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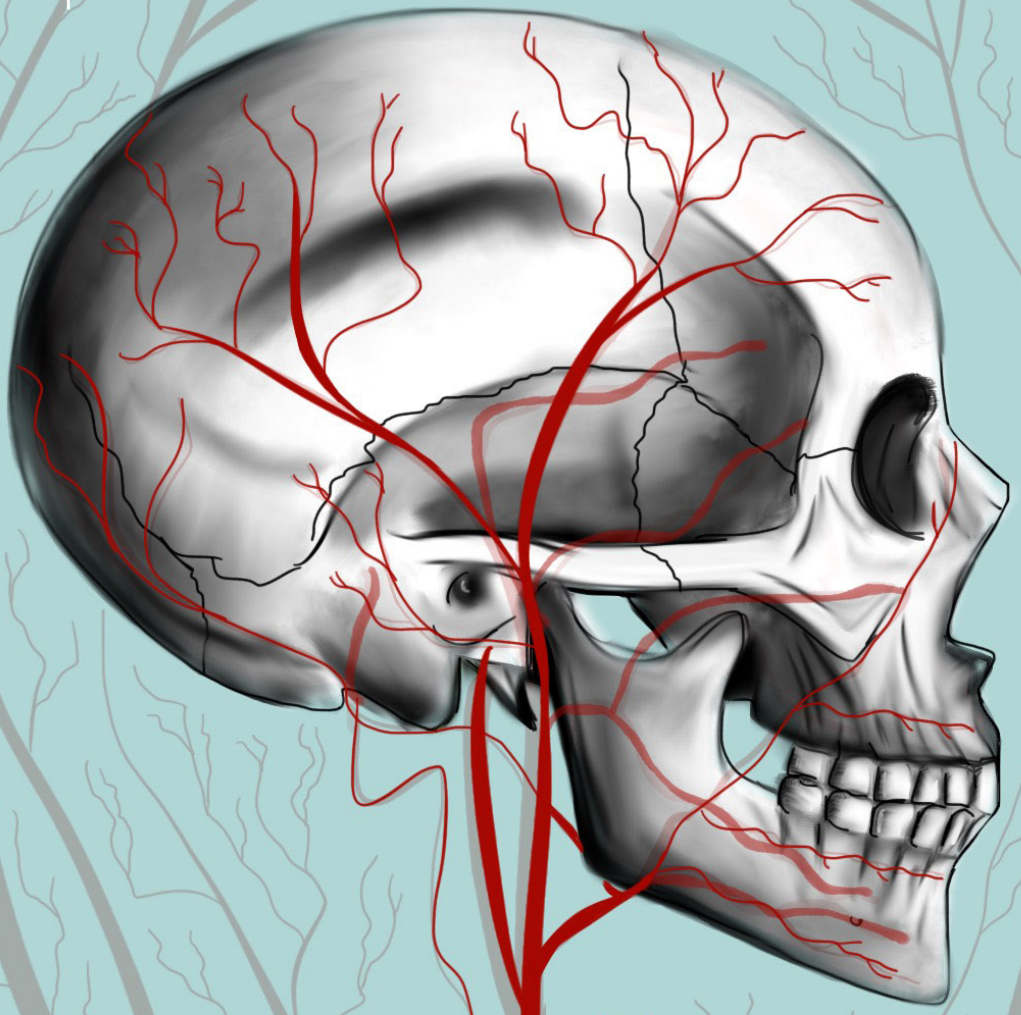

A-HEAD OF THE REST

Featuring: Facing the Future with Virtual Surgery

New: Swan Medal Essay Winner

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The Editorial Team is extremely grateful for the continued support from its donors and would in particular like to thank all its anonymous donors.

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Review Article

Finding the Needle in a Haystack: The Dominance of the Systematic Review

Nicholas Arrotta

Whenever I mention the term 'research' to my family, friends, and colleagues, their gaze drift skyward as they envision a serene laboratory full of flasks spewing colorful gaseous elements. Of course, in this elusive laboratory, all the paraphernalia is minded by Pinky and the Brain, and organized in an array of endless computers and test tubes illuminated by neon lights. Yes, there are basic medical science laboratories - the term basic refers to a fundamental type of research that seeks to improve understanding of phenomena, not rudimentary or unimportant work - that aren't too far removed from this fantastical notion. And yes, these labs provide a vital and everlasting contribution to the medical community. Without reservation, it is an understatement to say that without basic science laboratories, the vast majority of medical advancements we take for granted would cease to exist. I do not think anyone disputes this.

The immense amount of data generated from basic medical science laboratories increases every year. What most individuals -- both those involved and not involved in the medical community -- fail to consider is how all this information is amalgamated in to a story. Alas, a type of research endeavor that works to synthesize all available information from all over the world, in all languages, from all dates, in to a collective conclusion, doesn't have the shimmer and glory of the fantasy medical laboratory.

But to me, this type of scientific work sounds perfect: it's called a Systematic Review.

It's logical to think that, based on what basic medical laboratory labs must be like, these systematic review labs must be at a quantum stage of complexity; but, in reality, they most likely harbor your average computer in your average office. It's not the hardware or fancy laboratory instruments that make systematic reviews dominate the scientific community, but rather the scientific team behind the process.

In short, a systematic review uses a systematic approach to search nearly all available scientific literature to answer a question. Simple, straightforward, and immensely effective. You begin with defining a query. You then set your target population, the intervention of interest, and comparison to another intervention or control. Finally, you establish the outcomes of your study. In a world with exponential growth of medical information, the systematic review seeks to find the needle in the haystack of what type of data you're exactly looking for. It combines the conclusions from nearly every study of a topic of choice, ideally, using an unbiased methodology.

Basic science literature can produce breathtaking images, complex graphs, and unique figures. Of course, this draws the attention of any reader. However, when data is compiled, compared, and a conclusion is drawn in a systematic review, it really isn't much for the eye to behold -- maybe a table riddled with numbers, or charts here and there. To the new reader, it may look like every other systematic review is the same since most share similar types of tables and figures to keep their data presentation consistent. However, the ability to sift through so much data in a comprehensive and rigorous way, and present it in a neat, tidy, consistent, and logical format, is a powerful tool. The effort and time invested in a single basic science study to derive one conclusion can take years of dedication. A systematic review both acknowledges and compiles the effort of those involved in all these studies and tells a story. This an amazing feat. The seemingly mundane numbers and tables may not make the front cover of the leading scientific journal since, well, they're just plain numbers – they're not that pretty. But, what they represent significantly affects decision making and ultimately how medicine is practiced and how we live our lives.

The next time your eyes are half shut in the early hours of the morning, scrambling through every database to hunt down a manuscript to include in your own research paper, do not discount the paper that is titled 'systematic review'. Although it may not have the appeal and allure of an original research article and drain the color ink cartridge of your printer, the power and utility of its data is astronomical. It truly assimilates the work of the medical science community in to a message that can alter how we live our daily lives.

Virtual Surgery: Facing the Future!

Stephanie Rose

Background

In 1979, Hounsfield and Cormack won the Nobel Prize for medicine and physiology for their part in the invention of the CT scanner (Peeters et al, 1979). These images allowed human anatomy to be viewed in 3 dimensions for the first time, revolutionising medicine. Virtual surgical planning was used for the first time in craniofacial surgery during the 1980's (Vannier et al, 1984). With increasing popularity, computer technology now encompasses a number of uses in addition to surgical planning, across a number of specialities such as neurosurgery, cardiothoracics, plastics, ENT and orthopaedics. This report describes the use of a virtual surgical planning in an interesting maxillofacial case.

Presentation of Case

A 42 year old female Nigerian refugee was referred to the maxillofacial department at St James Hospital with a 2 year history of a painless swelling in the anterior of the mandible. She was medically fit and well with no other associated symptoms, and no surgical history. She was a non-smoker and non-drinker.

On clinical examination, she had mild facial asymmetry with swelling around the left symphyseal/parasymphyseal region of the anterior mandible. Intra-orally there was buccal and lingual expansion of the mandible anteriorly (Figure 1) with mild displacement of the teeth. Of note, there was no sensory alteration in the inferior alveolar nerve distribution. All other examinations were normal.

Investigations and Diagnosis

Differential diagnosis for a firm swelling in the anterior mandible includes; an odontogenic (dental origin) tumour, cystic lesion, fibro-osseous lesion, or malignancy. In order to make a definitive diagnosis, the patient underwent a plain film radiograph, CT imaging, and a bone biopsy. The orthopantomogram radiograph (Figure 6A) revealed a lesion extending from the lower left first molar to the lower right premolars in the mandible of mixed radiodensity. The lesion appeared to be circumscribed by corticated bone (seen radiologically as a white line around the lesion) suggestive of slow growth and a benign process. This radiological appearance was most consistent with a fibro-osseous lesion such as ossifying fibroma, fibrous dysplaisa or a giant cell granuloma. However, an odontogenic tumour such as an ameloblastoma could not be ruled out. Histology from the bone biopsy showed cellular fibrous tissue with mineralised components of bone confirming a diagnosis of ossifying fibroma. This is a benign fibro-osseous lesion.

