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FROM THE EDITORIAL BOARD

Dear readers,

As chair of the new editorial board, I feel very honoured to present you our ninth edition of RAMS. You might have read RAMS before or you might have just started your career in the most beautiful field that exists: (bio)medical sciences. Let me shortly introduce RAMS to our new readers. RAMS is a magazine and organization operated by and meant for (bio)medical students. Our goal is to enthuse (bio)medical students of the Radboud University Nijmegen to participate in research during their studies. Moreover, we offer students an easily accessible opportunity to publish their first paper in RAMS.

A new academic year, a new RAMS edition and a new team go accompanied by plenty of new ideas. On behalf of the editorial board and editors, I am very proud to announce a new rubric; the zebras of medicine. Most of you have probably heard of the saying: when you hear hoofbeats, think of horses, not zebras. Harvard Medical School even made a song and music video about this topic recently. It is a way of saying you should first consider common medical diagnoses before arriving at an exotic medical diagnosis. For example, a patient with hypertension is more likely to have a cardiovascular problem as the underlying cause than a pheochromocytoma. However, the aforementioned diagnosis will probably pop up in the minds of most medical interns. The saying is supposed to help you put your mind back to the most common medical diagnoses.

It turns out that the aphorism was first used by the American Dr. Theodore Woodward, professor at the University of Maryland School of Medicine in the 1940s. He used the aphorism to instruct his medical interns. By 1960, it was a widely used expression in medicine. Even though epidemiologically it is most likely a horse, we would like to shed some light on the zebras of medicine that you might spot once or twice during your rotations or career. This edition, the zebra we will discuss is “the genital arousal syndrome”. You can find our new rubric on page 14. Do you encounter a zebra you would like to know more about? Please let us know!

Apart from our new rubric, we present you a great diversity of articles. We discuss whether the effect of EPO is epic or episodic on page 17 and the fading line of the gender definition on page 4. We have also included a review that was written during the successful international summer school about neurosurgery that took place in July. You will find this review, which is about craniosynostosis, together with a short report about the summer school on page 19.

I wish you lots of joy reading this edition of RAMS. And remember: when you hear hoofbeats behind you, do not expect to see a zebra. Except when you are at the zoo, of course...

Yours faithfully,

Mirjam Schaap
Chair of the Editorial Board

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A STORY ABOUT GENDER

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Introduction

Insight

Our society is practically built on the difference between men and women. The first thing people ask when a baby is born is: 'Is it a girl or a boy?'. People organize baby showers to reveal the gender of the unborn baby and it does not stop there. Whether you sign up for a Facebook account, apply for a job or subscribe to a magazine, one of the first questions to be asked about is your gender. However, this distinct division between genders is fading.

A few weeks ago, the common broadcast: "Good evening ladies and gentlemen," as heard often by commuters by train, was changed to "Good evening travellers" by the Dutch railway company Nederlandse Spoorwegen (NS) [1]. This change was accompanied with much ado and even made it to the headlines, but why? By addressing travellers in this new manner, the railway company supports the statement that people should not be limited to the binomial concept of gender. The concept of sexes, which seemed obvious before, has now become subject of debate. To most people, identifying as a male or female is self-evident, but this is not the case for people who are intersexual, bigender or transgender. To be able to address all travellers, the NS chooses this gender neutral approach.

While this Dutch company was worried about insulting anyone by addressing them with gender specific greetings, a different problem regarding the subject of gender has arisen as President Trump has banned transgender people from serving in the military. According to Trump, transgenderism in the military is accompanied by 'tremendous medical costs' and 'disruption of the military' [2]. These two very opposite but substantial discussions about gender differentiation show the relevance of this topic.

The distinction between sexes seems clear, but this is not the case for everyone. How is it possible that something that seems so obvious can be so confusing? Why do some people feel like they should be part of the opposite gender or identify themselves as both male and female? In what way are transgenders, people whose gender identity does not match the sex they were assigned at birth, different from cisgenders, people whose gender identity does match the sex that they were assigned at birth? With this article, we hope to shed some light on the gender division by looking at three possible factors that could play a role in transgenderism: neuroanatomical, hormonal and environmental factors.

Neuroanatomical differences between genders

It has been speculated that the gender identity of a person is associated with certain structures in the brain. Many studies show that the brains of male-to-female transsexuals, so called trans women, are more like the brains of cis women's and less like cis men's or represent an intermediate form. One of the first studies that has been published concerning transsexuality studied potential volume differences between genders of the central part of the bed nucleus of the stria terminalis (BSTc) [3]. The stria terminalis is a brain structure that connects, amongst others, the amygdala and the hypothalamus. Noteworthy, this brain region contains important sex hormones such as androgen and oestrogen receptors. The size of the BSTc was found to be about 44% greater in cis men compared to cis women. The size of the BSTc of male-to-female transsexuals laid within the range of those of cis women and appeared to be independent of sexual orientation and sex hormone levels. A subsequent follow-up study focused on the number of neurons in the BSTc in various male, female and transgender brains and the previous finding of neuroanatomical gender differences was confirmed [4]. Moreover, the number of neurons in trans women was found to be similar to that in cis women and the number of trans men lay in the range of the cis men's number. Even more, the number of neurons was also independent of sex hormones, suggesting that hormone treatment does not affect neuron numbers and is therefore not responsible for the observed differences in brain structure. This indicates that these differences had to be established earlier during brain development. These differences are confirmed to become apparent later in an individual's life by Chung et al. [5].

Chung et al. aimed to clarify at what stage in life the differences in brain structure between men and women become apparent. BSTc volume and neuronal density were determined in human brain tissue from males and females residing in one of the following categories: fetuses or neonates, infants or adolescents, and adults. The volume of the BSTc increased with age in both males and females, but the sex differences in BSTc volume only became statistically significant in adulthood, which means that the BSTc volume in neonates, infants and adolescents are similar, independent of gender. However, the finding that sex differences of the BSTc occur later in life conflicts with the experience of many transgenders who often feel from childhood onwards that they have been born in the wrong body. This could suggest that sex differences in brain structure are not the cause of transsexuality. Yet, it is possible that the cause of transsexuality is determined very early in life and that this also has an effect on the structure of the BSTc later in life. For instance, the authors speculate that the most likely cause of the observed sex differences in brain structures are prenatal or neonatal androgens and estrogens levels. This speculation suggests that hormone levels early in life dictate the sexual differentiation of the brain, whereas hormone levels in puberty and throughout life are responsible for the sexual differentiation of the body. This could mean that both transsexuality and the differentiation in brain structure are consequences of hormone levels early in life or another unknown process. The same and other research groups found sex differences in other brain structures as well, such as the thalamus, midbrain and gyrus precentralis [6,7]. It remains unclear how and when these differences in brain structure develop and whether these are the cause of transsexualism or the result of some other unknown mechanism responsible for transgender people to feel they have been born in the wrong body.

Hormonal causes

Besides neuroanatomical factors, there are other influences that determine gender. A study published in the Journal Adolescent Health examined the association between hormones and the onset of trans-

genderism [8]. Transgender males and females aged 12 to 24 were included in the study. Researchers measured several hormone levels, including testosterone and estrogen. Since the findings were normal for the sex identities they were assigned to at birth, this would suggest that there is nothing 'wrong' with the hormone levels in transgender people. However, this particular study only looked at the hormone levels at the ages between 12 and 24. It is still unsure if variations in prenatal hormones or hormone levels before puberty have something to do with the feeling of having the body of the wrong sex. Unfortunately, there is no research concerning the difference in hormone levels before the age of 12 between transgender people and cisgender people. Executing such a study would be troublesome because it would require predicting whether a person would decide to change gender or not.

Experimental studies where hormones have been manipulated in a wide variety of mammalian species, show the role of testosterone in early development (prenatally or neonatally). Treating young female rodents with testosterone leads to decreased female-typical and increased male-typical behaviour while castrating male rodents leads to female-typical behaviour. These hormonal manipulations do not only lead to changes in behaviour, but also lead to neural changes in the brain in which the brain becomes more similar to the opposite sex [9]. Manipulation of estrogen levels, by removing the ovaries of female animals, does not have the same effects as manipulation of testosterone levels. The magnitude of the effect of testosterone depends on the phase of development of the animal. In one phase the animal is more sensitive to a hormone than in the other phase. And these sensitive periods can even differ between genders, as is examined in rats [9]. The link between testosterone levels in early development and gender behaviour might give more insight into the existence of gender related issues like sexuality and transgenderism. However, examining this would be problematic due to the unethical aspect of supplying hormones experimentally to pregnant women to test these hypotheses.

What can be studied, however, is the sexual behaviour of children with congenital hormonal imbalances such as congenital adrenal hyperplasia (CAH), which leads to an increase of prenatal androgen excess. A study published in the Journal of Sex Research studied the difference in core gender identity, sexual orientation and recalled childhood gender role behaviour between females and males with and without CAH [10]. No differences were reported between males with CAH and unaffected males. On the other hand, the females with CAH showed recalled male-typical play in childhood correlated with reduced satisfaction with the female gender and reduced heterosexual interest in adulthood. Although prospective studies are needed to confirm this, these results suggest that girls with CAH who show the greatest alterations in childhood play behaviour may be likely to develop a bisexual or homosexual orientation as adults or will be dissatisfied with their natal gender. This study supports the hypothesis that testosterone plays a role in critical phases of early development and thereby might have an influence on the sexual orientation and gender identity.

Environmental factors

Neuroanatomic and hormonal factors are possible somatic causes of transgenderism, but could environmental factors cause transgenderism as well? Unfortunately, it is nearly impossible to find any studies about possible environmental factors leading to the onset of transgenderism. A cohort study about this subject is difficult because it cannot be predicted whether someone is transgender. By that, it is necessary to recruit a large cohort and follow them for a long period, which would both be very expensive and extremely troublesome. A good retrospective study also needs a large cohort and allows for recall bias.

There is little research about a possible relation between transgenderism and environmental factors, but we have some hypotheses of our own. The first hypothesis is based on current knowledge on the relation between sexual orientation and environmental factors. Pre-homosexual children show more gender non-conforming behaviour on average than pre-heterosexual children [11]. It seems as if the difference in child behaviour is a result of homosexuality, but perhaps when a child has parents that support the behaviour of the opposite sex, this could lead to homosexuality. This is a really fragile hypothesis since we have to assume that the onset of homosexuality and transgenderism are very similar to each other. In addition, there are many cases that undermine this hypothesis [12-14]. An example is the David Reimer-case: David Reimer was a boy who accidentally lost his penis during surgery and was reassigned to live as a female by his social environment, making him and his cisgender twin brother perfect for research [15]. His twin brother with the same genetics as David served as the ideal control. Despite all the treatments David was given to live as a girl, he never felt like he was one. When his father finally told the truth about his gender, he underwent surgery to undo the caused damage. There is no happy ending to this sad story, since David and his brother both committed suicide, probably due to their traumatising youth.

