteoblast proliferation and early and late differentiation and stimulating osteoblast apoptosis.*

ded within a mineralized matrix like osteocytes, mineralized hyperthrofic chondrocytes and cementocytes do express the SOST-mRNA in the postnatal situation. Osteoclasts, osteoblasts and bone lining cells on the other hand cannot produce sclerostin after birth [37]. The function of sclerostin mainly consists of an inhibitory effect on formation of bone for it decreases the life span of the osteoblasts by stimulating their apoptosis [38]. In knockout mice, formation of bone seemed to be increased. The skeleton of these mice showed a significant increase in radio density, bone mineral density and cortical and trabecular bone volume, bone formation and bone strength [39]. Molecular studies discuss the molecular pathway of sclerostin (Figure 1) as a member of the so-called DAN (differential screening-selected gene aberrant in neuroblastoma) family of glycoproteins. These glycoproteins can be subdivided into two different categories, the BMP-antagonists and Wnt-antagonists respectively. LRP5, a cofactor in canonical Wnt signalling, seems to be of great importance in the formation of bone. Sclerostin has been shown to bind LRP5 and the closely related co-receptor LRP6 to antagonize Wnt-signaling, which shows that sclerostin is a member of the Wnt-antagonists. Stimulation of the G-receptors via the Wnt-pathway causes β-catenin, an intracellular signalling molecule, to accumulate and translocate into the nucleus of the cell where it initiates transcription of target genes and increases bone formation. However, as sclerostin is a Wnt-antagnost, stimulation of the G-receptors by sclerostin causes proteosomal degradation of β-catenin, resulting in bone resorption and decreased bone formation. In order to understand the pathogenesis of VBD, it is necessary to understand when sclerostin is not available. When sclerostin is not available, β-catenin will not undergo proteosomal degradation by formation of an intracellular complex of proteins, which indicates that the "off-switch" of bone formation is not present. A part of this cascade is depicted in Figure 2 [37].

Clinical appearances of VBD and sclerosteosis

Clinical features of VBD include craniofacial abnormalities such as a high forehead, frontal bossing and a widened and thickened chin, as is depicted in Figure 3. Interestingly, VBD may be differentiated from other forms of widespread bony sclerosis such as osteopetrosis (Albers-Schonberg's disease), myelosclerosis and progressive diaphyseal dysplasia (Camurati Engelmann disease) because it causes cortical bone thickening along the shafts of long bones, clavicles, ribs and to a major degree of the skull bones and mandible. The pelvis and metaphyses show less marked changes however [40,41]. Radiological findings were increased thickness and hyperostosis of the calvaria, base of the skull and the mandible. Also, thickening of the cortex of the metacarpal bones and the phalanges is

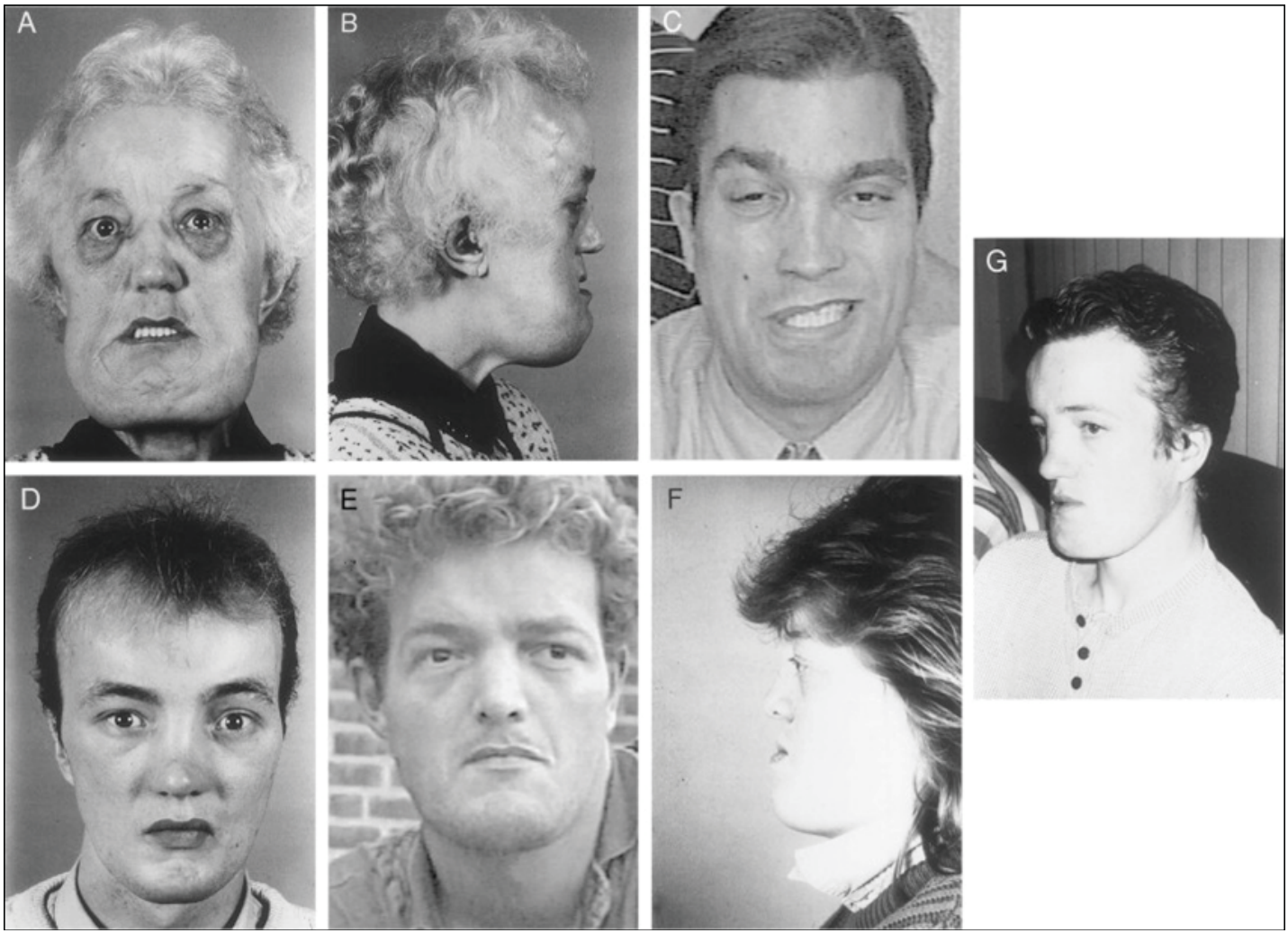

Figure 3: *Reproduced from Van Hul et al. [5]. Clinical pictures of seven patients showing characteristic features of van Buchem disease. Frontal (A) and lateral (B) views of patient 3. This patient, at age 65 years, was the oldest patient studied. C–G, Pictures of the five new van Buchem patients (patients 1, 2, and 9–11, respectively). All patients showed the characteristic features of protruding chin, high forehead, and facial nerve paralysis, as illustrated in panel C.*