Management

Following a multi-disciplinary meeting, a team decision was made to resect the ossifying fibroma of the anterior mandible, and reconstruct the defect using a vascularised fibula free flap. Due to the long length of bone needed, virtual planning was used to achieve the best aesthetic and functional outcome. In order to do this, DICOM data (Digital Imaging and Communications in Medicine: the standard format for medical images to be exchanged) was uploaded into the virtual planning software (Materialise) and 3-Dimentional reconstructions of the skull and fibula were made (Figure 2).

The ossifying fibroma margins were identified and the osteotomies (surgical cutting of bone) of the mandible planned with a 1cm margin to reduce the recurrence rate (Figure 2). Once the mandible was virtually resected, the reconstruction phase could begin. Approximately 10 cm of bone from the distal portion of the right fibula was chosen, making sure to leave 6

cm of bone distally to maintain the stability of the ankle joint. This 10 cm length of bone would then be segmented into thirds to create a curved neo-mandible as shown in Figure 3.

To translate this virtual plan into the operating theatre, custom-made surgical guides were designed to screw to the mandible and fibula intra-operatively (Figure 2,3). Access to the mandible was made through a visor incision in the skin crease of the neck (Figure 4) which was then reflected upwards so the ossifying fibroma could be fully viewed, resected and the remaining defect assessed. Simultaneously, the pre-planned portion of fibula was then removed from the donor site with a vascular pedicle made up of the fibular artery and 2 accompanying vena comitantes. Once the pedicle was cut, the ischaemic time began (maximum 6 hours) and the fibula was segmented into three, shaped, and attached to the reconstruction plate (2 screws in each segment) and then to the mandible with 4 screws bilaterally. The fibula was placed mid mandible (Figure 5) as a compromise between the best aesthetic and functional outcomes. For best facial contour, the fibula should be set to the level of the inferior border of the mandible, whereas for best functional outcome, the fibula should be set higher up, with the flat aspect of this triangular shaped bone superiorly to facilitate the placement of dental implants 6 weeks post-operatively. The anastomoses of the flap to recipient vessels was performed under an operating microscope using 9/0 sutures. (Figure 5) The fibular artery was joined end to end to the facial artery, and the 2 vena comitantes were joined end to side to the internal jugular and one of its branches. Post-operatively the area of the arterial anastomoses was marked using a superficial suture on the skin so that doppler ultrasound could be used to monitor the free flap. As there was no skin paddle, assessment of colour, capillary refill, temperature, skin turgor or the pin-prick test was not feasible in this case.

Outcome and Follow-Up

One month following her surgery, the patient was recovering extremely well. She was independently mobilising and eating a soft minced diet. The pre- and post-operative radiographs (Figure 6) demonstrate the full resection of the ossifying fibroma and the reconstruction with the segmented fibular and reconstruction plate. At 6 weeks post-operation, placement of titanium dental implants into the fibula will allow restoration of the missing teeth.

Discussion

Vannier is praised with being the first to use the three dimensional CT reconstruction images for craniofacial virtual surgical planning (3D planning, computer-aided design) and evaluation in 1984. More recently however, CT images have been utilised for a number of additional uses; construction of 3D stereolithic models, intra-operative navigation, individual implant design and fabrication, and outcome assessment (Zhao et al, 2012). Potential benefits of virtual planning include ease of use, and in comparison to conventional planning, improved surgical accuracy and reduced intra-operating time that may be reflected in a decrease in cost (Rodby et al, 2014). Virtual planning usually consists of 4 phases, namely; planning, modeling, surgical phases and post-operative evaluation (Kirke et al, 2016). One disadvantage therefore is that the planning phase is prolonged usually taking a minimum of 2-4 weeks, which may not be appropriate for some cases. Other disadvantages include increased initial costs, issues with the placement of the surgical guide, and limited literature with regards to cost benefit and specific quantifiable benefits (Rodby et al, 2014). The present case was ideal for the incorporation of virtual technology as a long 10 cm defect was resected from the mandible,

Figures

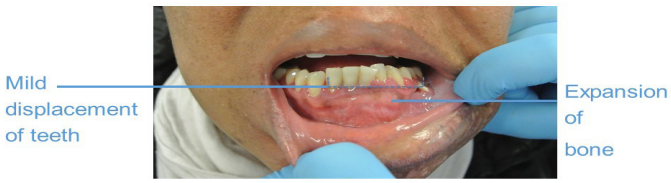

Figure 1. Clinical intra-oral photograph demonstrating bony expansion of ossifying fibroma

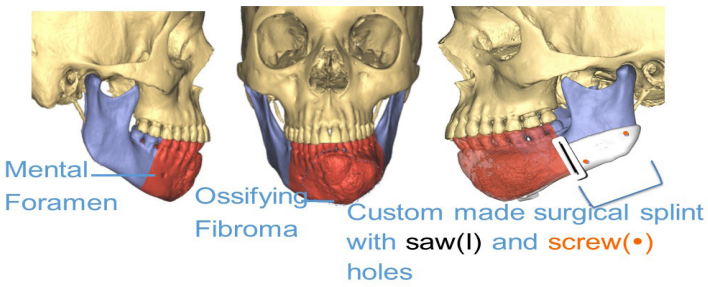

Figure 2. Digital reconstructions of facial skelton. Blue colour indicates mandible. Red colour indicates virtual planning of the proposed margins of the osteotomy.

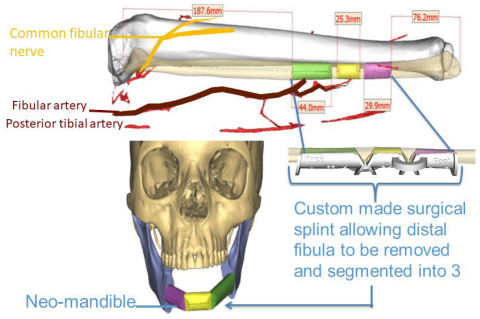

Figure 3. Virtual Planning of the reconstruction of the mandible. A distal portion of the fibula is planned to be cut into 3 segments using a surgical guide to reconstruct the shape of the mandible.

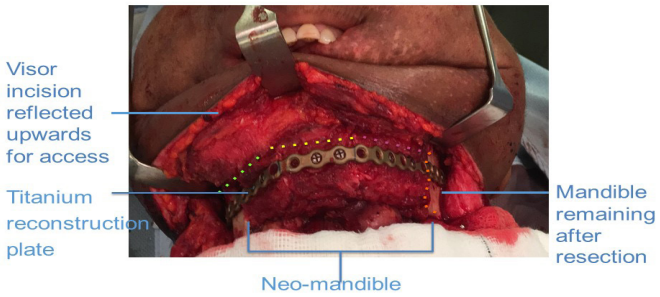

Figure 4. Intra-operative photograph of front view of neomandible fixed using reconstruction plate and screws, to remaining mandible.

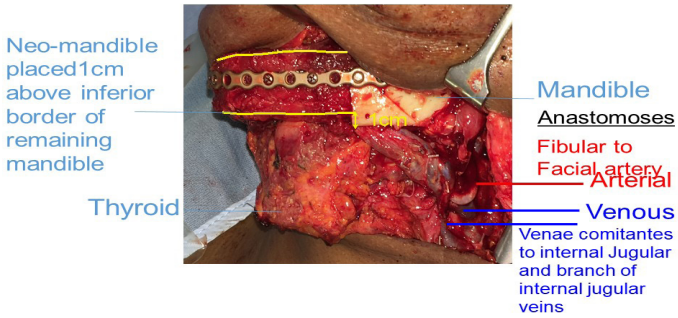

Figure 5. Intra-operative photograph. Side view of right side of the neomandible attached to remaining mandible posteriorly, and anastomoses.

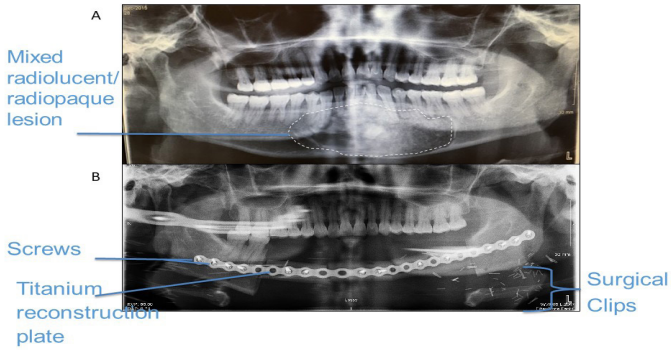

Figure 6. Pre and post operative plain film orthopantograms showing ossifying fibroma completely resected and reconstruction.