Like the previous hypothesis, the second hypothesis is also based on the assumption that there are similarities between homosexuality and transsexuality. Certain factors are associated with an increased odds for developing homo-romantic feelings. For men, these factors include having older mothers, divorced parents, absent fathers and being the youngest child. For women, maternal death during adolescence and being the only or youngest child or the only girl in the family are associated with an increased change for homosexual romantic feelings [16]. Hypothetically, there might also be such factors associated with transgenderism.

Like mentioned above, childhood behaviour and certain factors could play a role in the cause of transgenderism. Unfortunately it is very difficult to relate environmental factors to a future outcome unless the coherence between the factors is profoundly present.

Conclusion

We looked at three dimensions that could play a role in the onset of transgenderism: neuroanatomical, hormonal and environmental factors. Firstly, significant neuroanatomical differences exist between men and women, but these only seem to become apparent from adulthood on. This finding is contrary to the observation that transgenders seem to feel at a young age that they were born with the wrong sex. This suggests that the neuroanatomical differentiation between genders might be the result of an unknown factor rather than the cause of transgenderism itself. In addition, it is unlikely that an imbalance in hormone levels influences gender identity, since the hormone levels of transgenders before any hormone treatment show no difference with people that were assigned the same sex at birth. However, there are clues that indicate that prenatal or neonatal hormone levels are involved in the onset of transgenderism. Finally, the role of environmental factors was also discussed, but there is still insufficient quality research to draw any conclusion on this topic. All in all, researching the cause of transgenderism and gender identity is extremely complex, but hopefully new research will shed some light on the mechanisms behind gender.

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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!

We challenge you!

Question 1

Systemic Lupus Erythematosus (SLE) is an autoimmune disease which is characterized by the presence of autoantibodies against DNA, histones and a complex consisting of DNA and histones. Follicular helper T (Tfh) cells provide help to anti-DNA-specific autoreactive B cells.

The autoreactive B cells can receive help from Tfh cells by presentation in their MHC class II of ...
A. Only histone peptides
B. Only DNA fragments
C. Histone peptides in a complex with DNA

(Module Q4 Attack and Defence 2017)

Question 2

Immunodeficiencies lead to reduced resistance to pathogens. Which part of the immune system is deficient in people who have recurrent severe respiratory tract infections?
A. Immunoglobulins
B. Macrophages
C. T cells

(Module Q4 Attack and Defence 2017)

The answers to these questions can be found on page 12 in this journal.

RANDOMIZED CONTROLLED TRIAL COMPARING THE SHORT COLLUM FEMORIS PROSTHESIS WITH THE CORAIL PROSTHESIS: PRELIMINARY RESULTS

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ABSTRACT

Randomized Controlled Trial

BACKGROUND: A femoral neck preserving hip replacement is intended for the young and active patients. By preserving proximal bone load, the transmission to the proximal femur is supposed to improve and future revision surgery would be facilitated. We speculated that a more conservative resection of the femoral neck could lead to better clinical outcomes compared to a conventional resection. We therefore compared clinical- and the fixation associated outcomes with the use of a short stem with the outcomes associated with the use of a classic design.

METHODS: 83 patients were included in our randomized controlled trial. Patients either received a Collum Femoris Preserving (CFP) stem or a classic stem (Corail). Clinical outcomes were assessed using several validated scoring systems and stem fixation was determined by studying plain radiographs and using radiostereometric analysis. Follow-up took place after one year.

RESULTS: The clinical outcomes for both groups improved after surgery. The Harris Hip score increased from 52 to 93 in the CFP group and from 52 to 98 in the Corail group ($p < 0.01$). After one year the clinical outcomes (Oxford Hip Score, Harris Hip Score, EQ-VAS, satisfaction VAS and pain VAS) did not differ between the two groups ($p = 0.05 – 1.00$). The magnitude of the stem migration, measured by radiostereometric analysis, was similar in both groups ($p = 0.12$-0.33). The migration pattern however, differed. None of the hips were revised within the first year.

CONCLUSION: Both the clinical and fixation associated outcomes in both groups were good to excellent after one year. In the short time perspective we could not find any difference in clinical outcomes and stem fixation, indicating that there are no obvious advantages to the use of the CFP stem. Long-term follow-up is necessary to determine if the bone preservation associated with use of CFP prosthesis will ease future revision.

KEY WORDS: Collum Femoris Preserving, short stem, surgery, orthopedics

Introduction

It has been estimated that in 2030 the demand for revision surgery for hip replacements will increase by 31% in England [1] and 137% in the United States [2], mostly due to the increased life expectancy and the use of primary hip replacement surgery in younger patients. The stems used most frequently in primary hip replacement surgery have a stem length which could jeopardize future stem removal, should any late infection or instability occur. The concept of femoral neck preserving hip replacement with the use of a short stem was introduced for young and active patients as they, partly as a result of their longer life expectancy, have a higher risk of revision due to aseptic loosening. Preserving the femoral neck could ease future revision due to the higher cervical osteotomy and the more proximal physiological load distribution to the femur. It could also lead to better bone ingrowth due to conservation of the circumflex artery branches.

The Collum Femoris Preserving (CFP) stem was introduced by Pipino and Calderale in the eighties [3] and has been evaluated in multiple studies [4-11]. So far, the clinical documentation of the CFP stem indicates a stable fixation and good short- and intermediate-term results in terms of clinical outcome and durability [4-11]. We speculated that a more conservative resection of the femoral neck, associated with using the CFP stem, would lead to better clinical outcomes compared to a conventional resection, associated with the use of a conventional stem. Therefore we initiated a randomized controlled trial to compare the preserving CFP stem with the conventional Corail stem. Our primary aim was to compare the clinical outcomes between the groups. As a secondary outcome, the difference in fixation between the two prostheses was analysed using radiostereometric analysis (RSA).

Methods

Study Design

We conducted a randomized controlled trial at the Sahlgrenska University Hospital in Mölndal, Sweden. We included 83 patients with a painful hip and radiological evidence of osteoarthritis who were eligible for primary hip arthroplasty. Inclusion criteria were age between 35 and 75 years and hip anatomy suitable for both designs according to preoperative planning. Exclusion criteria were previous treatment with cortisone and low expected activity rate due to other diseases such as generalized joint disease. Patients were recruited between May 2012 and May 2014. 83 patients were randomly divided into two groups, using envelopes which were opened just before surgery. At the time of writing, all patients have been followed for one year. The study was approved by the ethical committee (DNR;243-12). Informed consent was obtained from all patients.

Implants and surgical procedure

The CFP stem (LINK, Germany) is a short, cementless, neck preserving stem. A left and a right CFP stem has been developed and those are available in six sizes with two different stem curvatures and with or without calcium phosphate (HX) coating. Only coated stems were used. The Corail stem (DePuy Synthes, USA) is a conventional, uncemented, hydroxyapatite-coated straight stem. It is available in 11 sizes and is widely used in Sweden. All patients received an uncemented cup (Delta TT or Delta-ONE-TT, LIMA, Italy). Surgery was performed between May 2012 and May 2015 by 14 surgeons. Two of the authors performed over half of the CFP surgeries. All patients were operated using a direct lateral approach with the patient in the lateral decubitus position. Full weight bearing was encouraged directly postoperatively.

Clinical outcome measures
Clinical parameters were measured using different questionnaires. The Oxford Hip Score (OHS), Harris Hip Score (HHS) and University of Los Angeles California Activity Scale (UCLA) were conducted pre-operatively and after 12 months. Quality of life was determined by using the SF-36, EQ-5D and EQ-5D-VAS, which we expanded with a visual analogue scale (VAS) for pain and satisfaction. The Swedish EQ-5D contains an additional question in which patients value their general health in comparison with the last 12 months. This question is scored separately and is not included in the EQ-5D scoring tool. These scores were determined pre-operatively and after 3 and 12 months. All questionnaires used were in Swedish. The EQ-5D was scored according to the new Swedish tariffs. The UCLA questionnaire was scored using the English scoring tool.

Radiography
Post-operatively and after 12 months, standard pelvic, anteroposterior (AP) and lateral radiographs were obtained. We used these radiographs to determine the length of the remaining femoral neck, the inclination-angle of the cup and the position of the tip of the stem in the femoral canal. The remaining neck was measured from the middle of the lesser trochanter to the proximal calcar, the position of the tip was expressed in a ratio (figure 1). Radiolucent lines around stem, which could indicate loosening, were determined according to the method of Gruen [12]. This method divides the perimeter of the stem into 7 zones on the frontal view and into 7 zones on the lateral view. To determine radiolucency around the cup we used the DeLee and Charnley method [13].

Radiostereometric analysis (RSA)
During surgery, 0.8 mm tantalum markers were placed in the femur and acetabulum bone. The Delta cup liner was marked at the time of operation with 5-10 markers. Uniplanar radiographs were taken 2 (range 0-5) days after surgery, using two detectors with an angle of 40° between the x-ray tubes and a cage 77. The post-operative RSA examination was performed after a median of 2 days (range 1-20). Follow-up investigations were performed 3, 6 and 12 months after the operation. To determine the precision of the RSA measurements we conducted double examinations post-operatively of 76 hips and calculated the 99% prediction interval of the precision based on presumption of zero motion between repeated exposures.