seen, albeit the epiphyses are typically spared. Different neurological problems such as a Bell's palsy, sensorineural-, conductive- and mixed hearing loss are mentioned [2,3,40]. The neurological symtoms and craniofacial abnormalities seem to start at the adolescent age and become more prominent throughout life. Exceptional paediatric cases have been described as well [42]. Surgical treatment for both decompression of cranial nerves and re-contouring of the mandible has been reported with satisfactory results, although treatment must be repeated multiple times [43]. Currently, antibodies against cathepsin K and SOST and ClCN7 inhibitors are being developed by several pharmaceutical companies [44].

Clinical features of Sclerosteosis are alike of those of VBD. Again gross sclerosis and hyperostosis of the skull can be observed, including faciesmandibular overgrowth and asymmetry. Characteristic for Sclerosteosis is proptosis, typical hyperosteosis of the pelvis, syndactyly and other digital malformations. Facial palsy, deafness, blindness and increased intracranial pressure are common complications [45].

Discussion

Although VBD is an extremely rare disorder, much is known about its pathofysiological pathways and genetic backgrounds. This discrepancy in uncommonness of the disease and the amount of knowledge seems striking but can be easily explained by the fact that VBD is one of many sclerosing bone disorders. The plurality of sclerosing bone disorders makes this a diagnostic challenge. Main disorders that can induce high bone mass in adults can be categorized as 1) acquired; 2) iatrogenic; and 3) genetic. The acquired disorders consist of sclerosing metastasis (i.e. neoplasms from prostate or breast), myeloma, myelofibrosis, secondary hyperparathyroidism or secondary to hepatic infection (i.e. hepatitis C). The iatrogenic disorders can be caused by a surplus of bisphosponates or fluor. A wide variety of genetic disorders exist. Genetic disorders that cause endosteal hyperostosis include VBD, Worth Syndrome and Sclerosteosis [44,46]. These rare hereditary sclerosing bone disorders have shed light on multiple physiological pathways of bone cell metabolisms. The newly discovered genes and the pathways that come forth from this are new targets for pharmacological treatment not only of extremely rare disorders, but also of more common disorders such as postmenopausal osteoporosis. For example, the aforementioned antibodies against cathepsin K and SOST and ClCN7 inhibitors that were developed by several pharmaceutical companies [44]. Still, many factors of VBD and Sclerosteosis remain largely elusive. For example, as paediatric cases are exceptional, it remains unclear why the foramina start to be subject to excessive bone formation later in life, rather than in childhood age. Further research on these topics can provide insight in the activity of bone cell metabolisms through life, enriching the knowledge about mechanisms involved in bone formation disorders.

Immense embryological questions, however, remain unanswered. For example, what prevents the foramina from being obstructed by new bone formation? To gain insights in the embryology of nerves and bony landmarks, classical embryological studies must be critically reviewed. However, studies that investigate the neuroanatomy and -embryology by staining and microscopic research of the cranial nerves and related neuronal migration remain of great importance. For example, a more recent published report discussed neural migration of the cranial nerves in the embryological development and provided new insights in the morphological features of cranial nerves [47].

Another project that sheds new light on embryological questions, is the 3D-project performed at the AMC in Amsterdam, which provides 3D-models of different embryological structures [48,49]. These new articles and projects herald the start of a new era in embryological research.

Conclusion

VBD and Sclerosteosis have proven to be diseases with a fascinating pathophysiological pathways that can provide many insights in normal bone cell metabolisms. These insights may contribute in better understanding and treating other, more common bone diseases such as osteoporosis. Furthermore, the symptoms of compression of the cranial nerves are a great vehicle to review the intricate embryological development of the cranial base and the cranial nerves.

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A FUNCTIONAL TREATMENT FOR A NON-FUNCTIONING ADENOMA

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Introduction

Editorial

Here is a riddle for you: it is a regulator of many physiological processes; it determines growth, temperature, blood pressure; it dictates whether you feel stressed or sleepy, or if you need to pee; it decides if you become fat or not, by controlling your energy metabolism. Have you guessed it yet? It is situated in the brain, the size of a pea and has no real autonomy, but is merely an executant, subject to higher control mechanisms. Yet, complications can arise with the dysfunctioning or absence of this tiny gland. The pituitary gland, sometimes also known as the hypophysis, is with its function of an endocrine gland, responsible for the production and secretion of hormones that influences other endocrine organs and many processes in your body.

The pituitary gland, situated in a small bone cavity called sella turcica outside the blood-brain-barrier, is broadly distinguishable into two lobes that have a different embryological origin. The anterior pituitary or adenohypophysis, formed from Rathke's pouch. The second lobe is the posterior pituitary, also called the neurohypophysis, which is neural tissue outgrowth from the hypothalamus (see figure 1). The different origins of the pituitary gland are still visible today, both anatomically and functionally. The anterior pituitary consists of endocrine cells that are also able to produce hormones. The posterior pituitary is continuous with the hypothalamus and consists of nerve endings in which hormones that are produced by the hypothalamus are stored. This means that the neurohypophysis is directly and anatomically connected to the hypothalamus, but the adenohypophysis is not. Still, the adenohypophysis receives input and is thus regulated by the hypothalamus. Neurons in the hypothalamus secrete neurohormones, like somatostatin, that reach the anterior pituitary via the hypophyseal portal vessels and stimulate or inhibit hormone production and secretion [1-3].