Table 1. Postive-negative analysis of free flap options. Adapted from information from Yilmaz et al, 2008.

Free flap	Pros	Cons
Fibula	Up to 25-30cm bone, excellent for dental implants Can include muscle bulk and skin paddle Allows 2 teams working simultaneously	Straight bone requires osteotomies for curvature Potential vascular compromise to the foot, foot drop (injury to common fibular nerve) and altered gait, and instability of ankle joint (avoided by keeping 6cm bone at distal end of fibula). Long scar along leg, possible need for skin graft
Iliac Crest	Natural curvature contoured for ipsilateral reconstruction Good vertical and horizontal height for dental implants Allows 2 teams working simultaneously	More difficult dissection Potential secondary hernias, pelvic pain, pelvic fracture or instability

including the symphasis (anterior region), which is a challenging defect to restore to a high standard using conventional methods. Expansion of the bone due to the OF meant that the mandible could not be used as a guide to pre-bend the reconstruction plate. Virtual technology allowed the expanded bone of the OF in the mandible to be virtually "shaved" by the surgeon to the desired shape, which could then be used to make 3D models and pre-bend the plate.

Ossifying fibromas (OF)

These are benign, well demarcated lesions composed of fibrocellular tissue and mineralised components such bone or cementum. They occur most frequently in females between the 2nd and 4th decades, although they can occur at any age. The mandible is more commonly involved than the maxilla (Slootweg and El-Mofty, 2005). Rarely, OFs may be found in the frontal, ethmoid, sphenoid, temporal bones, orbit and anterior cranial fossa (MacDonald-Jankowski 2014). Clinically, they present as slow expansion of the jaw bone which is often painless, as in the present case of the conventional OF. More aggressive subtypes, such as juvenile aggressive ossifying fibromas, also exist. Diagnosis is using a combination of orthopantogram plain X-ray demonstrating a lesion with ground glass appearance (Figure 6), CT imaging, and biopsy. OFs originate from the periodontal ligament of teeth and histopathology may aid in the distinction between OF and other fibro-osseous lesions. For example, fibrous dysplasia tends to have a more classical "Chinese lettering" appearance of the mineralised components, and merge more with its surroundings in contrast to the well demarcated/ encapsulated OF (Slootweg and El-Mofty, 2005).

Treatment options

OF is a benign process, and consequently the treatment options are curettage and enucleation, or resection. In the present case, the dimensions of the OF were so large that such an attempt at curettage and enucleation would most likely lead to instability of the anterior mandible and fracture. The anterior mandible is important for facial contour, aesthetics and function, as it contains teeth. It is the insertion point for the mylohyoid, genioglossus, geniohyoid and anterior belly of the digastric muscles. These muscles are important for airway stability, speech, deglutition, and mastication and consequently, any fracture could lead to serious

morbidity. The MDT decision was therefore to resect the anterior mandible.

There are a number of vascularised free flaps that have been used for reconstruction of mandibular defects in maxillofacial surgery. Bone and soft tissue may be included. Two types are summarised in Table 1 (Yilmaz et al, 2008). The fibula free flap was considered the best option in this case due to the length and quality of bone needed for restoration with dental implants 6 weeks post-operatively.

Potential complications

At the recipient site, flap failure, fixation failure or infection of the reconstruction plate, and injury to nearby structures were all potential complications. The patient was aware pre-operatively that both the left and right mental nerves (terminal branches of the mandibular branch of the trigeminal nerve) would be sacrificed as they were involved with the OF. During the consent process therefore the patient was fully aware she would have a numb lip and chin post-operatively. Also at risk, was the marginal mandibular division of the facial nerve that partially supplies the chin muscle mentalis, and is important for depressing the corners of the mouth.

A CT Angiogram of the lower limbs is performed pre-operatively to ensure 3-vessel run off to the foot (anterior, posterior tibial and fibular arteries) and ensure no vascular compromise is likely following flap harvesting. The common fibular nerve is preserved by leaving 6 cm of fibula proximally to avoid foot drop. Similarly 6cm of distal fibular is preserved, however this is to maintain the stability of the ankle.

Airway Management

In the case of head and neck surgery, the surgeon and anesthetist will often share the upper airway. In such cases a nasotrachel tube may be used, where an endotracheal tube or laryngeal mask airway would have otherwise been an option. In complex head and neck cases, it would be common to provide a tracheostomy surgical airway which is indicated where there is failure, or anticipated failure, to secure the airway in any other manor. In the present case, only the anterior mandible was removed, with no soft tissue resection or lymph node dissection; both potential causes of swelling and oedema that may threaten the airway. Therefore, the airway would be patent throughout the procedure, and the patient could be extubated the following morning. This allowed use of a nasotracheal tube, minimising the more morbid complications associated with a tracheostomy such as scarring, higher potential for bleeding, damage to the recurrent laryngeal nerves, pneumothorax, surgical emphysema and fistula formation.

Recovery

Recipient site:
The patient is fed by NG tube initially until the speech and language team are satisfied the swallow is intact (day 2 in the present case). The patient starts with sips of water and then is allowed a soft minced diet that must be maintained for 6 weeks until the placement of the dental implants is permitted.

Donor site:
At the donor site, the leg is kept elevated for the first 48 hours, after which the patient may ambulate with the use of a stroller. An orthopedic non-weight bearing splint is placed for 4-5 days, and removed at 5-7days at which point the patient is generally independently mobilising.

Conclusion

In conclusion, this case report describes the management of a 42 year old Nigerian lady diagnosed with an ossifying fibroma of the anterior mandible, and the use of virtual surgical planning for resection and reconstruction using a fibular free flap. The patient achieved an excellent surgical result and post-operative recovery was uneventful. In the future she will have her dentition restored with dental implants. This case demonstrates the use of virtual planning in a complex maxillofacial case, and reveals an insightful glimpse in to the direction of surgery in the future.

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Targeting the Inflammasome: A cure for Alzheimer's disease?

Mark Milner

Alzheimer's disease is the most common neurodegenerative disease in the world. Despite years of intense research, its pathogenesis remains quite controversial. Many different explanations have been proposed to describe its onset, the most established of which is the β-amyloid hypothesis. This hypothesis proposes that the disease is primarily caused by the formation of β-amyloid plaques in the brain. The presence of these plaques, it is suggested, ultimately leads to neuroinflammation, tau aggregation and, eventually, neuronal death and the often-cited neurocognitive sequelae observed in Alzheimer's patients. However, recent evidence suggests neuroinflammation may in fact be a root cause of the disease as opposed to acting as an eventual or coincidental manifestation. More specifically, it has been found that the activation of inflammasomes in microglia (the brains immune cells) contributes to the production of proinflammatory cytokines which then potentiates the neuroinflammatory response, with other downstream affects including increased β-amyloid plaque build-up, tau aggregation and a loss in cognitive function. Therefore, more and more studies are suggesting that neuroinflammation - and particularly the inflammasome - could be targeted therapeutically to prevent and treat Alzheimer's disease in patients.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world affecting more than 5 million people over the age of 65. It is often characterised clinically by a decline in cognitive function, worsening performance in the arenas of learning and memory and a battery of other, related behavioural issues (Anand et al., 2014). To date, while a proportion of patients are able to alleviate symptoms somewhat, an AD cure remains elusive. It is often believed that to identify novel therapeutic targets in the treatment of AD patients, both the macroscopic and molecular pathogenesis of the disease must be clearly understood.

This has been the subject of challenging research for many years and has culminated in the proposal of many hypotheses. This profound explanatory list includes the β-amyloid hypothesis, the cholinergic hypothesis, the tau tangle hypothesis, and the inflammatory hypothesis (Kurz & Perneczky, 2011) – with some crossover between ideas. Although the official pathogenesis of the disease remains controversial, it has been generally accepted that amyloid plaques and neurofibrillary tangles (NFTs) are the key features contributing to the pathogenesis of the disease (Ramirez-Bermudez, 2012) – especially given that these features are present in the autopsied brains of AD patients (Buée et al., 2000). Amyloid plaques are deposits of β-amyloid protein (Aβ) in the brain. Aβ is produced by neurons from amyloid precursor protein (APP) present in their membrane. APP is cleaved by enzymes, β-secretase and γ-secretase, to form Aβ in the extracellular matrix. NFTs on the other hand are composed of helical, hyperphosphorylated tau proteins. Over time NFTs destabilise axonal transport in neurons (Roberson et al., 2007; Shipton et al., 2011; Vossel et al., 2010) and result in interruptions in synaptic transmission, neural and synaptic loss, and ultimately leads to cognitive defects (Anand et al., 2014).