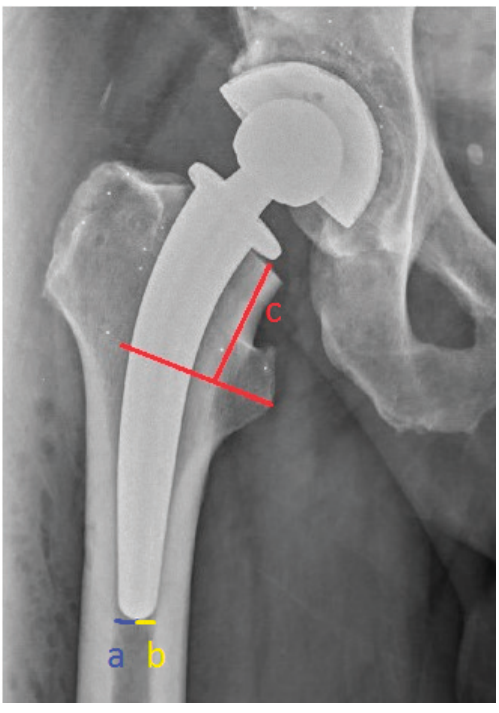

Figure 1: *Method of measuring the remaining neck (c) and the position of tip of the stem. We measured the distance between the tip of the stem and the inner cortex and calculated the ratio between these distances. Ratio between lateral and medial distance is a/b.*

The analysis of movement of the stem and cup was performed using the UMRSA analysis software 6.0 (RSA Biomedical, Umeå, Sweden). Only the center of the femoral head was used to measure translations of the stem, so stem rotations could not be analysed. Translations of the cup were analysed using both marker-based and model-based RSA analysis. Rotations of the cup could only be determined when using marker-based analysis. The mean error of rigid body fitting was accepted was 0.35.

Statistical analysis
The primary outcome of this study was the Oxford Hip Score. The secondary outcome was stem migration measured with RSA. A power analysis indicated that 30 patients in each group would give us the possibility to detect a difference of 4 points on the OHS between the groups with a power of 80%. All outcomes were analysed using IBM SPSS Statistics 23 (IBM SPSS New York, United States). Clinical data did not follow a normal distribution, therefore we used the Mann-Whitney test to compare the clinical outcomes between the Corail and CFP group. P-values less than 0.05 were regarded to represent a significant difference.

Results

41 patients received a CFP, 42 patients received a Corail prosthesis. The characteristics of the groups were comparable at baseline (table 1). There was no significant difference in amount of male and female patients (p=0.94). The majority of patients were diagnosed with primary osteoarthritis (91.6%) the rest of the patients had secondary osteoarthritis due to dysplasia (6.1%), idiopathic femoral head necrosis (1.2%) or trauma (1.2%). One patient dropped-out before surgery because of an unknown reason.

Clinical outcomes
No significant differences were found between the two groups after 3 months in the different questionnaires, except for the additional question in the EQ-5D questionnaire. 83.3% of the patients with a Corail stem valued their general health at the time of measurement to be better than the last 12 months compared to 63.4% with a CFP stem (p = 0.04). This result in favor of the Corail stem persisted after one year (table 2). After one year all clinical outcomes improved significantly compared to the pre-operatively measurements (table 2). For example the HHS improved from 52 to 92 in the CFP group and from 52 to 98 in the Corail group (p < 0.01). We found no other significant differences between the two groups. The analysis of the EQ-5D and SF-36 is pending.

Radiographic outcomes
The post-operative radiographs showed a mean neck preservation of 37 mm (SD 5.4) in patients with a CFP stem, compared to 28 mm (SD 5.4) in the Corail group (pc< 0.01). In both groups, the length of the remaining neck decreased in the first year (CFP group to 35 mm, the Corail group to 27 mm, p < 0.01 and 0.02).

The mean angle of inclination of the cup, in the total study population was 39 degrees (range 23-59) postoperatively. The lateral-medial ratio of the position of the tip after one year was 0.96 in the CFP group and 0.73 in the Corail group (p = 0.02). The anterior-posterior ratio of the tip was 1.30 after 1 year in the CFP group and 1.37 in the Corail group (p = 0.33).

Table 1: *Patient characteristics and baseline clinical measurements*

	CFP		**Corail**		
	Mean	95%-CI of the mean	Mean	95%-CI of the mean	*p*-value
Age in years	**58**	55 – 61	**58**	56 – 61	**0.72**
Harris Hip Score	**52**	47 – 58	**52**	46 – 58	**0.82**
Oxford Hip Score	**22**	19 – 25	**21**	18 – 23	**0.57**
EQ-VAS	**60**	52 – 68	**55**	47 – 62	**0.36**
Pain VAS	**65**	60 – 70	**63**	53 – 68	**0.58**
UCLA score*	**4**		**4**		**0.54**
General health**	**2/14/22 (3)**		**0/12/28 (2)**		**0.21**

**UCLA-score is in median and range*

***Number of patients that valued their general health as better / the same / worse than the last 12 months (missing answers)*

EQ-5D and SF-36 are not presented due to difficulties with the converting values

Table 2: *Clinical outcomes after one year*

		CFP	**Corail**	
		Mean (95%-CI of the mean)	Mean (95%-CI of the mean)	*p*-value
Harris Hip score (0-100)	*after 1 year*	**92** (88 – 96)	**98** (97 – 99)	**0.05**
	delta 0-12 m	**40** (31 – 49)	**45** (39 – 51)	**0.52**
Oxford Hip score (0-48)	*after 1 year*	**41** (39 – 44)	**43** (42 – 45)	**0.64**
	delta 0-12 m	**20** (17 – 23)	**23** (20 – 25)	**0.15**
EQ-VAS (0-100)	*after 1 year*	**78** (72 – 85)	**81** (77 – 85)	**0.87**
	delta 0-12 m	**17** (8 – 26)	**27** (18 – 35)	**0.14**
Pain VAS (0-100)	*after 1 year*	**13** (8 – 19)	**11** (7 – 15)	**0.97**
	delta 0-12 m	**-52** (-59 – -45)	**-52** (-58 – -46)	**0.81**
Satisfaction VAS (0-100)	*after 1 year*	**80** (73 – 88)	**88** (83 – 93)	**0.17**
	delta 3-12 m	**0.4** (-9 – 10)	**1.5** (-4 – 7)	**0.84**
UCLA-activity score (0-10)	*after 1 year**	**6** (2 – 10)	**6** (2 – 10)	**0.89**
	*delta 0-12 m**	**1** (-3 – 7)	**2** (-7 – 6)	**0.93**
General health	*after 1 year***	**28/8/3** (2)	**36/3/1** (2)	**0.04**
	*delta 0-12 m**	**-1** (-2 – 1)	**-2** (-2 – 0)	**0.02**

** Score is in median and range*

*** Number of patients that valued their general health as better / the same / worse than the last 12 months (missing answers)*

Table 3: *Mean translation of the center of the femoral head in milimeters at one year*

	CFP		**Corail**		
	Mean	Range	Mean	Range	*p*-value
Medial (+) – lateral (-) translation	**0.35**	-0.27 – 1.88	**0.27**	-0.76 – 3.76	**0.40**
Proximal (+) – distal (-) translation	**-0.51**	-6.59 – 0.30	**-0.48**	-5.37 – 0.32	**0.27**
Anterior (+) – posterior (-) translation	**-0.07**	-1.67 – 2.33	**-0.76**	-13.91 – 0.74	**0.02**

There was a significant change in lateral-medial ratio between the post-operative ratio and the ratio after 1 year in the Corail group (0.88 to 0.73, p<0.001), meaning the tip moved more lateral. No significant changes were seen over time in the CFP group.

Seven Corail stems showed radiolucent lines at one year follow-up in Gruen zones 1, 7 and 8. Less than 15% of the stem-bone interface was involved. Four CFP stems showed radiolucency in Gruen zones 1, 2 and 8 (8-31% of the interface). Postoperative radiographs showed radiolucent lines around the cup in 45% of the hips (range 1-74%) of the total study group. At one year follow-up, the radiolucent lines had disappeared in 20 hips, decreased with 4-37% in 4 hips and increased with 1-55% in 15 hips. None of the cups had been revised at the one year follow-up.

RSA results

The medial-lateral, proximal-distal and anterior-posterior translation could be measured with a precision of 0.18, 0.18 and 0.45 mm respectively. RSA analysis regarding the stem was performed in 81 patients. One patient had unstable bone markers. RSA analysis regarding the cup was performed in 78 patients due to poor bone marking in four patients.

After one year, the mean proximal-distal translation of the center of the femoral head was similar in both groups (p=0.27). The femoral head center showed a mean medial translation in both groups during the first year (table 3). Looking at the movement along the anterior-posterior axis, the Corail stem showed an increased mean posterior displacement compared to the CFP stem (p=0.02). However, taking out the vector of the movement, the mean absolute movement in the anterior-posterior direction (0.41 mm in the CFP group and 0.58 mm in the Corail group) did not differ (p=0.12). This indicates that the CFP stem moved both posterior and anterior (figure 2).

Separate evaluation of each individual stem revealed that translations below the detection level along any of the 3 axes postoperatively to one year were measured in 8 (19.5%) patients in the CFP group and 13 (33.3%) patients in the Corail group. 19 (47.86%) patients in the CFP group and 19 (48.76%) patients in the Corail group only showed movement during the first 6 months. 13 (32.6%) of the patients in the CFP group and 7 (17.9%) in the Corail group had detectable movements between 6 months and 1 year. One patient was not examined at 6 months due to unknown reason. The individual evaluation didn't reveal any significant differences between the two groups.

RSA analysis regarding the cup was performed in 78 patients due to poor bone marking in four patients. Analysis of the movement of the cups at one year showed no differences between the groups (table 4).

Revisions and complications

One patient who received a Corail stem had an intraoperative fissure which was treated with cerclage wires. Within the one year prospective there were no dislocations or infections.

Conclusion

The clinical outcomes were considered good to excellent after one year, with no significant difference between the groups. The magnitude of the stem migration was similar in both groups, but the pattern of stem migration differed. The femoral head center of the Corail stems was more frequently displaced posteriorly whereas the CFP stems showed a more equal distribution between anterior and posterior displacement. From a clinical perspective the use of a short stem and allowing preservation of the femoral neck did not result in better short-term clinical outcomes than the use of a conventional stem.

Discussion

Previous reports regarding the CFP stem showed good short- and mid-term results [4-11]. Whether the CFP stem improves the outcome in terms of hip function and patient satisfaction compared to a conventional stem, has not been investigated in previous studies. This has been investigated for an ultra-short stem. Thomaszeweski compared the clinical outcomes of patients with an ultra-short stem (Proxima) with a control group who received a classic design. He concluded that patients in the Proxima group had a better clinical status and a greater quality of life [14].

Although our findings indicate improved clinical outcomes, however we did not find any evidence that the patients in the CFP group had better outcomes in terms of hip function nor patient satisfaction.