The anterior pituitary

The adenohypophysis takes up approximately two thirds of the pituitary gland and can produce and secrete a wide range of hormones with diverse functions. One of the six most important hormones that is produced and secreted by the anterior pituitary is the growth hormone (GH), also known as somatotropin. About 50% of the cells in the adenohypophysis are somatotrophs and synthesise this hormone. GH exerts its influence all over the body and is the only major anterior pituitary hormone that does not stimulate target glands. Instead, it stimulates protein synthesis and overall growth of cells in virtually all tissues by promoting an increase in cell size and mitosis. GH release is controlled by growth hormone releasing hormone and growth hormone inhibitory hormone (somatostatin), released by the hypothalamus. The effects are not immediate; it can take months for GH to become effective. About 15-20% of other cells that occupy the adenohypophysis are corticotropes. Upon stimulation by hormones from the hypothalamus, these cells produce and secrete adrenocorticotropic hormone (ACTH, also called corticotropin). This hormone stimulates the adrenal cortex to produce glucocorticoids, like cortisol, and androgens, which have regulative functions for the metabolism of proteins, carbohydrates and fats. Another 10-25% of the cells in the adenohypophysis are lactotropes, synthesising prolactin. The release of prolactin is inhibited by prolactin-inhibiting hormone, more commonly known as dopamine. Its best known function is influencing the mammary glands to stimulate milk production and secretion. Gonadotropes produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and occupy about 10-15% of the anterior pituitary. LH and FSH are important for controlling gamete and sex hormone production. They stimulate, amongst others, testosterone production and ovulation, and they regulate spermatogenesis. The release of LH and FSH is promoted by gonadotropin-releasing hormone from the hypothalamus. Finally, thyrotropin-releasing hormone from the hypothalamus stimulates the release of thyroid-stimulating hormone (TSH) by thyrotrope cells. TSH stimulates the synthesis and secretion of hormones produced by the thyroid gland, namely T3 and T4, which in turn affect the body metabolic rate. Thyrotropes fill 3-5% of the adenohypophysis [1-3].

The posterior pituitary

Contrary to the adenohypophysis, the neurohypophysis does not produce hormones, but secretes them. Two known hormones are vasopressin, also known as antidiuretic hormone (ADH), and oxytocin. The nerve endings in the posterior lobe originate in certain nuclei of the hypothalamus, from which the hormones are transported to the pituitary gland. It may take several days before hormones produced in the cell bodies of the nuclei finally reach the posterior pituitary. Vasopressin is primarily synthesised in the supraoptic nuclei and serves to maintain blood osmolality and blood pressure. A slight increase in osmolality causes rapid secretion of vasopressin into the circulation, where it directly affects the re-

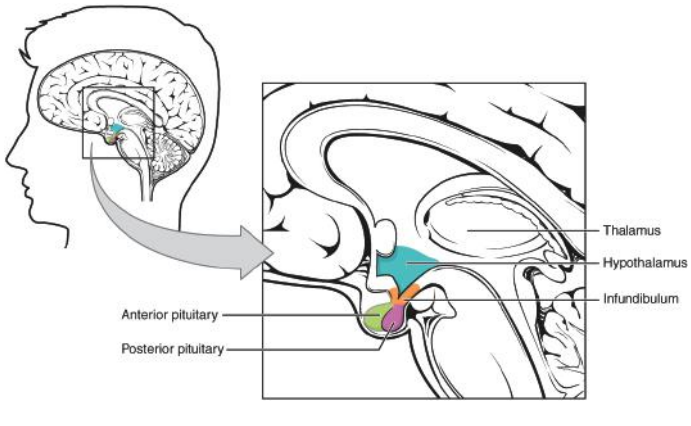

Figure 1: *Anatomy of pituary gland. OpenStax College. Anatomy & Physiology, Connexions Web site. Jun 19, 2013. http://cnx.org/content/col11496/1.6/*

absorption of water in the kidneys, more accurately, the collecting duct. There, vasopressin increases the permeability of the renal cell membranes by mobilising aquaporins: water permeable pores. This prompts the retention of water and decreases osmolality. The other function of vasopressin, maintaining blood pressure, works via the same mechanism, but is initiated by low blood pressure or blood volume. Furthermore, higher concentrations of vasopressin can induce vasoconstriction to increase blood pressure. Oxytocin is primarily produced in the paraventricular nuclei and is often called the "cuddle" or "love" hormone for its importance in social and emotional bonding between beings, and finding trust and intimacy. Moreover, this hormone is important for lactation in breastfeeding women and can induce contraction of the uterine muscles during labour. Oxytocin can be administered with the purpose of inducing labour in pregnant women [1-3].

Relevance of the pituitary gland

Both lobes serve the crucial function of secreting hormones and receive input from the hypothalamus, giving the pituitary gland barely any autonomy. Does this make the pituitary gland redundant? Can its functions not just be taken over by the hypothalamus? Are the extra steps with the stimulatory or inhibitory 'messenger' hormones needless and just causing another possibility for complications? The answer is simple: no. The role of the pituitary gland as described above is not as clear-cut and straightforward as may have been depicted; it involves many complicated pathways and processes. Although this gland is an intermediate between the hypothalamus and peripheral organs and its hormone secretion is mainly regulated by the hypothalamus, the latter is not the sole dictator of pituitary outputs. Research has shown that the regulation of the pituitary gland's function is also dependent on local interactions between pituitary cells. In the adenohypophysis, cells of the same cell type that produce the same hormones are called cell clusters. Cellular communication between the cells in the same cell clusters is important for the simultaneous activation of these cells. Upon activation of one of the cells in the cluster, second messengers can travel to the other cells via i.a. gap junctions. This way, cells in the same cluster are connected to each other, so that hypothalamic hormones can activate all cells in these clusters at once. Also communication between pituitary cells that secrete different hormones is important. This can be managed through soluble factors. Thus, the pituitary gland also regulates its own function and is not only controlled by the hypothalamus [4].

Pituitary adenomas

All these complicated processes can be disturbed, leading to a variation of diseases. One of these is a pituitary gland adenoma, which can either be a 'functioning' tumour, which secretes pituitary hormones, or a non-functioning tumour, which does not produce pituitary hormones. Functioning tumours secrete hormones like ACTH, GH, prolactin or TSH. This can result in disorders like Cushing's disease, gigantism, hyperprolactinemia or hyperthyroidism. Here, we will focus on the non-functioning pituitary adenomas (NFPAs) and their development, symptoms and possible treatments.

Pathogenesis

Most pituitary adenomas, especially NFPAs, are sporadic and often detected by accident. Usually, tumours evolve due to the manifestation of oncogenes like RAS and the inactivation of tumour suppressor genes such as P53, but in the development of a pituitary adenoma mutations in such genes rarely play a role. Although some genes that give an individual a predisposition to pituitary neoplasms have been identified, like GNAS and MEN1, they are mostly not involved in the pathogenesis of sporadic pituitary tumours [5]. Pituitary adenomas are often monoclonal in origin, meaning that all tumour cells are derived from a single, abnormal pituitary cell. The gene expression can be altered by epigenetic modifications, and it has been shown that this is frequently the cause for a different expression of genes in pituitary adenomas. One of the genes that is often epigenetically modified in both functioning tumours and NFPAs is the pituitary tumour transforming gene (PTTG), which is usually highly expressed in pituitary tumour cells. PTTG acts as a controller of the separation of sister chromatids during metaphase and is a proto-oncogene that facilitates cell cycle progression [6]. Because PTTG inhibits the separation of the sister chromatids by inhibiting the activity of separase in anaphase, they are pulled to the same pole. This results in aneuploid daughter cells and chromosomal instability [7]. All in all, the pathogenesis of pituitary adenomas is complicated and not completely understood.