Although the Aβ hypothesis is widely accepted as the root cause of AD, certain experimental evidence calls the role of Aβ into question. It is interesting to note that while low levels of Aβ are found in all aged brains, only some individuals go on to develop AD (Lesné et al., 2013). Furthermore, while the experimental concentration of Aβ needed to simulate the toxicity observed in the AD brain have been found to be in the micromolar range (Forloni et al., 1993; May et al., 1992; Yankner et al., 1989), the concentrations of Aβ actually found in the brain of AD patients is in the much lower picomolar concentration (Brody et al., 2008; Steinerman et al., 2008; Xia et al., 2009). This is

complicated by the in vitro studies examining induced pluripotent stem cell (iPSC) neurons from AD patients, which found that neuronal Aβ production was inconsistent between patients (Israel et al., 2012; Kondo et al., 2013). Furthermore, there is evidence to suggest that targeting the Aβ plaque alone is not enough to prevent the disease from occurring (Pimplikar, 2009; Sala Frigerio & De Strooper, 2016). Therefore the question remains: is Aβ synthesis and deposition an adequate explanation of what is causing the AD neurodegenerative cascade? It would seem, from the new studies being published, that there must be other factors causing or coinciding with Aβ synthesis in the AD brain.

The level of inflammation present in the AD brain has been significantly overlooked or has been considered secondary in nature and importance. However, a number of groups have proposed that inflammation - in the presence of Aβ - results in plaque neurotoxicity (McGeer & McGeer, 2013). Studies have shown that patients using non-steroidal anti-inflammatory drugs (NSAIDs), if started early enough, have up to a six-fold sparing effect in the context of AD (McGeer et al., 1990). Similar evidence has supported and further developed the inflammatory hypothesis, which now states that it is the inflammatory environment in the brain that drives the pathogenesis of AD. Inflammation is complicit with Aβ in causing AD rather than appearing as an eventual by-product of plaque overload (Heppner et al., 2015). However, neither the Aβ hypothesis nor the inflammatory hypothesis can be taken alone. Both must be considered in order to properly propagate further research into AD.

It is supported that Aβ, found in all aged brains, can lead to inflammation. Recent research showed inflammasome activation is heavily involved in the neuroinflammatory response. Aβ can directly, and indirectly through reactive oxygen species (ROS), activate the inflammasome – thereby causing its oligomerization into a large protein complex that catalyses an intracellular caspase cascade (Parajuli et al., 2013; Saresella et al., 2016). Activating the caspase cascade results in proinflammatory mediator production – specifically IL-1β and IL-18 (Halle et al., 2008). These cytokines ultimately potentiate Aβ production by affecting the enzyme β-secretase (increasing its activity) (Sastre et al., 2008). This marks the entry of the effected brain tissue into a proinflammatory-Aβ cycle (Figure 2b).

Aβ plaques are thought to increase tau aggregation (Braak & Braak, 1991), leading to neuronal degeneration and death. Unfortunately, there is a lack of clear experimental evidence explaining how Aβ causes tau aggregation. However since Aβ plaque exacerbates inflammation, it is often believed that the higher proportion of pro-inflammatory mediators present may upregulate tau, resulting in its aggregation (McGeer & McGeer, 2013). Once tau aggregates are formed, they are self-sustaining. Therefore, targeting inflammation could be critical in decreasing or preventing tau aggregation and, subsequently, neuronal death in AD. Since it has been shown that microglial inflammasomes are activated in AD in the context of neuroinflammation (Saresella et al., 2016), the inflammasome therefore stands out as a potential novel therapeutic target in the treatment of AD.

This review aims to outline the connection between inflammasome activation in the brain and the pathogenesis of AD, as well as discuss the inflammasome is a potential therapeutic target to both prevent and treat AD.

What is the inflammasome?

Inflammasomes are protein complexes that amplify the innate immune responses to certain stressors, which can involve the production of pro-inflammatory mediators or the induction of an inflammation-related form of cell death. Inflammasomes are particularly useful in protecting us against pathogens and in preventing persistent infections (Guo et al., 2015). In the brain, they are expressed and activated in microglial cells (Greter et al., 2015). The inflammasomes are activated through pattern recognition receptors (PRRs). PRRs can either be NOD-like receptors (NLRs), nucleotide-binding domains (NBDs), or absent in melanoma 2 (AIM2)-like receptors (ALRs) (Takeuchi & Akira, 2010). The best studied inflammasome, and most relevant to AD, is the NLRP3 inflammasome, which can be activated by a wide range of stimuli (Sutterwala et al., 2014).

All NLRs are found as inactive monomers intracellularly (Sutterwala et al., 2014). They

Figures

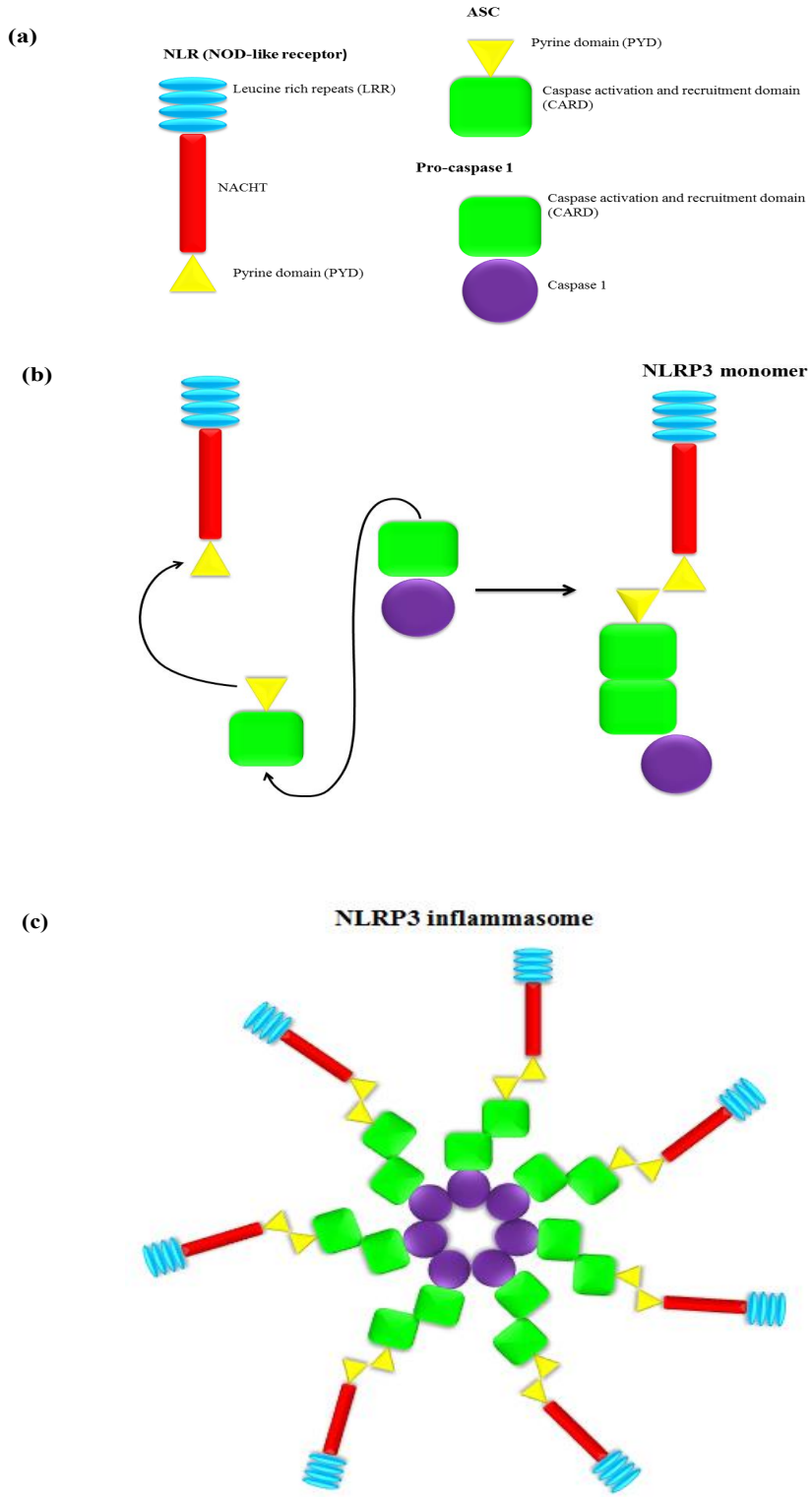


Figure 1. The components and formation of the NLRP3 inflammasome. (a) The protein complexes that make up a single monomer of the NLRP3 inflammasome, and the important domains found in each complex that allow for protein-protein interaction. (b) The structure of oligomerised NLRP3 monomer. (c) Seven NLRP3 monomer bind to form the cyclical structure of the NLRP3 inflammasome.