We note several limitations. First, the follow-up time was limited to one year and even though the data of the RSA looks quite promising, several stems showed migration up to one year. Two of these stems proceeded to clinical loosening but it requires 2 year data on the entire cohort to make any more definite conclusions. Also, a follow-up of several years is necessary to draw conclusions about long-term function. Second, multiple surgeons operated patients included in our study. The CFP stem was implanted by 11 different surgeons, meaning some of them only inserted a few CFP stems. In these cases they were assisted by more experienced colleagues. Since the Corail stem is often used, all surgeons are experienced in the use of the Corail stem. Third, due to the lack of markers on the Corail stem it was impossible to measure rotations of the femoral head. With the center of the head of the prosthesis as only reference, we can only assume the direction of movement of the stem by using the possibilities of movement of the stem in the femoral bone. With that in mind, distal and medial translation of the head center can be interpreted as varus tilt and posterior translation as retroversion or posterior tilt of the stem. It is not possible to convert the observed head translation to magnitude of rotation in a more accurate way. Finally, not all patients completed all clinical questionnaires, reaching a maximum of 10% missing answers. Although this study has some limitations, the strength is the randomized design and the inclusion of comparatively many patients. Several outcomes were used and both stem and cup fixation was monitored with RSA analysis.

Table 4: *Mean translations and rotations of the cups after one year*

	CFP			**Corail**			
	n	Mean	Range	*n*	Mean	Range	*p*-value
Medial (+) – lateral (-) translation	39	**0.13**	-0.24 – 0.95	39	**0.10**	-0.85 – 1.15	**0.29**
Proximal (+) – distal (-) translation	39	**0.16**	-0.22 – 0.85	39	**0.58**	-0.15 – 0.78	**0.70**
Anterior (+) –posterior (-) translation	39	**0.11**	-0.94 – 1.00	39	**-0.03**	-0.57 – 1.03	**0.09**
Anterior (+) – posterior (-) rotation	33	**0.18°**	-2.54 – 3.98	31	**0.60°**	-0.76 - 4.93	**0.12**
Ante- (+) – retroversion (-)	33	**0.61°**	-1.98 – 4.17	31	**0.58°**	-1.61 – 6.46	**0.76**
Decreased (+) – increased (-) inclination	33	**0.11°**	-1.71 – 4.06	31	**-0.03°**	-1.47 – 2.54	**0.24**

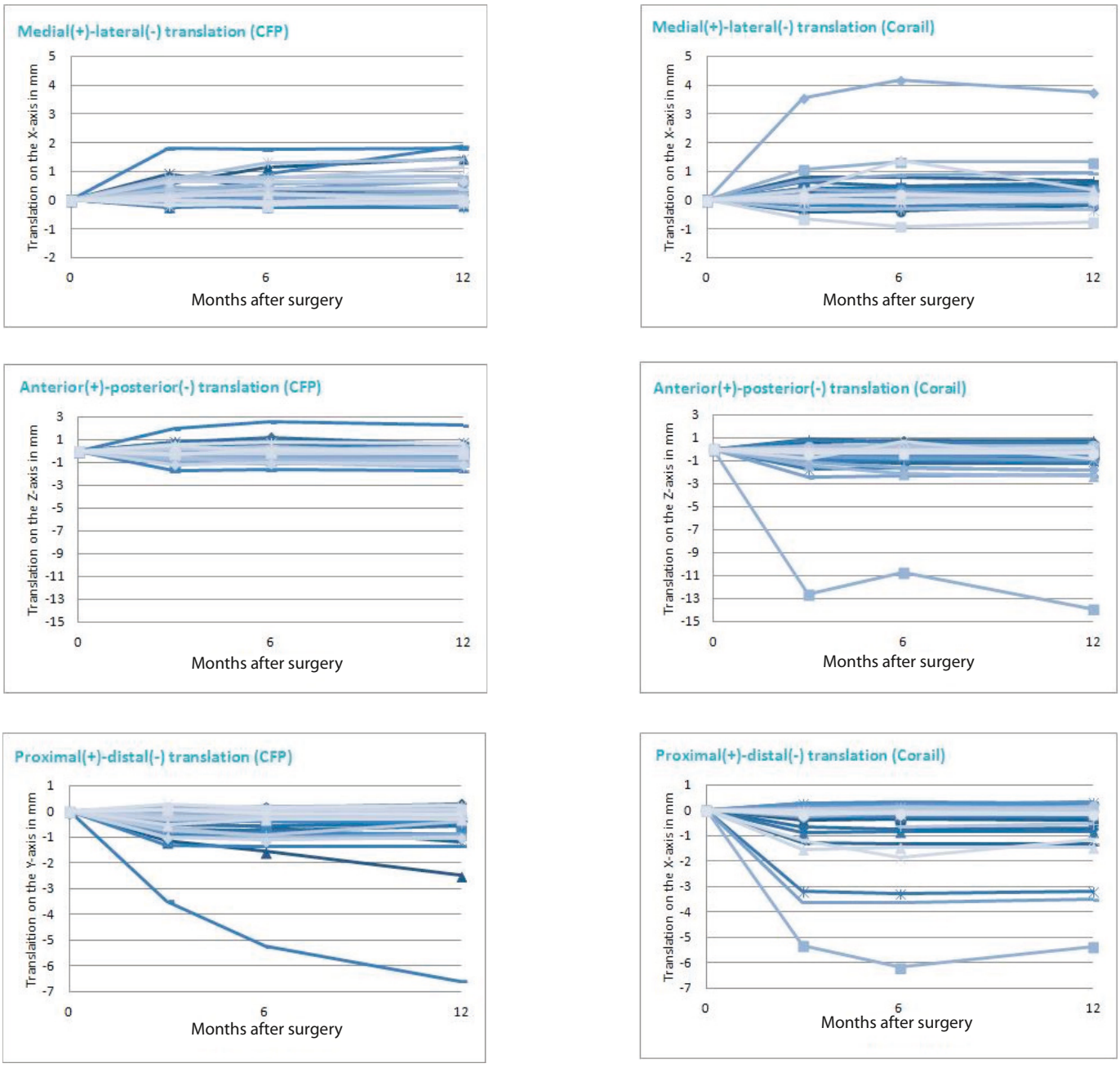

Figure 2: *Migration of each individual stem along the three different axis, divided in the two groups.*

Previous studies investigating the CFP stem showed an improvement of the HHS to at least 82 points [11], but mostly above 90 points [4-10] in the first year after hip replacement surgery. The HHS in the CFP patients improved to 92 in our study. The difference we found between the two groups in the additional question to the EQ-5D is difficult to value since it is only one question. We would like to analyze the outcomes of the SF-36 and EQ-5D to make a reliable comparison between the two groups.

Previous studies evaluating the CFP stem indicate a stable fixation and good short- and intermediate-term results on durability [4,6-11]. Hutt et al. showed a survivorship of 100% after a mean follow-up of 9.3 years [5]. Survivorship of the CFP stem in our study was 100% after one year. We found radiolucent lines in Gruen zones 1, 7 and 8 in several patients in both groups which is comparable to what others describe [9-11].

Using the RSA techniques, we did not find any differences in the absolute motion on the axes between the groups. However, we found a significant difference between the mean anterio-posterior motion after one year. We noticed that the centre of the femoral head in the Corail group moved posteriorly in most cases, while the centre of the femoral head in the CFP group moved both posteriorly and anteriorly. We assume that this translation is a result of the rotation of the stem into retro- or anteversion. Two studies, investigating the CFP stem using RSA, both showed retroversion of the stem using the mean translation and rotation [7,10]. The range of the data, published by Lazarinis (-0.26 – 0.55 mm) suggest that the CFP stem moves both in retro- as in anteversion [7].

At one year follow-up, the mean proximal-distal translation was 0.48 mm in the CFP group. We assume this to be the subsidence of the prosthesis. The other RSA studies regarding the CFP stem showed a mean

subsidence of 0.05 and 0.13 mm [7,10]. This difference could be explained by the fact that the patients in the study by Röhrl et al. were advised to only partially bear weight in the first 6 weeks, whereas in this study full weight bearing was encouraged directly postoperatively [10]. A RSA study concerning the Fitmore short stem showed a mean subsidence of 0.39 mm. [15].

The migration of the Corail stem along the three different axes that was found in this study, is in line with other another RSA study regarding the Corail stem [16]. RSA studies show that early micromotion is a good predictor for future revision [17,18]. Lazarinis et al showed that only 1 CFP stem subsided after two years. Röhrl et al described little migration in the first two years. It requires two year results to determine primary stem fixation [7].

The use of a short stem and preservation of the femoral neck did not result in any short-term advantages compared to a standard stem. Two year data should help to draw more definitive conclusions.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1: A. Only histone peptides
During the exam, 27% of the participants answered this question correctly.

B cells can receive help from Tfh cells by presentation of peptide fragments in the MHC class II of the T cells. Other molecules than peptides, such as DNA, cannot be presented in the MHC class II. Thus, anti-DNA-specific autoreactive B cells in Systemic Lupus Erythematosus (SLE) can only receive help from Tfh cells by presentation of histone peptides in their MHC class II.

Question 2: A. Immunoglobulins
During the exam, 43% of the participants answered this question correctly.

Immunoglobulins are important for the immune defence against pathogens in the respiratory tract such as *Streptococcus pneumoniae and Pneumocystis jirovecii*. Respiratory tract infections are therefore often seen in patients with deficient immunoglobulin production. Macrophages are important in phagocytosis, immune regulation and wound healing. Deficiencies in T cells often lead to an increased susceptibility to intracellular pathogens.

The exam questions can be found back on page 6 in this journal.

MYTH OR SCIENCE: THE SOUND OF MUSIC IN THE OPERATING ROOM

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Introduction

Critical Appraisal

For millennia, music has been used as a tool to lighten the burden of labour. The Egyptian pyramids were built while great masses were chanting, Native Americans would be accompanied by playing flutes during healing rituals, and soldiers have been led into battle to the sounds of beating drums. It appears this habit is being continued in the operating room (OR). Have you ever wondered how surgeons can stay awake during an 8-hour long surgery? Well, apparently music has the ability to enhance concentration and subsequently improve your performance [1]. However, there are debates as to whether music in the OR is actually helpful or harmful.

Whereas hospitals once were famous for their quiet and serene environment, one could state that this is no longer the case. While the hallway and cafeteria are clear frontrunners in the race for 'noisiest place in a hospital', an underestimated contestant is the operating theatre. With noisy equipment, loud operation-related activities, and conversations during surgical procedures, ORs are becoming increasingly tumultuous. Peak noise levels in the OR can even exceed 120 decibels, which is louder than a busy highway [2]. According to health and safety regulations in the workplace (ARBO-wet), a daily exposure of >80 dB could already be harmful to your hearing [3]. Furthermore, these high levels of background noise may impair concentration and communication between OR staff where miscommunication is one of the leading causes of errors [4]. However, does music actually act as an extra hurdle or does it, in fact, lead to a less stressful environment?