Treatments

There are a couple of options to treat NFPAs, like surgical resection, radiation therapy, medical management or observation. Surgical intervention has been the preferred method of treatment in symptomatic patients because the refinement of surgical approaches to the sella turcica has been improved.

The outcome of surgical intervention has been very positive. It results in an immediate tumour volume reduction of up to 64%-90% in nearly all patients and both visual function and hypopituitarism improve. But, as with every treatment, complications can occur. Halvorsen et al. [8] demonstrated the complication rate of surgical intervention. They describe a total complication rate of 7.1%. These complications include cerebrospinal fluid (CSF) leak, meningitis and visual deterioration.

Despite these side effects, surgical intervention seems to be the best treatment for NFPAs. The second best options for the treatment of NFPAs are radiation therapy and radiosurgery. The effects of mono-radiation therapy are minor compared to the effects achieved by surgical resection, and risk of tumour progression and radiation-induced hypopituitarism are major barriers for radiation monotherapy. An example for radiosurgery is gamma knife radiosurgery, which differs from traditional surgery because there is no incision. The gamma knife technique uses 200 tiny beams of radiation with submillimetre accuracy [17]. Studies about the effect of gamma knife radiosurgery revealed that not all patients showed a reduction of the tumour and some even showed a progression in tumour size [9, 10].

Another option of the treatment of NFPA is medical therapy. Unfortunately, this has not been proven effective in the primary management of NFPA. Dopamine agonist and somatostatin analogs are useful medicine in the treatment of hormone producing pituitary adenoma. Unfortunately, these medications haven't shown a significant therapeutic effect on the adenomas [11]. Thus, surgical resection remains the preferred method for treating NFPA.

Surgical possibilities

Pituitary adenomas are usually removed through a transsphenoidal approach, during which an endoscope is or instruments are inserted through the nose and the sphenoid bone. However, larger adenomas are best operated with a transcranial approach, where the brain is exposed through the skull, or a combined approach that include both approaches [12]. Han et al. confirmed that the transsphenoidal and transcranial approaches for giant pituitary adenomas (diameter >4 cm) should be combined flexibly based on the characteristics of the tumour. In certain cases, this simultaneous combined approach maximizes the tumour extirpation and lowers the risk of swelling and bleeding of the residual tumour [13]. The transsphenoidal route has not always been the preferred operation technique, because the space the surgeon has to work in is very narrow which makes it very difficult to perform. However, since

the availability of more sophisticated endoscopes that provide a more optimal angle of view, the transsphenoidal approach is less invasive and more effective than it has ever been.

Besides the endoscopes, more technological adjuncts are used during transsphenoidal surgery for NFPAs. Both endoscopes and operative microscopes can be used for the visualization during NFPA surgery. Other technological adjuncts are neuronavigation, intraoperative magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) diversion, and dural closure techniques. Neuronavigation uses a computer program in which an image of the brain of the patient is imported. A tracking system very similar to a GPS-system gives the surgeon insight into which part of the brain his instruments are located at that moment. Intraoperative MRI improves the rate of gross total tumour resection but is not recommended, since it results in an increased false-positives rate. CSF diversion, used as treatment for hydrocephalus, is a procedure that is used to drain fluid from the brain and spinal cord, usually to the abdomen. Perioperative CSF diversion might prevent postoperative CSF leak. Unfortunately, there is still insufficient evidence for the use of neuronavigation, CSF diversion or dural closure techniques [14]. More research is needed to determine whether these techniques can be used to optimise the transsphenoidal surgery.

The endoscopic or microscopic transsphenoidal surgery is the preferred treatment for symptoms by NFPA. However, not all patients are suitable for this technique.

Operation indications

Not every patient with NFPA has an indication for surgery. Visual disorders, pituitary deficiency and headaches are symptoms that are an indication for surgery. Of course, the doctor must be sure that nothing else is causing these symptoms. Especially for headaches a surgery might not help, because there's not always a direct causal relation between a headache and an adenoma.

Messerer et al. recommend surgery at the asymptomatic stage of macroadenoma, because of the improved endocrinological and visual outcome [15]. Currently, some patients with asymptomatic adenoma have an indication for surgery. Whether a patient without symptoms gets an indication for operation depends on several factors: patient age, natural course of non-functioning adenoma, the risk of onset of visual disorders, risk of onset of pituitary deficiency and risks inherent to the surgery. Young patients will be more likely to get an indication for non-emergency surgery, because of the almost inevitable progression of adenoma over the long term and lower risks inherent to surgery. Like every patient, each NFPA is different. They are subdivided into macroadenoma and microadenoma. These two subdivisions differs in the progression, the progression is slower in microadenoma in comparison with macroadenoma. Microadenoma is almost never an indication for surgery: it is unlikely that the tumour progresses. Due to the slow tumour growth, problems will not occur during a person's life.. However, macroadenoma may indicate non-emergency surgery, based on its natural progression. An NFPA is almost always a macroadenoma [16].

Conclusion

Because there are no medicines available for NFPA, surgery is the preferred treatment for NFPAs. There are a few options to operate, but transsphenoidal surgery seems to be the best choice. This technique immediately reduces tumour volume and it is less invasive in comparison with transcranial surgery. However, as with every operation, there are risks attached. Therefore, it's necessary to only select the patients who are really in need of such an operation. When a patient shows symptoms, the time is right to operate. But the decision to operate or not becomes more complex when a patient doesn't show any symptoms. More evidence is needed to determine whether a patient without symptoms benefits more from a preventive operation.