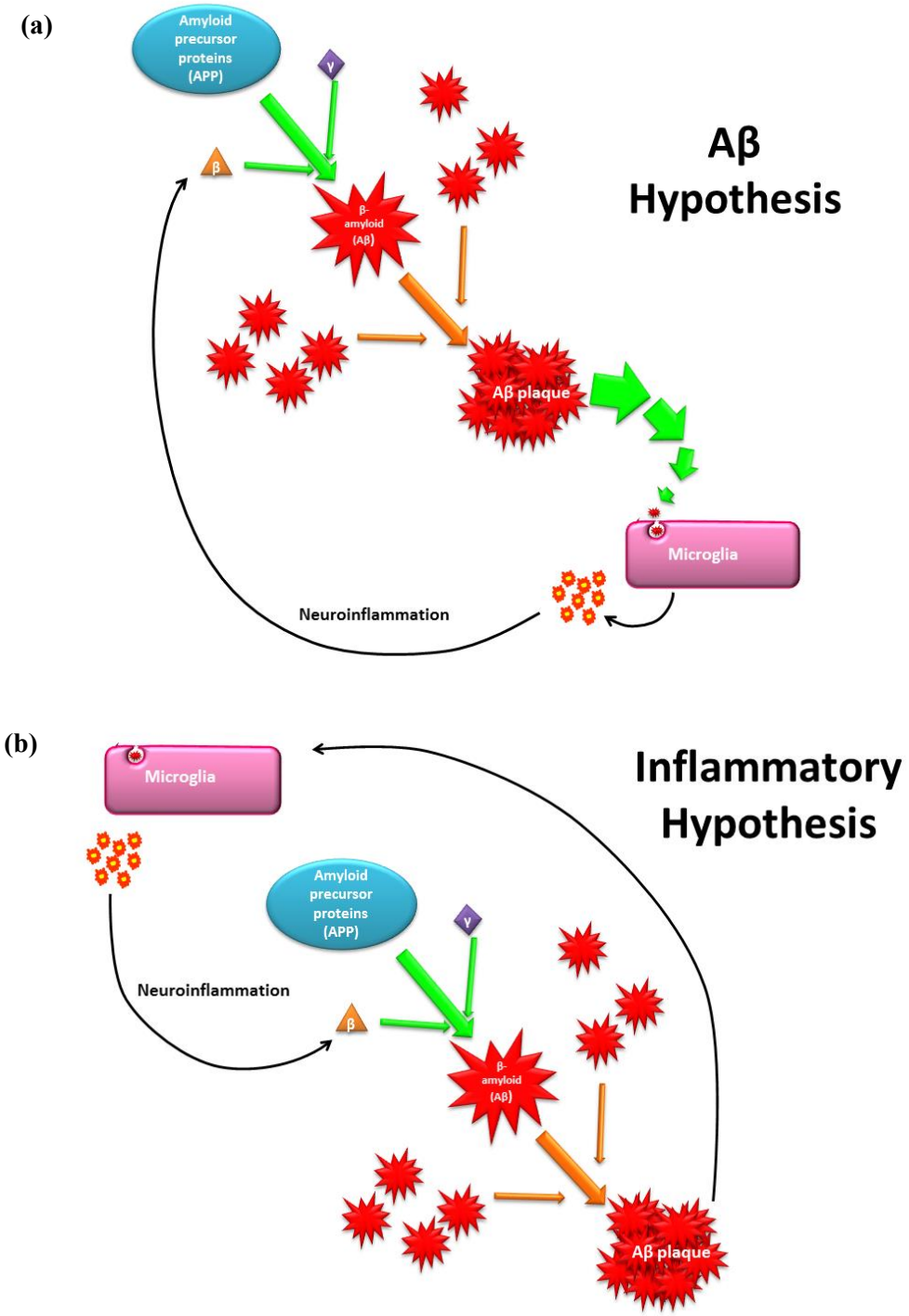
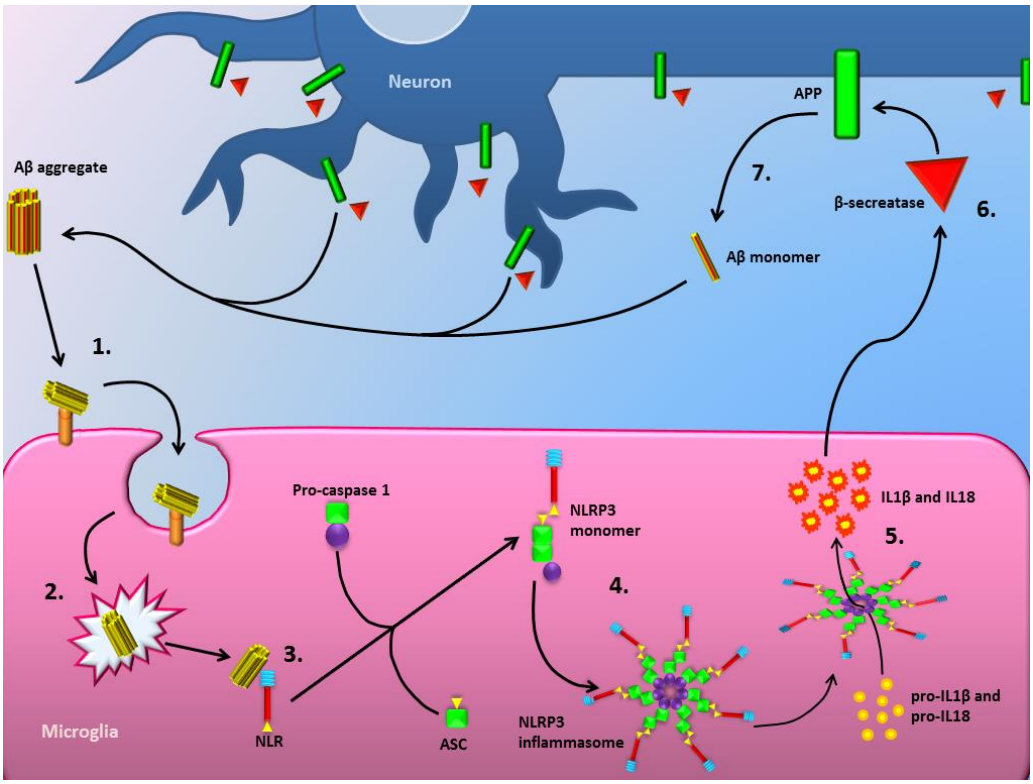


Figure 2. The Aβ hypothesis compared with the inflammatory hypothesis. (a) Sporadic cleavage of APP by β-secretase and γ-secretase leads to the production Aβ. Aβ aggregation occurs spontaneously, forming Aβ plaques. The Aβ plaques are phagocytosed by microglia, which become activated and produce proinflammatory cytokines. These cytokines act on the β-secretase enzyme, upregulating its activity and increasing APP cleavage and Aβ formation. (b) Naturally present Aβ or other PAMPs/DAMPs are phagocytosed by microglia. Microglia become activated and produce proinflammatory cytokines. These cytokines act on the β-secretase enzyme, upregulating its activity and increasing APP cleavage and Aβ formation. Aβ aggregation occurs forming Aβ plaques.

(a)



(b)

Figure 3. (a) Schematic of the inflammatory hypothesis. (b) Steps to the inflammatory hypothesis

consist of leucine rich repeat domains, a NACHT domain, and a pyrine domain (PYD) (Figure 1a). When an NLR becomes activated, it binds to an adaptor protein, called apoptosis-associated speck-like protein containing a CARD domain (ASC). ASC is composed of a PYD and caspase activation and recruitment domain (CARD) (Figure 1a). The binding of the NLR to the ASC is called oligomerisation. NLR binds ASC through PYD-PYD interactions (Cai et al., 2014; Lu et al., 2014). The CARD of ASC brings protein monomers of pro-caspase 1 into close proximity and ASC binds pro-caspase 1 through CARD-CARD interactions. When all components are bound, this structure is called a NLRP3 monomer (Figure 1b). Seven NLRP3 monomers form the NLRP3 inflammasome ring structure (Figure 1c). The inflammasome initiates pro-caspase 1 self-cleavage, producing active caspase 1 (Guo et al., 2015).