Regarding the effect of music on the operating room staff's performance, various effects have been described. A questionnaire conducted by Ullmann et al. demonstrated that >60% of OR personnel listens to music in the OR. Interestingly, 1 out of 10 participants indicated that it had a negative effect on communication due to excessive noise, but at the same time, many (77%) reported that music created a calm atmosphere and enhanced their work efficiency [5]. Another study found that autonomic reactivity was lower and the speed and accuracy of cognitive tasks increased in surgeons listening to self-selected music compared to no music or stress-reducing music [6]. In a multicenter trial, around 80% of the OR staff reported that music alleviated anxiety and elevated their mood, which allowed them to be more calm and thoughtful in stressful situations. Especially in nurses and female responders, who showed the highest preference for music during surgery [1,7].

However, it is important to note that the effects of music may vary depends on several factors. For instance, in one randomized controlled trial of less experienced surgeons, music during training procedures was perceived as distracting and impaired performance [8]. Likewise, in the UK, an observational study of teamwork in operating rooms through video recordings was conducted and revealed that repeating questions occurred five times more in settings that involved playing music [9]. Anesthesiologists in particular declared that music can reduce the ease and accuracy of carrying out their tasks. 26% believed that music negatively affected their alertness and their communication with other staff members. 51% felt that music was distracting when a complication was encountered, especially with music that they disliked [10]. In contrast, Hawksworth et al. found that the anaesthetist's performance was not affected by self-chosen or classical music compared to silence [11]. Interestingly, music also affected patients in the OR by showing an anxiolytic and sedative effect before, during, and after surgery. It even helped patients physically and mentally relax during unpleasant or invasive procedures and enhanced their cognitive function [12-14].

Overall, these individual studies show the challenge to research such an easily influential topic. The effect of music on the different staff members in the OR is dependent on many factors including personal taste, the required tasks and environmental factors. However, it is clear that music does have a certain effect on all individuals, whether positive or negative, and this should be taken into account when deciding who controls the playlist for that day. Even though 'Staying alive' has the best rhythm for CPR, the search for the best song during other OR activities continues!

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ZEBRAS OF MEDICINE

PERSISTENT GENITAL AROUSAL DISORDER AND RESTLESS GENITAL SYNDROME: AN OVERVIEW OF THE CURRENT LITERATURE

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Abstract

Review

BACKGROUND: Persistent Genital Arousal Disorder (PGAD) and Restless Genital Syndrome (RGS) cause women to experience sexual arousal of the genitals without being psychologically aroused. This may be possible due to the fact that women have a lower degree of concordance, the agreement of physical and psychologically arousal, compared to man.
OBJECTIVE: This review will give an overview of the literature on PGAD and RGS to summarize the current knowledge of these syndromes and to explore starting points for future research.
RESULTS: PGAD physical symptoms exist of genital swelling, tingling, lubrication, throbbing and contractions. These symptoms may lead to women isolating themselves, developing a depression and eventually suicidal tendencies. Triggers for these symptoms can be visual, physical, or emotional. Masturbation, orgasms and exercise may give some form of relief, but will never completely resolve the symptoms. PGAD may be part of a bigger syndrome called Restless Genital Syndrome. Women with RGS would be afflicted by PGAD and Restless Legs Syndrome and/or Overactive Bladder. Currently, there is no consensus yet on the underlying pathology of PGAD/RGS. The most plausible hypotheses focus on neurological, vascular, or hormonal pathology or use/withdrawal of antidepressants. Currently, there are no evidence-based treatments, but clonazepam showed promising results. Other possible treatments like oestrogens and tramadol were only tested in smaller groups or case reports.
CONCLUSION: PGAD and RGS are relatively newly discovered syndromes with potentially socially invalidating symptoms which need more research to fully understand the pathophysiology of the syndromes and to find a successful, evidence-based treatment.

KEYWORDS: female, sexual, Restless Legs Syndrome, gynaecology, neurology

Introduction

Persistent Genital Arousal Disorder (PGAD) is a disorder solely found in women and causes almost constantly aroused genitals, while the brain is not aroused [1,2]. A comparable disorder in men is called priapism and is usually caused by Viagra [1]. PGAD may be part of a bigger syndrome called Restless Genital Syndrome (RGS) [2]. At the moment, it is still unclear how many women are affected by this disorder, mostly because afflicted women often feel ashamed of their symptoms, which prevents them from seeking the help of physicians [3,4]. This review aims to give an overview on the literature of PGAD and RGS to summarize the current knowledge of these syndromes and to explore starting points for future research.

Sexual arousal

To understand how and why PGAD exists, we first need to know some of the physiology of sexual arousal in women. Sexual arousal can be divided into physical and psychological excitement and may be described as "a combination of objective and subjective signs; the physical reactions as vulvar swelling, vaginal lubrication, heavy breathing and increased sensitivity of the genitalia, combined with the subjective experience of feeling pleasure and excitement" [5]. The correspondence of the physical and psychological excitement is called concordance [5]. Women have a lower degree of concordance compared to men, meaning that women may report sexual arousal when their genitalia aren't. The concordance also works the other way, women may report that they aren't sexually aroused while their genitalia are. Currently, it is still unclear how much of the physical and psychological arousal contribute to the full experience of arousal [6], however the lower concordance could explain how women can have genital sexual arousal without physiological arousal.

Persistent Genital Arousal Disorder

To diagnose a woman with PGAD, the symptoms she is experiencing needs to fulfil 6 criteria [4,7]:

1. The symptoms are those of sexual arousal (vulvar swelling and hypersensitivity) that last for hours or days and do not completely disappear on their own.
2. The physical symptoms of arousal do not resolve after one or multiple orgasms.
3. The physical symptoms are not related to a psychological sense of arousal.
4. The arousal can not only be triggered by sexual activity, but also by non-sexual stimuli or no stimuli at all.
5. The women experience these symptoms as intrusive, unbidden and unwanted.
6. The symptoms cause at least a moderate degree of distress.

Clinically, women with PGAD experience genital swelling (74.8%), tingling (78.6%), lubrication (75.7%), throbbing (72.2%) and contractions (70.9%). Triggers for these symptoms can be visual (60%), physical such as intercourse (50%), or emotional like stress or anxiety (30-45%) [3]. Driving in a car or riding a bus is one of the most reported non-

sexual triggers, caused by the vibrations. Although there are no known factors which completely resolve the symptoms, there are some that are frequently reported to give some form of relieve: masturbation (51%), orgasm (50%), distraction (39%), intercourse (36%), exercise (25%), and cold compresses (13%) [3,8]. Important to note is that these symptoms may cause afflicted women to isolate themselves, leading to depressions and some women eventually develop suicidal tendencies [4,7]. The exact prevalence of PGAD is still unclear. A survey in a sexual health clinic in the United Kingdom found that 1% of the questioned women met all the criteria of PGAD and 33% met at least 1 criterion [9].

Restless Genital Syndrome

Based on several studies and case reports, a group of Dutch researchers introduced the term Restless Genital Syndrome [2,10]. RGS consists of the criteria of PGAD accompanied by the symptoms of either Restless Legs Syndrome (RLS) and/or overactive bladder (OAB). This group of researchers came up with 16 arguments why PGAD and RLS could be part of a bigger syndrome of which the most important ones are summarized below [2].

The prevalence of RLS in women with PGAD is 67% compared to 3-19% in the general population [2,11]. In 39% of the women, reported symptoms of RLS started shortly after the onset of PGAD. Secondly, RLS and PGAD may both be caused by starting SSRI treatment, or withdrawal of the SSRI [12,13]. Furthermore, patients find it hard to describe the physical unpleasant sensation felt in PGAD and RLS, but in both cases movement and rubbing of the afflicted body part suppresses the unpleasant sensation. Although it is still unclear if RLS and PGAD are caused by varices, in both syndromes the prevalence of varices (leg or pelvic) is higher compared to the general population [14]. Lastly, successful treatment of both syndromes is hard to achieve, but clonazepam and tramadol have been reported to relieve the symptoms in both syndromes [15,16].

Although the authors did not specifically involve OAB in their arguments for the existence of RGS, they did find a prevalence of 67% in women with PGAD (39% started shortly after onset of the PGAD symptoms), compared to 15% in the general population.

Pathophysiology

There is no consensus yet on the underlying pathology of PGAD/RGS. The most plausible hypotheses focus on neurological, vascular, or hormonal pathology or use/withdrawal of antidepressants (mostly SSRIs and SNRIs).

Neurological: PGAD may be caused by small-fibre neuropathy of the n. dorsalis clitoridis, which would cause hyperesthesia and hyperalgesia of the genital area. Firstly, women with PGAD reported an increase in the genital symptoms when wearing tight underwear and/or after prolonged periods of sitting [17]. Secondly, researchers tested women with PGAD for several trigger points using a cotton swab. All women showed genital arousal, even up to orgasmic sensations, when slightly touched by the cotton swab in a certain area. The area which lead to arousal differed per woman. Other neurological causes may be mechanical compression of the n. pudendus possibly caused by varices or a tarlov cyste, a cerebrospinal-fluid-filled sac most frequently located in the sacral region of the spinal cord [17-19].

Vascular: Another possible cause is the existence of pelvic varices [2,10,19]. A study found a prevalence of pelvic varices of 55%, in contrast to a prevalence of 9,9% in healthy women [10]. In another study the same researcher found even higher prevalences of varices; in the wall of the vagina (91%), the labia minora/majora (35%) and uterus (30%) [2]. The varices could mechanically compress the n. pudendus which could lead to the symptoms as described in PGAD and RLS. However, these studies were small with 18 and 23 women, and the researchers mentioned that most of the varices were small to moderate in size, making it unlikely to really cause mechanical compression. Furthermore, because of the design of the study only correlation but no causation can be demonstrated.

Antidepressants: Several studies found adverse effects of antidepressants on sexual function [20-23]. Administration of paroxetine (SSRI) and venlafaxine (SSRI), and duloxetine (SNRIs) inhibited the increase in blood flow after pelvic stimulation in rabbits. Although these drugs all increase the amount of serotonin, administration of serotonin or escitalopram (a highly selective inhibitor of serotonin reuptake) did not result to inhibition of the blood flow. Therefore, the inhibition of blood flow after stimulation is not due to the increase of serotonin, but due to other effects of the drugs. The same study showed that administration of L-arginine (a precursor of nitric oxide (NO) which causes vasodilation) reversed the inhibition caused by paroxetine. Phentolamine, an alpha-adrenergic antagonist which also causes vasodilatation, prevented the inhibitory effects of venlafaxine. Both L-arginine and phentolamine partly blocked the inhibition of duloxetine. These data suggest that it's not the increase in serotonin, but rather the inhibition of the production of NO (countered by L-arginine) or the increase of norepinephrine (countered by phentolamine) that causes the vasoconstriction. However, it's still unclear if and how the inhibition of blood flow leads to the development of RGS.