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EVIDENCE IN NEUROSURGERY ACCORDING TO NEUROSURGEONS: PRELIMINARY RESULTS OF AN INTERNATIONAL SURVEY

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Abstract

Original Research

BACKGROUND: The publication rate of neurosurgical guidelines had increased immensely over the past five years. But it seems only a small proportion of the clinical decisions is based on high-quality evidence. Surgeons do not seem to implement new evidence quickly.
OBJECTIVE: To evaluate the criteria of evidence within neurosurgery and its value within clinical practice according to neurosurgeons.
METHODS: A web-based survey was sent to 2552 neurosurgeons, who were members of the European Association of Neurosurgical Societies (EANS).
RESULTS: 82 neurosurgeons responded within the first five days and were subject of the current study. According to 49.4% of the responders, neurosurgery is based on less evidence compared to other medical specialties, and enough high-quality evidence is not available to base clinical practice on. Although, 86.7% of the responders believed neurosurgery is amenable to evidence. A statistically significant difference existed between neurosurgeons with and without formal training in Evidence Bases Medicine (EBM) in understanding, criticising and interpreting statistical outcomes in journals ($P = 0.001$).
CONCLUSION: According to the responders, neurosurgery is less based on high-quality evidence compared to other medical specialties. Formal training in EBM is desirable, so neurosurgeons can understand, criticise and interpret statistical outcomes in journals better.

WHAT'S KNOWN: Evidence-based practice is the golden standard in medicine and is believed to be wide spread in medicine.

WHAT'S NEW: According to neurosurgeons from different countries, evidence-based practice within neurosurgery is not so evident as might have been suggested.

KEYWORDS: neurosurgery, evidence, survey, opinion

Introduction

Evidence-based practice is the golden standard in multiple medical specialties, including neurosurgery [1-3]. Sackett et al. [4] defined evidence-based medicine as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'. Evidence is defined as 'the available body of facts or information indicating whether a belief or proposition is true or valid' [5].

The publication rate of neurosurgery guidelines in the past 5 years is nearly 10-fold that from the preceding decades [6]. Nevertheless, it is estimated that only 10 to 25% of clinical decisions are based on high-quality evidence [7]. Surgeons do not seem to implement new evidence immediately. Especially when the new evidence is involving new procedures. They prefer to wait for trusted and influential leaders in the community to pronounce their verdict about the new knowledge [7-8].

Before evidence is implemented in clinical practice, surgeons form a judgement about the available evidence. This study evaluated the opinion of neurosurgeons worldwide on the evidence available and if it is implemented in clinical practice of neurosurgery.

Methods

A 'cross-sectional' survey among 2552 members of the European Association of Neurosurgical Societies (EANS) was performed. The survey focused on the opinion on the levels of evidence of neurosurgical studies, on the understanding of the levels of evidence, and to what extent neurosurgeons implement evidence in clinical practice. Table 1 shows an example of the different levels of evidence in neurosurgery [9].

The survey was made with Google Inc. Forms and e-mailed directly to the participants by the administration of the European Association of Neurosurgical Societies (EANS). The survey consisted of 13 sections containing 22 questions in total. Sections with multiple questions within the survey were randomised, in order to minimise the influence of the sequence of questions on the answer. Participants were asked their opinions on high-quality evidence, the usability of researches, the amenability of neurosurgery to evidence, the quality of guidelines in their hospital and of the guidelines used by the neurosurgeon, and the important factors for choosing between treatments. (Table 2 shows the questions within the sections.) Also, the participants were asked if they received formal training in Evidence Bases Medicine (EBM) and if they considered themselves capable of understanding, criticising an interpreting statistical outcomes in journals. Most questions had answers as a five-item Likert scale. This scale was chosen because each item is of equal value so that respondents are scored rather than items, it is likely to produce a highly reliable scale, and it is easy to read and complete [10]. The remaining questions were polar questions or choices between statements. Participation was voluntary and completely anonymous, and the purpose of the survey was explained to the participants.

Table 1: *Diferent levels of evidence in neurosurgery.*
Rutka JT. Classes of evidence in neurosurgery. J Neurosurg 2016; July 1; 1-2

Evidence Level	Description
I	1) Randomized controlled trial (RCT); 2) Meta-analysis of randomized controlled trials with homogeneous results
II	1) Prospective comparative study (therapeutic); 2) Meta-analysis of Level II studies or Level I studies with inconsistent results
III	1) Retrospective cohort study; 2) Case-control study; 3) Meta-analysis of Level III studies
IV	1) Case series
V	1) Case report; 2) Expert opinion; 3) Personal observation

Data was collected over a period of five days from the date of first mailing. Questionnaires of all responders until the 27th of May 2017 were included in the first analysis. Two reminders will be sent.

Statistical analyses
For statistical analyses SPSS version 22 (Statistical Package for the Social Sciences) was used. For continuous data student t-tests were used, whereas for categorical data Chi-square tests. A P-value < 0.05 was considered statistically significant.

Results

A total of n = 82 responses was collected (response rate of 3,2% after five days), and 1 response was excluded because the responder was still a resident. Thus, n = 81 responses were taken into consideration.

Table 2 describes demographics from the responders. 30.9% of the responders, were working as a neurosurgeon between five and ten years, and almost all responders, 97.5%, were specialized in one or more subspecialty. Of the 81 included responders, 65 responders came from 24 EU-countries, mostly from Germany, Greece, Italy and the Netherlands. The 16 remaining responders came from 11 countries outside of Europe, mostly India, Iraq, Mexico, Saudi Arabia and the United States of America. The overall results of the survey are summarised in Table 3.

Figure 1 shows the opinion of the responders regarding the level of evidence in respect to high-quality and use in clinical practice. According to 53.0% of the responders, Level I or Level I and Level II are considered high-quality evidence. The results of research of all levels of evidence were used for implementation in clinical practice, except for randomised controlled trials (RCTs) with inconsistent, but promising, results (45.7%) (Figure 2).

Neurosurgery is amenable to evidence according to 86.7% of the responders. However, in the opinion of 49.4% of the responders, neurosurgery is less based on evidence compared to other medical specialties. Of those who thought that neurosurgery was amenable to evidence, 45.1% said neurosurgery was less based on evidence compared to other medical specialties as opposed to 80.0% of the group who did not think neurosurgery was amenable to evidence. The difference was statistically significant (P = 0.048).

The treatment options used were considered to be based on no high-quality evidence by 9.9% of the responders, whereas 72.8% stated that they were, and 17.3% had no opinion.

Formal training in EBM was received by 42.0% of the responders. The responders with and without formal training in EBM did equally consider their treatment options as high-quality, 73.5% respectively 71.4%. Of the responders with formal training in EBM, 5.9% considered their treatment options as not based on high-quality evidence as opposed to 17.1% of the responders without formal training. Comparing neurosurgeons with and without formal training in EBM a difference existed in their opinion to be able to understand, criticise and interpret statistical results in published studies, 94.1% respectively 65.7% (P = 0.001). This difference was not present when neurosurgeons with additional qualifications were compared with those without, 84.5% respectively 75.0% (P = 0.064).