Caspase 1 is an enzyme that activates many cellular processes. It proteolytically cleaves proteins such as proIL-1β and proIL-18 into active IL-1β and IL-18, and it amplifies immune responses (Agostini et al., 2004; Bryant & Fitzgerald, 2009; Halle et al., 2008; Horvath et al., 2011; Kanneganti et al., 2006; Lamkanfi & Dixit, 2014; Mariathasan et al., 2006; Martinon et al., 2004; Martinon et al., 2009; Martinon & Tschopp, 2004; Wen et al., 2013). These proinflammatory mediators are found in high concentrations in the brains of AD patients (Saresella et al., 2016). Activation of the inflammasome can lead to proinflammatory cell death, called pyroptosis (Lamkanfi & Dixit, 2012; Strowig et al., 2012). Pyroptosis leads to the release of the intracellular cytokines into the extracellular matrix. These cytokines interact with β-secretase, upregulating it activity, and leading to increased APP cleavage and Aβ production. More Aβ production and aggregation results in further microglial and inflammasome activation, and creates a pro-inflammatory cycle, as seen in AD (Strowig et al., 2012) (Figure 2b). Another component released from pyrotosed cells is the ASC protein. This protein is responsible for cell-cell communications and amplifying the activated inflammasome signal i.e. when cell death occurs through inflammasome activation, ASC specks build up extracellularly, maintaining IL-1β production in the extracellular fluid. ASC is also taken up by microglia, resulting in lysosomal damage and more inflammasome IL-1β production. Essentially, minimal signals that only activate a few NLRs can be amplified to cause large multicellular responses mediated by ASC (Baroja-Mazo et al., 2014; Franklin et al., 2014). This ASC protein could be a potential therapeutic target for AD, in order to reduce neuroinflammation. As Aβ plaque in the brain of AD patients is in such low concentration (Brody et al., 2008; Steinerman et al., 2008; Xia et al., 2009), it may only directly activate a few microglia and inflammasomes. However, through IL-1β, IL-18, and extracellular ASC, the inflammatory signal could be amplified and spread, causing huge neuroinflammation, resulting in more plaque build-up, and further exacerbate the disease.

In terms of NLRP3 inflammasome activation, the signalling cascade has yet to be defined. However, agonists which activate the NLRP3 inflammasome are well known, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), ion gradient changes across cell, ROS (Abais et al., 2015), cytokines, and, in the case of AD, Aβ (Halle et al., 2008). Engulfed PAMPs and DAMPs can enter the cytosol through lysosomal rupturing. The release of lysosomal contents intracellularly results in NLRP3 inflammasome assembly and activation. The lysosome contains phagocytosed particles, such as Aβ, ROS (Zhou et al., 2011), and cathepsin B (Hornung et al., 2008). Cathepsin B is an important component of the lysosome, which has been linked to AD pathogenesis, making it a possible target in AD.

The inflammatory hypothesis

Neuroinflammation in AD is not a new concept, and was proposed almost two decades ago (McGeer et al., 1996; Rogers et al., 1996; Stewart et al., 1997; Verri et al., 2012; Yao et al., 2009). It was established that there was increased Aβ plaque build-up in the AD brain, and that these plaques were surrounded by microglia trying to phagocytose the plaques (Simard et al., 2006). These microglia simultaneously produced pro-inflammatory cytokines, such as IL-1β and IL-18 (Zhu et al., 1999). Therefore, it was deduced that increased inflammation in the brain was a consequence of Aβ plaque, and further exacerbated the condition.

Although neuroinflammation has been known about for years, the inflammatory hypothesis is a

relatively new idea (Zotova et al., 2010). While the Aβ hypothesis states that Aβ plaque build-up is the cause of neuroinflammation and tau aggregation (Figure 2a), the inflammatory hypothesis suggests that inflammation may actually precede Aβ plaque build-up, and drive the pathogenesis of the disease itself (Miller et al., 2013; Zhang et al., 2013) (Figure 2b,3). It has been claimed numerous times that Aβ plaque deposits are what activate microglia, and cause the neuroinflammation. However, recent studies show increased microglial dysfunction in severe AD brains compared to healthy controls (Krabbe et al., 2013). It is thought that chronic activation of microglia in the early stages of AD, due to the neuroinflammatory environment naturally found in aged brains, overwhelms the microglial response. This dysfunction reduces Aβ clearance and promotes further Aβ plaque deposition. It has been found that inhibiting neuroinflammation through downregulation of the NLRP3 inflammasome leads to decreased Aβ deposition in AD (Heneka, Carson, et al., 2015; Heneka, Golenbock, et al., 2015; Heneka et al., 2014; Heneka et al., 2013; Tan et al., 2013).

The inflammatory hypothesis is further supported by more studies, which demonstrate that increased chronic inflammation through TLR and inflammasome activation initiated the deposition of Aβ plaques in wild type (WT) mouse models, as well as exacerbated Aβ plaques in the AD mouse model (Krstic et al., 2012). Other studies have suggested that increased peripheral inflammation in AD patients damages the blood brain barrier (BBB), causing a more rapid decline in cognitive function (Holmes et al., 2009; Perry et al., 2007). The inflammatory milieu impairs synaptic transmission (Camacho-Arroyo et al., 2009; Hein & O'Banion, 2009; McAfoose & Baune, 2009; Rao et al., 2012), and results in a large cognitive decline, as seen in AD with chronic peripheral immune system activation.

Despite convincing evidence, the inflammatory hypothesis has been overlooked in favour of the Aβ hypothesis. However, despite evidence favouring one hypothesis over another, both hypotheses must be considered in order to ameliorate the disease. The question is how neuroinflammation can be targeted specifically to protect the brain from degeneration? There have been promising results with the use of NSAIDs, with many epidemiological studies suggesting that long term use could protect against AD development (Stewart et al., 1997; Vlad et al., 2008). However, another prospective clinical trial on mild AD patients showed that NSAID treatment had very little effect on AD pathogenesis (Martin et al., 2008). Although results using NSAIDs were found to be inconsistent, these trials have started investigating the possibility of inflammation leading to and exacerbating AD.

Through current emerging literature, it seems as though the inflammasome plays a huge role in neuroinflammation in AD. Targeting the complex itself could be a more specific way of lowering inflammation and disease progression. A direct link between the NLRP3 inflammasome and AD was demonstrated in in vivo mouse models, by knocking out NLRP3 and caspase-1. These mice showed decreased AD-related pathogenesis, less neuroinflammation, reduced Aβ plaque deposits, and less cognitive impairment than the control WT mice (Heneka et al., 2013). Another recent study also showed an increased expression of caspase-1 in AD brains compared to healthy controls, again, denoting the importance of the inflammasome in the pathogenesis of the disease. Collectively, studies have pointed to the importance of the inflammasome in AD and how it could potentially be therapeutically targeted to treat and prevent the pathogenesis of the disease. Inhibiting the NLRP3 inflammasome activation would decrease Aβ plaque deposition (Heneka, Carson, et al., 2015; Heneka, Golenbock, et al., 2015; Heneka et al., 2014; Heneka et al., 2013; Tan et al., 2013), decrease the level of proinflammatory cytokines in the brain (Schroder & Tschopp, 2010), and prevent tau aggregation and neuronal dysfunction and death.

However, despite growing evidence for the inflammatory hypothesis, many studies still suggest that inflammasome activation is secondary to Aβ plaque deposition, through Aβ-mediated ROS production and oxidative damage (Kurz & Perneczky, 2011), and Aβ targeting alone will be enough to cure AD. ROS can go on to activate the inflammasome, exacerbating Aβ production, and worsening the disease. IL-1β, as well as other proinflammatory cytokines, such as TNF-α and IFN-γ produced by the inflammasome, stimulate

astrocyte and neurons to produce more Aβ oligomers, stimulating further dispersal of Aβ (Dal Prà et al., 2015) (Figure 3). It is clear that although Aβ plaque deposition is an important target for therapies, both Aβ and inflammation are key mediators in the pathogenesis of AD, and both should be considered in the aim of finding a therapeutic agent that can prevent and treat the disease pathogenesis. So far many clinical trials targeting the Aβ hypothesis have failed (Aisen et al., 2011; Doody et al., 2013; Karran & Hardy, 2014; Karran et al., 2011; Siemers et al., 2016), so new approaches are needed if we are to potentially wipe-out AD.

Current and future therapeutics

Currently, the only pharmacological treatments available for AD are three cholinesterase inhibitors (CIs), donepezil, rivastigmine, and galantamine, and one N-methyl-D-aspartate (NMDA) inhibitor, memantine. The CIs are used to treat mild-moderate AD and prevent the breakdown of acetylcholine at relevant synapses. They counteract the loss of cholinergic neurons due to poor synaptic function that characterises the disease, and attempt to decrease the rapid deterioration in memory and cognitive function (Bartus et al., 1982; Cummings & Back, 1998). The NMDA antagonist, memantine, is used for patients with moderate-severe AD, and attempts to protect neurons from excitotoxicity and preserve neuronal function (Yiannopoulou & Papageorgiou, 2013).