Hormonal: Another possible cause of RGS is dysregulation of the hormones, usually caused by the menopause [23]. Animal studies showed that estrogen treatment increase the amount of norepinephrine in adrenergic nerves, demonstrating that hormones can also affect the physiology of our nervous system [24,25]. Interestingly, in contrary to increasing the amount of noradrenaline, estrogen reduces the density of innervation. Another study showed an increase in the density of the nerves in the vaginal area in rats that underwent an ovariectomy [26]. Furthermore, this density reduced when the rats where treated with estrogen. The increase in density was attributed to true axonal proliferation and not just altered tissue volume. Ting et al. also reported that the new nerves could mediate vasoconstriction and nociception, suggesting that these changes may explain the sensitivity and hyperalgesia of the vagina in postmenopausal women (and possibly women with RGS). However, another study found no such increase in density in rats after an ovariectomy [23].

These studies suggest that our hormones also regulate our innervation and neurotransmitters, but more research is needed to clearly define the roles of the different hormones.

Treatment options

Since PGAD and RGS are relatively recently discovered syndromes, no randomized controlled trials are conducted yet. Most known possible treatments are the result of case reports or small trials. Waldinger et al. treated 16 women with clonazepam in different dosages [2]. In two women no effect was found, while one woman reported a reduction of symptoms of 20%. The other 13 women reported a reduction of the symptoms of at least 50%. The women in this trial who did not experience any, or only a temporary effect, agreed to try other treatments. This included estrogens (one woman had beneficial effects, but both women were against continuing because of potential side effects of hormonal replacement therapy), pramipexol (a dopamine agonist, without beneficial effects in all three women but with disturbing side effects), tramadol (which did have a significant effect in all three women, but has the downside of lasting only four hours and thus needs to be taken often which in turn leads to addiction) and oxazepam (with successful effect in one of the three women).

Other case reports showed positive effects of electro-convulsion therapy [27], pudendal neuromodulation [28] and hypnotherapy [29].

Conclusion

PGAD and RGS are relatively recently discovered syndromes and much research still needs to be done to fully understand the pathophysiology. Also, it is still unclear how many women suffer from PGAD or RGS. Since these symptoms are accompanied by a lot of shame, it might be of value that physicians (mostly gynaecologists and neurologists) actively inquire about PGAD symptoms in women with restless legs and/or overactive bladder. Furthermore, although clonazepam shows some promising results, well-constructed studies are needed to find an evidence-based treatment for these potentially socially invalidating syndromes.

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THE EFFECTS OF EPO: FROM EPIC TO EPISODIC?

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Introduction

Perspective

The use of doping is still common practice in many competitive sports, despite strict supervision by the World-Anti-Doping Agency (WADA) and public rejection of doping users such as Lance Armstrong and other cyclists in the past. Interestingly, scientific evidence supporting the ban of certain doping substances turns out to be scarce. Researchers from the Centre for Human Drug Research (CHDR) in Leiden questioned the performance-enhancing ability of recombinant human erythropoietin (rHuEPO), an infamous type of blood doping. In a recent double-blind, randomized, placebo-controlled trial, they proved that rHuEPO did not significantly improve the performance of well-trained cyclists in representative exercise tests. Here, we discuss the introduction and development of rHuEPO in medicine and sports (medicine). Looking critically at the CHDR study, both the evidence on its stimulating effects and potential adverse effects will be evaluated. Finally, we speculate about the potential concerns when EPO turns out to be nothing more than a placebo.

About EPO

Erythropoietin (EPO) is a hormone produced by the kidneys that regulate red blood cell production (RBC) in the bone marrow. Additionally, this glycoprotein is crucial for the synthesis and functioning of several erythrocyte membrane proteins, particularly those facilitating lactate exchange. Normally, this hormone is released after a decline in RBC concentration or a decrease in arterial blood pressure [1]. The first time researchers discovered the effects of erythropoietin was in 1863, when Denis Jourdanet found that people living at high altitude had more viscous blood than those living at sea level. Soon it became known that hypoxia or a loss of red blood cells seemed to stimulate red blood cell production. Evidence for a humoral factor influencing erythropoiesis came in 1906, discovered by professor Paul Carnot. He extracted serum from rabbits that had experienced bleeding and injected this into healthy recipient rabbits, resulting in increased red blood cell production in the recipient rabbits. In 1977, EPO was purified for the first time and a few years later it was discovered that exogenous recombinant human EPO, rHuEPO, was effective as a treatment in anaemic renal disease patients. In the late '80s, the Food and Drug Administration (FDA) approved rHuEPO and since then it has been used to treat patients with chronic renal failure, as well as anaemic HIV patients, cancer patients with anaemia-induced chemotherapy and pregnant and anaemic women [2]. A six-week treatment with EPO increases haemoglobin and haematocrit (the percentage of RBCs in whole blood) with 12%, which was - at least previously - supposed to improve endurance exercise performance. Self-administration is believed to increase haematocrit levels by even more than 60% [1].

Shortly after the FDA gave approval for the therapeutic use of rHuEPO, athletes discovered the potential of EPO to enhance their performance and soon the widespread use of rHuEPO was a fact, especially in endurance sports [3]. In the early '90s, the use of rHuEPO was officially banned as a performance enhancing substance as it was assumed to result in unfair play [4]. Since its abuse could not be detected at that time, haematocrit was used as an indirect measure, with a maximum allowed of 50% [5]. The first doping-test for artificial EPO was introduced at the Olympic Games in 2000 and was composed of blood screening combined with a urine test [4]. Other detection methods are the use of serum blood markers and electrophoretic testing of urine and blood [3]. Since 2000, new detection methods for EPO have been developed with refined sensitivity and new interpretation criteria [4]. However, it remains difficult to detect exogenous EPO [6,7], either because athletes - or their (team) doctors - will develop ways to mask the use of the substance or because new types of EPO will become available, e.g. with a shorter half-life. This is typical for the continuous 'doping arms race' between WADA and athletes or their support teams.

The efficacy of EPO

The demonstrated increase in haematocrit and VO_{2max} after EPO injections leads to the assumption that EPO has performance enhancing abilities. In 2013, however, a research group from the CHDR published a qualitative systematic review of the available literature on the actual effect of EPO, in which the authors concluded that there is a lack of evidence concerning the efficacy of rHuEPO on endurance performance in elite cyclists [8].

In their review, Heuberger et al. explain that many studies on the effects of rHuEPO in cyclists are difficult to translate to real-life cycling performance. First of all, a population mismatch between the study population and professional cyclists often exists. Many studies included either 'recreational athletes', 'well-trained individuals' or 'healthy normal subjects', but - albeit logically - never professional cyclists. In some cases, the level of training of the study population was not even reported, but it was clear that none of the subjects would be able to compete with professionals. Secondly, eight out of thirteen studies were placebo-controlled, only five of which were double-blinded. Finally, the measure VO_{2max}, e.g. the maximal oxygen uptake, was often reported primarily, whereas other endurance performance factors remained unstudied. In the review, four main key factors are mentioned that influence and determine the endurance performance of elite cyclists: VO_{2max}, the lactate threshold (LT, reflecting the onset of anaerobic metabolism), work economy (C, the ratio of speed or power and oxygen cost) and the lactate turnpoint (LTP, when lactate concentrations suddenly rise in a sustained manner). The authors claim that the relative importance of each factor varies per training level: whereas moderately trained athletes can easily improve all factors, elite athletes can mainly increase performance by adapting LT, LTP and C. In line with this, they suggest it would be more relevant to look at the effect of EPO on submaximal intensities. Professional cyclists often compete in multi-day events (e.g. the Tour de France), during which they need to distribute their powers and only work for a small amount of time at their peak intensities, approaching only 3% of the total race time [9,10]. Other performance-related factors that could additionally be taken into account include capillary density, heart rate and volume, muscle mass and breathing pattern.

The authors conclude that not VO_{2max} distinguishes recreational from professional athletes, but rather other parameters such as LT and C, which is why these parameters should be studied. Furthermore, the methodologic quality of studies on rHuEPO should be increased regarding both design and study population. In addition, the awareness of the possible harmful effects of rHuEPO in athletes should be raised. Next to some case reports on professional cyclists, patient studies have reported several negative cardiovascular effects, an increased risk of thrombotic events, encephalopathy and other complications. The authors suggest these risks may be even higher in cyclists, due to improper handling and storage of rHuEPO associated with its illicit use. Further research on the effectiveness of rHuEPO on endurance performance in professional cyclists may elucidate the matter. According to the authors, it may even incline cyclists to stop taking rHuEPO and officials to cease the costly and perhaps unnecessary efforts to detect rHuEPO [8].

The CHDR study

To put this into practice, the same researchers from the CHDR set up an experiment to determine the actual effect of EPO on sports performance [11]. Forty-eight well-trained, Dutch cyclists (male, 18-50 years) were recruited and divided into two groups: one received a weekly injection of rHuEPO, the other received a placebo. Both researchers and athletes were blinded for the treatment. During eight weeks of therapy and training, the performance of the athletes was monitored in maximal and submaximal exercise tests. The study was concluded with an uphill road race on the Mt. Ventoux, to more closely mimic the "clinical" setting. In addition to exercise performance as primary outcomes, the occurrence of adverse events was reported. This study by Heuberger et al. showed that rHuEPO significantly improved performance in maximal exercise test, but submaximal exercise test performance and road race performance - supposed to be more clinically relevant - were unchanged. Additionally, except for increased thrombogenic markers in rHuEPO-users, no difference was observed in incidence or severity of adverse effects between study groups [11].