Table 2: *Demographics of the responders*

Years working as a neurosurgeon	
1-5	16 (19,8%)
5-10	25 (30,9%)
10-15	16 (19,8%)
15-20	7 (8,6%)
20-25	4 (4,9%)
> 30	10 (12,3%)
Academic qualifications	
Yes[1]	45 (55,6%)
Professor	10 (17,55%)
PhD	30 (52,6%)
MSPH	2 (3,5%)
MPH	5 (8,8%)
Other	10 (17,55%)
No	36 (44,4%)
Subspecialty	
Yes[2]	79 (97,5%)
Neurocritical care	30 (12,9%)
Cerebrovascular neurosurgery	31 (13,3%)
Neuroendovascular surgery	5 (2,2%)
Spinal neurosurgery	55 (23,6%)
Neurosurgical oncology	58 (24,9%)
Pediatric neurosurgery	22 (9,4%)
Peripheral nerve neurosurgery	14 (6,0%)
Stereotactic and functional neurosurgery	14 (6,0%)
Other	4 (1,7%)
No	2 (2,5%)

[1]24,4% of the neurosurgeons that answered 'Yes', had more than one academic qualification
[2]86,1% of the neurosurgeons that answered 'Yes', had more than one subspecialty
PhD = Doctor of Philosophy, MSPH = Master of Science in Public Health, MPH = Master of Public Health

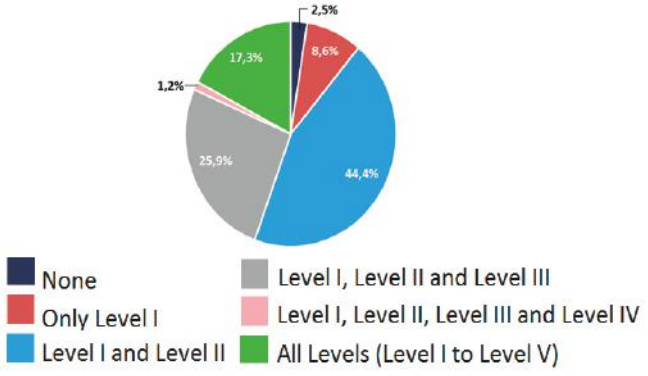

Figure 1: *Opinion of levels of evidence considered high-quality evidence and usable in clinical practice.*

Table 3: *Summery of the overall results of the survey*

Factors important for choosing a treatment	**Strongly agree or agree**	**Indifferent**
Local context and environment are important factors for choosing a treatment	72.9%	25.9%
Knowledge from patients and carers is an important factor for choosing a treatment	74.1%	22.2%
Research is an important factor for choosing a treatment	91.4%	7.4%
Clinical experience is an important factor for choosing a treatment	100%	
Usage of researches in clinical practice	**Strongly agree or agree**	**Indifferent**
Usage of (meta-analysis of) RCTs with inconsistent, but promising results in clinical practice	45.7%	37.0%
Usage of case reports, expert opinions or personal observations in clinical practice	59.3%	29.6%
Usage of case series in clinical practice	61.8%	29.6%
Usage of case-control studies in clinical practice	61.8%	23.4%
Usage of (meta-analysis of) retrospective cohort studies in clinical practice	72.9%	24.7%
Usage of (meta-analysis of) RCTs with homogenous results in clinical practice	72.9%	22.2%
Usage of meta-analysis of prospective cohort studies in clinical practice	75.3%	21.0%
Usage of prospective cohort studies in clinical practice	77.8%	18.5%
Guidelines and treatment options	**Strongly agree or agree**	**Indifferent**
Guidelines at my hospital are based on high-quality evidence	64.5%	19.0%
Treatment options I use are based on high-quality evidence	72.8%	17.3%
The neurosurgeons at my hospital do have a say in drawing up neurosurgical	72.8% (Yes)	2.5% (Other)
Training	**Strongly agree or agree**	**Indifferent**
Receive formal training in EBM	42.0%	14,8%
Can understand, criticise and interpret statistical outcomes in journals	80.3%	11,1%
Neurosurgery is amenable to evidence	86.7%	9.9%

RCT = Randomised Controlled Trial, EBM = Evidenced-based Medicine

Discussion

This study is unique since it is, in our opinion, the first that evaluated the opinion of neurosurgeons in several countries regarding evidence-based medicine in neurosurgery. Level I or Level I and Level II are considered high-quality and usable evidence by 53.0% of the responders (8.6% resp. 44.4%). But it seems that all levels of evidence are used by most neurosurgeons. Several neurosurgeons commented that the lack of evidence is an important issue in neurosurgery and reason for this finding. One commented: "The issue is, RCTs are expensive and difficult to perform. Well designed, prospective, pragmatic comparative studies could be equally informative and easier to run. Yet, RCTs are the higher level of evidence and form the basis of guidelines. It is my observation that we therefore 'dismiss' other study design. If true, this is holding us back." RCTs are more difficult and expensive to perform and are probably therefore less performed. In addition, 8,6% of the responders find only Level I, RCTs, is considered evidence. This is a well-known myth of evidence-based medicine (EBM) [11]. But, EBM evaluates the quality of evidence, based primarily on the likelihood that evidence is biased. A powerful RCT is the best standard for evaluating the inherent bias, but it does not follow that EBM requires only RCTs to justify clinical practice. EBM requires that we attempt to audit our decisions by obtaining the highest level of evidence that is ethically or logistically possible [3, 11]. Rothoerl et al. [12] and Yarascavitch et al. [13] published investigations into the levels of evidence in the neurosurgical literature in 2003 resp. 2012. These studies assigned a level of evidence to all published clinical papers in 3 major neurosurgical journals for the years 1999 resp. 2009-2010. The authors found that 22.8% resp. 10.3% of the literature was higher-level evidence (Level I and II). Level I, RCTs with homogeneous results, were only 3.8% resp. 2.1%. It had decreased, but was still significant higher than what had been reported in some other surgical specialties, including general plastic surgery [14] and maxillofacial surgery [15]. However, neurosurgery is still lagging behind on many other specialties, including orthopaedics [16], ophthalmology [17], otolaryngology [18], aesthetic surgery [19], and urology [20].