The problem with the current available treatments is that they are only symptom modifying interventions; they do not slow its progression or target the root cause of the disease (Citron, 2010). In order to definitively cure AD, therapeutic agents must specifically target the underlying pathophysiology of the disease.

To date, major pharmaceutical companies have run clinical trials for new therapies which aim to decrease Aβ plaque load in the AD brain (Scarpini et al., 2011; Yiannopoulou & Papageorgiou, 2013). The mechanisms of action of these therapies have involved either inhibiting the proteases producing Aβ e.g. semagacestat (Doody et al., 2013), decreasing Aβ aggregation, e.g., tramiprosate (Aisen et al., 2011), or favouring Aβ clearance by immunotherapy, e.g., solanezumab (Siemers et al., 2016). However, studies have shown, it may not be enough to target plaque deposits alone (Pimplikar, 2009). Previous animal model data suggests that targeting inflammation through the inflammasome could be used in combination with Aβ inhibitors to completely prevent the development of AD (Hook et al., 2008). Addressing both the Aβ hypothesis and the inflammatory hypothesis together could be the key to treating and preventing the disease.

The NLRP3 inflammasome has been shown to initiate Aβ plaque deposition (Krstic et al., 2012). It is activated by Aβ plaque (Halle et al., 2008), and is upregulated in AD (Saresella et al., 2016). Many aspects of the NLRP3 inflammasome could be targeted in order to reduce neuroinflammation, and therefore prevent exacerbation or onset of AD. Studies have suggested that inhibiting the deubiquination of the inflammasome prevents its activation (Juliana et al., 2012; Py et al., 2013). Deubiquination is a key step in the priming of the NLRP3 inflammasome, needed for its response against a stimulus (Guo et al., 2015). There is also increasing evidence that inhibiting caspase-8 would prevent priming and activation of the inflammasome (Allam et al., 2014; Ganesan et al., 2014; Gurung et al., 2014), and processing of pro-IL-1β.

The surface receptor CD36 on microglia was found to be responsible for the uptake of Aβ intracellularly, and results in NLRP3 inflammasome activation, exposing another potential target (Guo et al., 2015; Sheedy et al., 2013). As activation is due to Aβ plaque causing lysosomal rupture and the release of cathepsin B intracellularly (Halle et al., 2008); there has been a study carried out that showed that the inhibition of cathepsin B improved the memory deficits in AD significantly, and simultaneously decreased Aβ plaque deposit load in the AD brain in vivo (Hook et al., 2008). This finding could be a huge step towards not only preventing neuroinflammation, Aβ build-up, and cognitive dysfunction, but perhaps could repair damage caused by AD itself.

As discussed above, it was recently discovered that ASC, a major component of the inflammasome, is released from dying cells (Bryan et al., 2009; Franklin et al., 2014; Huang et al., 2009). This can lead to cleavage of extracellular pro-IL-1β and can activate caspase-1 in the microglia that phagocytose the ASC specks. The phosphorylation of ASC is a key checkpoint in speck formation, so targeting the

kinases, Syk and JNK, could be used to therapeutically neutralise the ASC, ultimately decreasing neuroinflammation and Aβ plaque (Hara et al., 2013).

As the inflammasomes role in AD pathogenesis is a relatively new concept, to date there have been no clinical trials targeting this protein complex directly. However, trials targeting the inflammasome and its products have been carried out for other diseases, such as atherosclerosis, metabolic syndrome, and age-related macular degeneration (Ozaki et al., 2015). Currently, the best therapy seems to be inhibition of the inflammasome product IL-1β. Antibodies specifically targeting IL-1β, such as canakinumab, are available for rheumatoid arthritis. These antibodies may also be useful for AD (Moll & Kuemmerle-Deschner, 2013). In terms of inhibiting inflammasome components, some drugs have been identified and investigated. These include parthenolide and pralnacasan (caspase-1 inhibitors) (Dinarello et al., 2012; Heinrich et al., 1998), and a cysteinyl leukotriene receptor antagonist acting as an ASC inhibitor. The latter molecule has prevented the oligomerisation of ASC and NLR in certain models of disease (Coll et al., 2011).

These newer, more specific therapeutic molecules have not been tested in any AD clinical trials so far. However, their existence opens doors for future clinical trials, and eventually, one or more of them could be available for the treatment of AD in the clinic.

Conclusion

For years, it was thought that curing Alzheimer's disease could only involve the targeting and clearing of Aβ plaque deposits. However, new studies have demonstrated that Aβ plaques alone are not sufficient to cause AD and thus their clearance may not be sufficient to cure it. Nowadays, an increasing number of groups are attempting to more accurately dissect the disease's multifaceted pathogenesis. To date, the therapeutic agents used to treat Alzheimer's disease have been quite non-specific and aim to alleviate disease symptoms rather than the mechanisms underlying its onset. More exact targeting of molecular components in the AD inflammatory cascade is needed. Only recently has the importance of inflammasome activation in AD been elucidated and importantly, it seems to play a role in the initiation of Aβ plaque deposition in the brain. This highlights the therapeutic potential of the inflammasome in AD. With time and effort, inflammasome modulators may be integrated into routine clinical practice alongside existing therapies and could facilitate the eradication of the disease entirely.

Take home points:

- Alzheimer's disease is the most common neurodegenerative disease in the world, affecting over 5 million above the age of 65.
- The current AD treatments only modify symptoms of the disease - they do not target the root cause.
- For years, it has been assumed that β-amyloid plaque deposition in the brain is what causes the pathogenesis of AD, but recent clinical trials targeting and eliminating these plaques have shown poor results.
- Recent studies suggest that inflammation could play a key role in AD pathogenesis.
- The inflammasome complex has been found to be upregulated in the brains of AD patients, and is responsible for the production of proinflammatory cytokines. The presence of these mediators is associated with increased β-amyloid plaque deposition, increased tau aggregation, and increased neuronal death.
- Therapeutically modulating the inflammasome may be the key to ameliorating and preventing AD, and could wipe the disease out entirely.

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Game-changers in the making of contemporary vascular surgery

Chelsea Chia

In June 1902, a 29-year-old French surgeon published an original technique of vascular anastomosis that was never conceived before in the field of surgery, together with his work on organ transplantation. His interest in the field of vascular anastomosis led him to be the youngest physician to be awarded a Nobel Prize [1].

This French surgeon was Dr. Alexis Carrel. He was highly disappointed with the inability of the surgeons of his faculty to save the French President Sadi Carnot's life after a fatal stabbing which caused the portal vein to be severed. This spurred Dr. Carrel to design a novel procedure to perform the anastomosis: eversion of the edges of the endothelial surfaces with smooth jawed forceps to avoid endothelial injury that could precipitate thrombus formation [1]. His techniques laid the groundwork for other surgical techniques such as organ transplantation to develop; and his technique was used in Vienna to perform the first successful autotransplantation of a kidney in a dog in 1902.

In the 1940s-1950s, little was known on the definitive treatment for an abdominal aortic aneurysms (AAA) and cellophane was being experimented with as a material to reinforce vessels by inducing fibrosis [3]. It was used to wrap around the aorta like a constrictive wrapper, and the immune response that is triggered against the "foreign body" leads to fibrosis that narrows the aorta where it is affected. This technique was used to reinforce Albert Einstein's aortic aneurysm by an eminent surgeon, Dr Rudolph Nissen in 1948. When it finally ruptured 7 years later, doctors could not stop the internal bleeding [2].

Dr Michael DeBakey's contribution to vascular surgery

After Einstein's death, in the mid-1950s, prosthetic graft replacement for aortic aneurysms had become a reality, thanks to the creative efforts of Dr. Voorhes, Dr. Edwards and Dr. DeBakey. Their innovative ideas led to the change in paradigm of management of vascular disease in their time. The Dacron® graft replacement was the brainchild of Michael DeBakey and his wife. Before that, there was no effective treatment of abdominal aortic aneurysms that could prevent lethal rupture in patients. Dacron® was used only because the departmental store ran out of nylon material and he was offered that [4]. He bought the Dacron®, and used his wife's home sewing machine to create Dacron® tubes. After years of laboratory work and surgical experimentation with dogs, he was convinced to try it on patients. Aneurysm repair using Dacron® tubes is still widely used today.

He also developed the technique of endarterectomy of occluded superficial femoral arteries from Dr Joao Cid dos Santos in 1953 and used it to relieve atherosclerotic occlusion of carotid arteries [12]. Now, carotid endarterectomy is a surgical procedure widely used to reduce the risk of stroke from stenosed arteries, commonly in the common carotid or internal carotid artery. [13]

How did the other techniques of minimally invasive surgery come into the picture?