In two controversial ways, the CHDR study marks a turning point in doping history. On the one hand, it weakens the effect of a substance that has been used intensively by many professional cyclists in the 1990s and 2000s. On the other hand, as claimed by the authors, the study design provides a basis for subsequent clinical trials into the (adverse) effects of other potential doping substances. Still, the study definitely has its limitations. Although participants were carefully selected, their performance can - inevitably - still not be fully compared to elite cyclists. According to the authors, the VO_{2max} and maximal power output of the subjects are similar to those of elite-cyclists when tested in a relatively long, more representative protocol. They seem, however, to have forgotten the contribution of other relevant parameters as discussed in their review: the comparison of factors such as LT and C with those of professional cyclists is lacking. Moreover, it should be noted that the amateur cyclists tested are physically less adapted to cycling performance regarding, for example, capillary density, muscle mass and breathing pattern. The effect of rHuEPO could potentially be more pronounced when all factors are optimised, like in professional cyclists. To make it even more complicated, other studies have suggested effects of EPO on, for instance, recovery after exercise, skeletal muscle or motivation. In case rHuEPO partially or only has an effect on these parameters, the current study protocol is suboptimal, as the authors acknowledge. Furthermore, we doubt whether the authors possess all information on rHuEPO use from back in the days. Although the researchers claim to have used similar doses as known practices in cycling (based on a book by Olympic gold medalist Tyler Hamilton), the administration of rHuEPO in their study is more controlled and safer compared to that in the real-life, illicit and therefore, obscure practice. For this reason, also the severity of the side effects in the CHDR study might be an underestimation. Finally, during the '90s and '00s, a period known for the widespread use of rHuEPO, cyclists did not limit their doping supply to EPO: testosterone, steroids and later, blood transfusions, were common practice as well [12]. Although this justifies the aim of the CHDR study - what does rHuEPO actually contribute? - it also complicates the relevance of the study design. Perhaps it was a combination of substances that lead to peak performance.

Further speculations

Irrespective of the translatability of the CHDR study, its results call for new questions. For instance, what if rHuEPO does not enhance endurance performance in professional cyclists? It is important to note that encouraging fair play is not the only reason why WADA promotes a clean sports culture. The agency also aims to protect athletes from the dangers and consequences of doping use. The safety of rHuEPO can still not be warranted, based on both patient studies and case reports on professional cyclists. Despite some translational limitations, the CHDR study might comprise a small ray of hope by offering a study protocol for further clinical trials into performance-enhancing drugs. This will often be too late for the cheating athlete, though, who will keep looking for novel substances and methods that are not yet under investigation. Finally, would we advocate for compensation for the athletes that were tested positive and suspended? Probably not, as the athletes broke the existing rules and thus intended to cheat. It is, moreover, not unlikely that these athletes used multiple doping substances to maximally enhance performance. And if they did not, they did quite well on a placebo!

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SURGICAL MANAGEMENT AND OUTCOME OF ISOLATED, NONSYNDROMIC SAGITTAL SUTURE CRANIOSYNOSTOSIS

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Abstract

Review

Craniosynostosis jeopardises neonatal development both neurologically and physically. Surgical intervention is the main treatment strategy, though the method and timing of this surgery varies depending on the child's specific form of craniosynostosis and the parents/doctors' personal preference. To date, there is no internationally agreed consensus on the safest and most aesthetically efficacious method. In this article we summarise the pathophysiology of the disease, with a brief mention of the current understanding of the aetiology, to thus provide the basis for comparing the three main surgical intervention methods: spring-assisted cranioplasty (SAC), cranial vault remodelling (CVR) and strip craniectomy (SC).

Introduction

Craniosynostosis (cranio (skull); syn (together); ostosis (bone)), first described by Otto in 1830, is when one or more of the fibrous sutures in a neonate's skull ossifies prematurely. This has consequences for cranial and cephalic development by limiting the expansion perpendicular to the fused suture. You may think of the condition as an expanding balloon (the cranial vault with growing brain) that has been pinched at a specific section of the material so that expansion can only occur around this hindrance. It may be an isolated defect or a symptom of a syndrome – for example the Apert, Crouzon or Pfeiffer syndromes. Craniosynostosis on average presents in 1 in 2000 to 2500 births worldwide, of which 75% of the cases are boys. Saggital/scaphocephalic synostosis is the most common of nonsyndromic cases (50%), then coronal/anterior palgiocephalic (25%), metopic/trigonocephalic (10%), complex (10%) and lambdoid/posterior palgiocephalic (5%) (Figure 1,2) [1,2]. The prognosis of craniosynostosis is often bleak without surgical intervention. The "expanding brain in a rigid skull" means that there are almost always abnormalities in head shape and facial features as the unaffected suture regions undergo compensatory overgrowth to preserve the volume needed for normal brain growth. More severely, it may result in brain underdevelopment and cranial hypertension, which in turn may cause mental retardation, visual impairment, obstructive sleep apnea, and the Chiari malformation: the four most severe complications [3]. In this literature review we aim to compare the three main treatment forms, spring-assisted cranioplasty (SAC), cranial vault remodelling (CVR), and strip craniectomy (SC), using isolated, nonsyndromic sagittal synostosis as our case study. This is significant as these traditional treatment approaches involve surgical remodelling of the cranium and face, which carry significant morbidity and mortality risks. The future of craniosynostosis care looks to rely upon optimising these operations and on more effective screening and prenatal treatment.

Pathophysiology

To appreciate the pathophysiology, we must first understand the normal physiology. In normal skull development, ossification of the cranial vault commences around day 25 of gestation in the centre of each cranial bone, extending outward to the cranial suture [4]. The cranium is formed of eight bones separated by sutures: the sagittal suture to separate the two parietal bones; the coronal to separate the two frontal bones from the parietal bones; the metopic to separate the two frontal bones; the lambdoid separating the occipital bone from the two parietal bones.

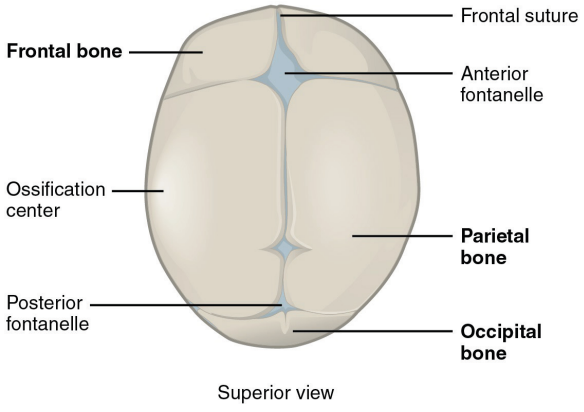

Figure 1: *Normal skull of the newborn*

Normal expansion occurs perpendicular to each suture: the anatomy allows expansion to be distributed across the entire skull. The sutures of the skull grow in response to tension within them generated by intracranial pressure. Thus, the primary factor that keeps sutures open is ongoing brain growth - as illustrated by the synonymously small cranium that is symptomatic of microcephaly.

If a suture fuses before 12 months of age, but typically before birth (craniosynostosis), skull growth is restricted perpendicular to the affected suture before the cranium has finished growing. In order to accommodate the growing brain, compensatory skull growth occurs parallel to the affected suture. The resulting skull deformity is dependent upon which suture(s) is/are affected. Scaphocephaly (from the Latin scaphoid, meaning boat) is the deformity where the sagittal suture is solely affected, resulting in restricted lateral expansion and compensatory anteroposterior growth, namely growth at the coronal and lambdoid sutures. The neonate presents with frontal bossing and occipital coning. This is the most common craniosynostosis.

The aetiology of isolated, nonsyndromic craniosynostosis is still to be elucidated, though the associated syndromes provide some light on possible mutational causes: most syndromes show mutations in the genes that code fibroblast growth factor receptor (FGFR) [5]. Though management is mostly focused on surgical remodelling of the neonate's skull, it is important to note the future potential therapeutic interventions using prenatal/intrauterine methods based on evolving molecular and genetic

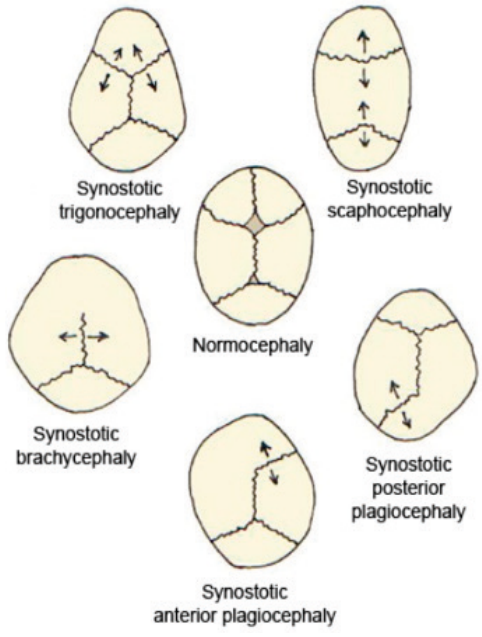

Figure 2: *Different types of craniosynostosis*

understanding (Wan DC, 2008). Three of the four FGFRs have been associated with premature pathologic suture fusions, providing a doorway for pharmacotherapeutics.

Surgical management

Surgical interventions for sagittal suture craniosynostosis aim to sufficiently remodel calvarial shape for brain development, reduce intracranial pressure (ICP), and improve aesthetic appearance. The primary aesthetic measure of most studies concerning surgical intervention for scaphocephaly is the cephalic index (CI) – the biparietal diameter (width) of the head multiplied by 100 and divided by its occipitofrontal diameter (length). To date there are three main treatment forms: spring-assisted cranioplasty (SAC), cranial vault remodelling (CVR), and strip craniectomy (SC). SAC involves a small-scale craniectomy at the fusion, small osteotomies either side of the fused sagittal suture and the placement of metal springs that gradually widen the gap to encourage new osteogenesis between the two cut surfaces. CVR involves open surgery to temporarily remove the cranium (a craniotomy), reshaping of these removed bones, and reinsertion of these bones secured using synthetic plates and dissolving secures. CVR is the most invasive procedure. SC is performed by placing small incisions at both ends of the sagittal suture, through which the fused suture and approximately two inches of surrounding bone is removed. SC is the least invasive but requires the use of a moulding helmet to guide the bone growth.

With regard to timing, there is a distinction to operate before or between 6 and 12 months – almost all surgeries occur within the first year of life. Before six months the used techniques are the SAC or SC. After six months, more commonly an open CVR is performed. The best treatment of craniosynostosis would keep blood loss and recovery time to a minimum, whilst achieving the desired intracranial volume. Note that, unsurprisingly, when there is an associated syndrome involved the mortality and morbidity are higher because these children have an increased risk for complications and often a more challenging surgery [6].