Of the responders, 27.2% do not think or know if the treatment options they use, are based on high-quality evidence. Ducis et al. [6] investigated

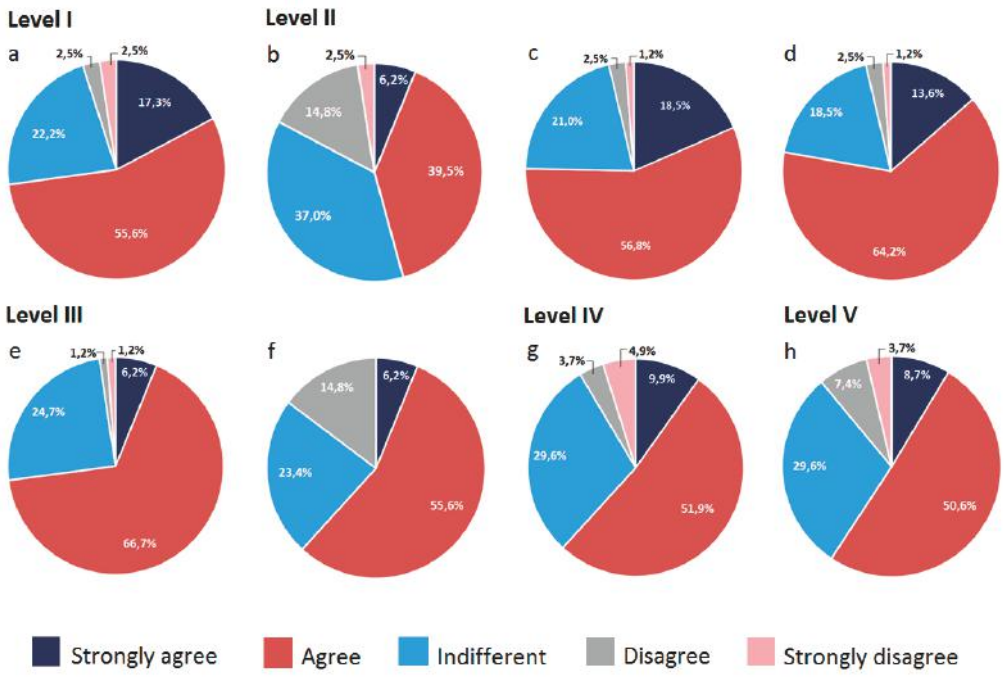

Figure 2: *Researches used by neurosurgeons in clinical practice: a) (Meta-analysis of) RCTs with homogeneous results; b) (meta-analysis of) RCTs with inconsistent, but promising, results; c) meta-analysis of prospective cohort studies; d) prospective cohort studies; e) (meta-analysis of) retrospective cohort studies; f) case-control studies; g) case series; h) case reports, expert opinions and/or personal observations. Results are presented on a five-item Likert scale ranging from (1) strongly agree, (2) agree, (3) indifferent, (4) disagree, to (5) strongly disagree.*

the quality of neurosurgery clinical practice guidelines. In neurosurgery, 24.4% of the guidelines are mainly based on Level I recommendations, which is statistically significant higher with neurosurgical vascular guidelines. Vascular neurosurgery is also the subspecialty with the highest publication rate in neurosurgery [13]. Some other specialties have similar Level I recommendations, including endocrinology [21], infectious diseases [22] and hepatology [23]. The proportion of Level I recommendations in these specialties have been ranging from 14.0%-22.4%. Almost half of the neurosurgeons, 49.4%, do think their specialty is based on less evidence compared to other specialties, but that seems contradictory with the literature available.

The difference in confidence regarding adequate interpretation of statistical outcomes presented in literature between those with and without formal training in EBM is also striking. Since evidence-based medicine is based on implementation of research results after correct interpretation, our results may be an argument to introduce formal EBM training in the medical curriculum.

Possible participants were all members of the EANS. EANS is an independent, supranational association of national European neurosurgical societies and individual members. The responders are a small selection of a large population of neurosurgeons that was addressed. This might introduce bias. It might introduce an underestimation of the real opinion, since only motivated or neurosurgeons trained in EMB could have responded. Participants did have the opportunity to give socially desirable answers. However and in our opinion, this was counteracted by emphasising the anonymity of the survey.

Lastly, the survey was made in Google Inc. Forms and therefore did not have the option to exclude more than one completed survey from the same IP address or have a login page. The login page from Google was not activated, so participants were not obligated to have a Google-account. All completed surveys were manually checked, so two identical surveys could be excluded. Furthermore, since this was a survey without any obligations we are convinced that nobody would feel the need to contribute more than once.

Conclusion

According to the responders, high-quality evidence is less frequent available in neurosurgery. The responders show they are willing to base their treatment options on the results of other studies than just RCTs. The results of the survey shows neurosurgeons think there is few high-quality evidence available in neurosurgery. It could be an important development to update the original idea of high-quality neurosurgery to match the opinions of the neurosurgeons today.

Also, less than half of neurosurgeons receive formal training in EBM. Training in EBM enhanced the ability of neurosurgeons to understand, criticise and interpret statistical outcomes in journals better. Therefore, more training in EBM is desirable for neurosurgeons to improve this ability in order to facilitate implementation of results into clinical practice.

Acknowledgments

I would like to express my thanks toprof. Dr. J.A. Grotenhuis for supporting the distribution of the web-based survey by the EANS. Also, I would like to thank Prof. Dr. G.P. Westert and Prof. Dr. M.M. Rovers for giving feedback on my work.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1
B. move eyes up and down

Locked-in syndrome is a condition in which patients are nearly completely paralyzed except for the vertical eye movement. Their cognitive abilities are still intact and they are able to communicate using the vertical eye movement. For example, looking upwards means " yes" to a question and looking downwards means " no".

Bloktoets Zenuwstelsel, september 2016
During the exam, 24% of the participants answered this question correctly.

Answer question 2
C. pons

The most probable causes for this syndrome are a stroke or lesion in the brainstem (more specifically the ventral pons) or basillary artery. The pyramidal tracts cross through the ventral pons, meaning that any infarction here will paralyze the whole body except the head. As seen in the figureto the right, the nuclei of the n. facialis and n. abducens are also situated in the ventral pons. We can also see that the nuclei of the n. oculomotorius and n. trochlearis are not situated in the ventral pons, but find their origin more cranial. This would mean that patients who are 'locked-in' can blink, move their eyes vertically and towards their nose. However, although the n. trochlearis originate from above the ventral pons, the nerve first goes downwards towards the pons before returning to the eyes. Therefore, any damage to the pons could also disable the nervus trochlearis.

Bloktoets Zenuwstelsel, september 2016
During the exam, 93% of the participants answered this question correctly.

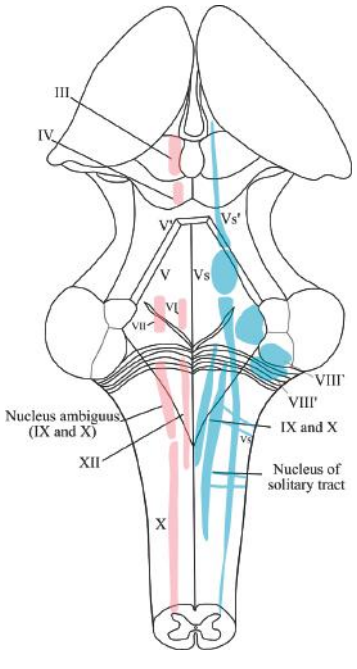

Figure 1: *Dorsal view of the brainstem with the cranial nerve nuclei in red (motoric) and blue (sensoric). The nucleus of the oculomotor nerve (III) is situated largely above the pons. Image from https://commons.wikimedia.org/wiki/File:Gray696.svg, reuse under CC-BY license.*

The exam questions can be found back on page 5 in this journal.

RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Janneke Elzinga[1]

With over 3000 publications per year, scientific research is a cornerstone of the Radboud University Medical Centre (Radboudumc). In this section, recent high-impact papers – published by researchers from the Radboudumc – will be discussed.

[1]Master Student Molecular Mechanisms of Disease, Radboud University Medical Center, Nijmegen, the Netherlands

The road to superior memory

According to researchers from the Donders Institute and collaborators, superior memory can be trained using so-called mnemonic strategies. Twenty-three memory athletes from the top 50 of the memory sports world ranking list, known to be trained in mnemonic strategies, were examined. Functional magnetic resonance imaging (fMRI) was used to evaluate brain anatomy and function during rest and during participation in a word learning task. Compared to participants in the control group, these athletes demonstrated the capacity to correctly recall significantly more words shortly after encoding. Next, untrained controls were assigned to six weeks of mnemonic training, which significantly improved memory performance compared to active controls undergoing a different type of training (n-back working memory training) and passive controls without training. The effect persisted for at least four months. Additionally, fMRI analyses revealed that changes in brain connectivity induced by mnemonic training were correlated with the network organization underlying mnemonic expertise. Moreover, a superior memory capacity can be attributed to changes in functional connectivity, rather than adaptations in single brain regions. Results from this study could inspire the implementation of novel strategies to improve memory [1].

Reward-processing in addictive behaviour

People with addictive behaviour, such as substance users and gamblers, show disrupted reward processing, known as the reward deficiency syndrome theory. Researchers from the Radboudumc and collaborators characterized these disruptions more accurately during both anticipation and outcome notification of (non-addiction related) monetary rewards. In an image-based meta-analysis, fMRI of individuals with addictive behaviour (substance and gambling) showed decreased striatal activation during reward anticipation compared to healthy controls. The striatum is a critical brain region in the reward system: a decreased activity indicates low expectancy of the reward, which is in line with the reward-deficiency theory. During reward outcome, however, individuals with substance addiction show hyperactivity in the ventral striatum, which can be explained by the learning-deficit theory. As rewards are critical in learning processes, the authors suggest that the individuals fail to predict upcoming rewards, reflecting a learning deficit. During (unexpected) reward outcome, this results in abnormally large errors, accompanied by enhanced ventral striatum activity. Uncovering the mechanisms contributing to addiction could further guide the development of adequate treatment [2].

Neurons on a chip - visualized

Using neurons derived from human induced Pluripotent Stem Cells (hiPSCs), researchers from the Radboudumc and Radboud University developed a protocol to study neuronal networks on a chip. By forced expression of the transcription factor neurogenin-2, as previously described [3], a homogeneous population of excitatory neurons could be created in a rapid and efficient manner. Next, microelectrode arrays, with electrodes embedded in a substrate on which the cells can be cultured, were used to measure and characterize the electrophysiological properties of the neuronal networks. This method will allow the comparison of different (e.g. patient-specific) hiPSC lines as well as provide robust consistency for pharmacological studies. Remarkable about this study is that the results are published in the Journal of Visualized Experiments, which means that the entire protocol can be watched online [4].

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A Word from the Board of RAMS

Dear reader,

Our brain is a magnificent and complex organ where dreams originate from and where ideas are born. Still, the impact of one brain is nothing compared to multiple brains joined together. We, as the board of RAMS, have experienced this in the past year. We have had the honour of working with an extraordinary team of enthusiastic students with whom we have accomplished great things. Without these hard working students, we would not stand where we are today. We have already organised two marvellous symposia, a great series of masterclasses, an excellent Summer School, published three editions of RAMS and contributed to the improvement of the curriculum of our faculty, and RAMS will continue to do many more great things.

Even though our year as the board of RAMS has come to an end, RAMS will continue to flourish. And you can be a part of this! With your enthusiasm, knowledge and commitment, RAMS can continue its goal of enthusing (bio)medical students of the Radboud University Nijmegen to participate in research during their studies. We want to continue offering students an easily accessible opportunity to publish their first article in RAMS. Besides that, we want to bring science to the students by organising more master classes, symposia and Summer Schools. Have you written a research article, case report or essay? Submit it! Do you want to write about topics that interest you in a more informal manner or work on your scientific skills? Join us! RAMS is the perfect opportunity to immerse yourself in more than what the standard curriculum can bring you.

You are invited to become a part of RAMS. Like our Facebook page www.facebook.com/ramsresearch and visit our site www.ramsresearch.nl to read about our upcoming events and keep in contact!

Board of RAMS 2016-2017

General Board

RAMS is directed by the general board, which consists of five medical students. As members of the board they frequently meet to make sure all activities run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional or financial subjects, you can contact the general board of RAMS via vice-voorzitter.rams@ru.nl.

Editorial Board

The editorial board is responsible for the contents of the journal, from reviewing the submitted papers to their rejection or publication. Furthermore, the editorial board is in charge of writing editorials and determining the general layout. For questions concerning the content of the journal please contact the editorial staff via hoofdredactie.rams@ru.nl. To submit papers, consult the 'for authors'-section on our website or mail to submit.rams@ru.nl.

Reviewers

This is the largest group in our team. RAMS counts on the support of over twenty reviewers who have been trained by professors and teachers at Radboudumc. With the help of specially developed master classes and use of their own specific knowledge, the reviewers are able to judge the submitted scientific articles.

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