Outcomes

The effectiveness of SAC has been compared to the modified pi-cranioplasty regarding morphological outcomes and procedure safety – there needs to be an increase in the baby's intracranial volume and the establishment a more "normal" craniofacial appearance. All three techniques achieve a relatively similar morphological outcome. The pi-plasty group has a CI slightly closer to the normal range at the age of 3, than after SAC. But regarding blood loss, transfusion requirements, operative time, ICU time, recovery time and total hospital stay the SAC group was superior compared to the pi-cranioplasty group [7]. Additionally, endoscope-assisted surgery is also commonly used in sagittal craniosynostosis surgery. Iyer et al. [8] concluded that a single incision technique improves the classical surgical procedure by decreasing invasiveness, reduces intraoperative blood loss, reduces surgery time and has a cosmetic advantage because only one incision must be made. After six months, the techniques above are limited in their efficacy. In this case CVR is performed.

Chummun et al. [9] compared CI after different types of CVR: the open calvarial, subtotal remodelling and the more conservative strip craniectomy. The results showed an improvement in the CI after all types of cranial vault remodelling. The open calvarial vault surgery resulted in a greater CI and a more mesocephalic shaped head. However, the age at which the surgery was performed varied considerably, so a selection bias cannot be excluded. Gerety et al. [10] demonstrate that CVR, SC and SAC provide adequate correction of CI in the short term. When CVR is compared with SMC, no significant difference in correction of CI was observed (weighted mean difference (WMD = 0.94 (95% CI: -0.23-2.11; I^2=55%, p = 0.12)). When compared with SC, CVR creates a small but significantly greater improvement in CI (WMD = 1.47 (95% CI: 0.47-2.48; I^2=66%, p = 0.004)). Average postoperative CI was correlated with average follow-up across techniques; this correlation demonstrated that as average follow-up increased, CI increased in the SC and SMC groups and decreased in the CVR group.

In a systematic review conducted by Maltese et al. [11], two out of the three studies involving the use of SAC did not show any difference in postoperative CI between the methods, while the third study showed

Table 1: *Comparisons of the different types of surgery*

	Spring-assisted Cranioplasty	Cranial Vault Remodelling	Strip Craniectomy
Performed	3-8 months of age	> 6 months of age	< 6 months of age
Procedure time	3-4 hours	5-6 hours	2-3 hours
Recovery time	2-3 days	4-7 days	2 days
Blood transfusion rates (% of total blood)	~50%	Highest (~100% blood transfusion)	~50%
Aesthetics (scarring, CI)	Sagittal scars; normal CI	Ear-to-ear scar; normal CI	Two scars on top of scalp (anterior and posterior); normal CI
Other notes	Will require a second surgery 8-12 weeks after in order to remove the springs		Helmet required

that SAC was slightly worse than the pi-plasty technique. Since the studies had a high risk of bias, it can be concluded that it is uncertain whether the SAC technique is comparable to alternative techniques regarding CI as outcome. However, it should be noted that the quality of evidence was very low.

Conclusion

The prognosis of craniosynostosis is often bleak without surgical intervention. Based on the literature, surgical intervention procures a better prognosis than no intervention. Nowadays there is a broad range of modern surgical techniques available to treat sagittal craniosynostosis. All the techniques reach an improvement in the CI and reduce ICP. The pi-plasty reaches a more 'normal' skull, the SAC and endoscope-assisted techniques score better on factors like blood loss. After six months, the CVR involves more complications but also reaches a CI enhancement.

Future research

Further research may focus on standardisation of the mean human skull, comparative surgical reduction of morbidity and generating international care guidelines, as presented by the working group of craniosynostosis from the Netherlands. This can be reached by performing an RCT where the different surgical techniques are compared and the CI is mapped as well as international collaboration into the neuro-cognitive development assessed with IQ postoperatively.

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INTERNATIONAL SUMMER SCHOOL NEUROSURGERY: BRIDGING GAPS

RAMS is and will always be about inspiring people, exchanging knowledge and creating engaging communities of aspiring academics. Every year, an omnifarious set of lectures, workshops and journals is presented to an audience of students and staff of Radboud University and the Radboud University Medical Center. A new chapter was started this summer, when RAMS organised its premiere major international event: the very first International Summer School in Neurosurgery, bridging gaps for the second year in a row after the successful first Nijmegen edition last year.

Students from all over Europe and beyond took part in a week full of engaging and motivating activities. Together with the staff of the Neurosurgical Centre Nijmegen (NCCN) and various national and international European collaborators, many lectures, discussions and workshops were organised by the Summer School Committee to emerge forty students in the field of neurosurgery. In addition to taking part in discussions covering future perspectives and state-of-the-art operating procedures, students discussed neuroanatomy in the dissection rooms of the medical faculty, performed surgery with professional Stryker equipment on 3D-printed crania from Delta Surgical and presented their own ideas and expectations of the field in front of a jury of neurosurgical representatives.

Bridging gaps is all about finding a fitting interdisciplinary approach, which the committee found in a collaboration with the Donders Institute for Brain, Cognition and Behaviour. This way, the Summer School not only covered neurosurgical practice, but students also discussed neuroscientific backgrounds and were encouraged to extrapolate research questions from the various activities.

The evaluation of the participants was very positive and will be of great help for RAMS' future international activities. RAMS has entered a new era of international activities and will continue its journey, giving voice to academic potential.

Special thanks to the Summer School Committee for making the International Summerschool unforgettable: Jules Janssen Daalen, Dirk Loeffen, Jill Martens, Barof Sanaan and Daan Viering.

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 [1]. 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

Stem cells as origin of relapse in AML

Long term-survival in acute myeloid leukaemia (AML) is poor because most patients relapse despite initially successful therapy. Previously, the occurrence of relapse was thought to be due to chemotherapy-induced mutations, leading to the development of drug-resistant tumour cells. Researchers from Toronto have now demonstrated that already before diagnosis, therapy resistant tumour cells are present in patients' blood. Peripheral blood mononuclear cells were collected from 11 AML patients at both diagnosis and relapse and thereafter transplanted into immunodeficient mice. Genetic and functional analysis of purified subpopulations and xenografts revealed the complex evolution of AML within individual patients during the course of the disease. In some instances, the cellular origin relapse could be traced back to a rare, stem-cell like population. In other cases, relapse developed from larger subgroups of leukaemia cells retaining strong stemness transcriptional signatures. Both relapse patterns confirmed the previously-identified relevance of cancer stem cells in AML and strongly suggest the development of new therapeutic strategies targeting this stemness in AML, and eventually, also in other types of cancer [2]. Rene Marke, currently a researcher at the Department of Pediatric Oncology, performed his MMD Master thesis in this research group and contributed to the work.

Expensive, toxic therapy more effective in HIV-associated Talaromycosis

Infection with the fungus Talaromyces marneffei, or Talaromycosis, is a major cause of human immunodeficiency-related (HIV) death. International guidelines recommend initial treatment with amphotericin B deoxycholate (amphotericin), which is associated with toxic effects and high costs, followed by itraconazole therapy, with fewer side effects and available in a cheaper, oral form. Randomised clinical trials evaluating these treatment strategies were lacking until now. Prof. dr Wertheim from the department of Medical Microbiology contributed to an international collaboration that compared both regimens in a 24-week open-label, noninferiority trial in Vietnamese HIV-patients (n=440). Despite significantly higher prevalence of adverse events such as infusion-related reactions, renal failure, hypokalemia and -magnesia and anaemia, amphotericin treatment resulted in a lower risk of death at the end point of week 24 (11.3% vs. 21.0%) and was associated with a better clinical response and higher fungicidal activity than treatment with itraconazole alone. The data also suggest that amphotericin treatment could be shortened, as sterile cultures were obtained already after 8 days (versus 14 days of treatment). This would reduce the number of toxic effects and could reduce treatment associated costs [3].

The IL-1 cytokine family in hematological disorders

In a Blood-review, researchers from the Radboudumc (a.o. Department of Hematology), discuss the family and pathway of IL-1, 'the master cytokine of inflammation', in hematological patients. The role of the IL-1 family is dichotomous: IL-1 is involved in the local and systemic inflammatory responses during infection, but its dysregulated production in signalling can aggravate tissue damage during infection, inflammatory diseases and chemotherapy-induced mucosal barrier injury (MBI). The authors shortly introduce the different members of the cytokine family, explain its pathophysiological contribution to hematological malignancies and review studies in which the IL-1 pathway was targeted to treat these malignancies. Inhibition of IL-1 to relieve cancer-therapy induced complications, such as MBI and graft-versus-host disease, are also discussed, followed by the limitations of targeting IL-1. The authors emphasize the need for further research into the role of IL-1 targeting in hematological malignancies where a proinflammatory microenvironment and dysregulated signalling are implicated in disease development. Additionally, the role of IL-1 in cancer therapy-related or post-stem cell transplantation complications could be studied. Despite the complexities of these clinical settings and the dual role of the IL-1 family members, the authors are very optimistic about IL-1 as a therapeutic target in hematology [4].

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A Word from the Board of RAMS

William Shakespeare once wrote a line in his tragedy Hamlet (act 4, scene 5): "We know what we are, but know not what we may be".

As former board member Public Relations and current Chair of RAMS, I am proud to say that last year has been phenomenal for RAMS. The extraordinary team of enthusiastic (bio)medical students of RAMS gave the Faculty of Medical Sciences a scientific boost. Besides the three beautiful RAMS-editions last year, RAMS organized a couple of masterclasses and two marvellous symposia about 'Forensic Medicine' and 'Sports Medicine'. In addition, last academic year ended spectacularly with a Summer School about neurosurgery. It was the first time RAMS organized an International Summer School and it was fantastic! Forty students from all over the world visited Nijmegen to participate in this inspiring week. It was definitely worth repeating!

A great year passed by and I am convinced RAMS can become even bigger and more successful in the upcoming years. As Shakespeare wrote, we cannot know where we will be standing as RAMS next year. However, dreaming gives birth to growth. A new chapter of RAMS is waiting to be written. A new academic year, a fresh start, and brilliant ideas. The new general and editorial board is ready to write this chapter, but we cannot do this on our own. Did you write a research article, a case report or an essay? Do not hesitate. Seize the opportunity and submit your article to *www.ramsresearch.nl*.

Our first symposium of the academic year 2017-2018 will take place in November. Visit *www.ramsresearch.nl* and like our Facebook page at *www.facebook.com/ramsresearch* for the latest updates.

Cheers to a new academic year and a chance for us to write a new chapter.

Carmen Lageweg
Chair of RAMS 2017-2018

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.

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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 masterclasses and use of their own specific knowledge, the reviewers are able to judge the submitted scientific articles.

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