Dr Charles Dotter, a radiologist from the University of Oregon was the first to describe and perform an endovascular

intervention. In a 1963 address at the Czechoslovakia Radiologic Congress, he envisioned that "the angiographic catheter can be more than a tool for passive means for diagnostic observation; used with imagination it can become an important surgical instrument." [5]. His idea was to treat vascular disease from within the blood vessel, a procedure known as percutaneous angioplasty, which does not require a huge exposure of the artery and can accelerate post-surgical recovery time.

Dr Dotter described the procedure of transluminal angioplasty in 1964, coined "dottering the lesion" [4] for arterial stenosis and occlusions using graduated Teflon dilators passed endoluminally under fluoroscopic guidance.

However, the greatest contribution to vascular surgery was probably from Dr Juan Parodi, who bridged the divide between general surgery and vascular surgery by combining the technology of Dacron® graft with the innovation of endovascular therapy, thereby changing the paradigm of the management of vascular disease. He performed the first successful endovascular aortic repair (EVAR) of an abdominal aortic aneurysm in 1990, subsequently used not only for aortic aneurysms but dissections, transections and other aortic pathology [4].
After the invention of the Dacron® graft, open replacement of the aorta was the gold standard for treatment to repair an abdominal aortic aneurysm. The minimally invasive procedure of endovascular aneurysm repair (EVAR) had been rejected initially in the field of vascular surgery, because it had been way ahead of its time.

Contemporary vascular surgical techniques paving the way for vascular neurosurgery

At the same time, advancements in vascular surgery began to influence the field of neurosurgery, paving the way for endovascular treatment of brain aneurysms. The treatment of vascular disease led to the conception and development of endovascular balloons, which would be inflated with a solidifying substance and then detached, thereby occluding the blood supply of the aneurysm but preserving the parent artery. However, this presented different problems such as delayed rupturing or recanalization (blood clots forming in the vessel and causing chronic obstruction) and was surpassed by the use of coils in the late 1980s. The early coils were rigid and inflexible, and proved to be inadequate as an alternative to the use of balloons. Then in 1991, Guglielmi et al developed platinum coils that were electrolytically detachable which could adopt the shape of the aneurysm and not have the same deforming pressure on fragile vessel walls. Recurrence of the lesion with bare platinum coils were a problem but 10 years later, these coils were further developed to release bioactive substances to promote better "healing" of vessel walls [10].

How would Einstein's situation be changed by the advancement of modern techniques?

It was said that his repaired aneurysm was "the size of a grapefruit" which would have measured at least 10cm. A 2001 review of life expectancy of patients whose aneurysm measured > 7cm and refused surgery showed that the median survival was only 9 months [6]. Hence, his prognosis would not have been much different, although we now have guidelines that require doctors to refer any patient with an abdominal aneurysm larger than 5.5cm for surgery repair [7]. When performed electively, the operative mortality rate is about 5% while the mortality rate is about 50% if the aneurysm has ruptured [8]. Operating on aneurysms <5cm does not seem to improve the long term survival of

patients.
The combination of vascular grafts with the innovation of endovascular therapy has completely transformed our understanding and management of arterial disease. Multiple randomized trials confirms the benefit of endovascular repair in relation to post-operative mortality rates, allowing EVAR to become a commonly accepted treatment option in the modern day [9]. Improvement in modern imaging technologies have also contributed significantly to the management of these patients, where CT / MRI angiography has replaced arteriography to allow rapid and accurate visualization of the abdominal aorta, and evaluation of disease severity, greatly improving patient survival rates.

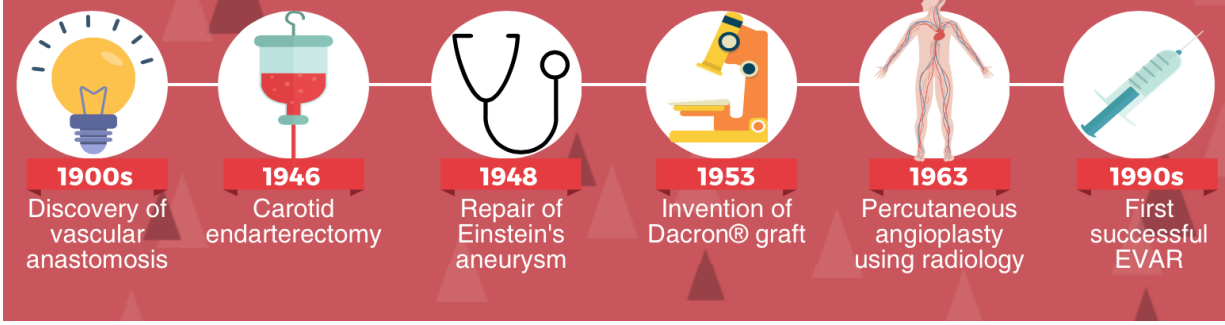
The landscape of modern vascular surgery since its recognition as a unique specialty in the 1960s is rapidly changing with creative innovation and novel technologies, disrupting the established order and creating a new order. The success of vascular surgery is not without the efforts of these surgeons and innovators, who had the vision and foresight to challenge existing paradigms and ways of thinking, establishing its independence as a unique specialty.

What is the future for contemporary vascular surgery?

Moving forward, it is paramount for vascular surgery to stay ahead and keep an open mind to new technology and innovations, as evidenced by its history. The use of imaging techniques was pivotal to the success of vascular surgery in order to allow measurement of physiological blood flow objectively and noninvasively. Newer techniques such as rotational digital angiography now allow 3-dimensional assessment of the aneurysm [10], vastly improving surgical outcomes.

Three-dimensional (3D) printing is also a highly advantageous strategy in the field of surgery as it allows planning of the procedure by mapping out precise anatomy, making prosthesis and implants that are tailored to each patient. Although trials and studies are still underway to ensure that we can make the best use of the given technology with the lowest cost and greatest efficacy, it may well be the answer to the already bright future of contemporary vascular surgery [11].

Game changers in the making of contemporary vascular surgery



1964 **Intracranial catheterisation**

1974 **Balloon angioplasty**

1988 **Platinum and bioactive coils**

Different modalities of vascular disease management

- **Carotid endarterectomy**
  - Carotid stenosis
  - Peripheral arterial disease
- **Endovascular aneurysm repair (EVAR)**
  - Abdominal aortic aneurysm
  - Aortic dissection
- **Vascular neurosurgery**
  - Intracranial aneurysms
  - Arteriovenous malformation
- **Future treatment options**
  - Rotational digital angiography
  - Three-dimensional printing

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Education in abortion care in Ireland: Medical Students For Choice (MSFC) taking a lead

Michael O'Shea

Abortion is a common topic of discussion in Ireland. Provision of abortion care by healthcare workers is restricted in a number of ways by legislation. Among Medical Students and Non-Consultant Hospital Doctors, there is consensus that abortion care should be covered in core curricula. However, current evidence indicates these groups lack knowledge surrounding issues such as legislation and and abortion care in an Irish context.

Guidelines dealing with termination of pregnancy provide information on how best to support women considering abortion, however information provided by Government Organisations contains inaccuracies. Both fail to deal with issues surrounding abortion through online Telemedicine services, and legislative ambiguity may prevent healthcare workers from providing information which could make at-home abortions safer.

This paper advises medical students and trainee doctors how best to deal with practical situations, such as women seeking advice on abortions overseas or through online providers. It provides a toolkit for clinicians to draw upon, which is in line with current legislation, guidelines and best practice. Further educational opportunities are available to students through Medical Students For Choice, through clinical attachments and student-led events. The educational benefits of such activities are discussed.

Introduction

Abortion has been illegal in Ireland since 1861 ("Offences Against the Person Act," 1861), and is currently prohibited under the Irish Constitution ("Constitution of Ireland: Article 40,"). Despite this, large numbers of Irish women undergo Termination of Pregnancy (TOP), either abroad or through online services.

This article looks at the unmet needs for abortion education in Ireland. It highlights restrictions, regulations and requirements surrounding this area of medicine, with a view to providing a toolbox which aspiring clinicians may draw upon when dealing with such issues. Areas which doctors are likely to encounter include medical abortions through online providers and abortions provided in other countries. Relevant contextual information will be given about these services.

This paper aims to highlight a number of key factors in abortion care. In recognition of the complexities of this area of medicine, further reading and experience is recommended. A secondary function of this article is to highlight the resources, opportunities and educational events available to medical students. With this in mind, there will be a discussion of the organisation which inspired the writing of this review; Medical Students For Choice.

Why is Abortion Education important in Ireland?

There is a need for abortion care to be addressed in medical education in Ireland at a postgraduate and graduate level. However, there is a lack of Irish guidelines, which may result in clinicians making assumptions which are not based on evidence. Further, tendency exists towards discouraging termination. Thus, the teaching of abortion care in Irish curricula is needed.

Abortion care is common in Irish Healthcare

Irish doctors deal with issues relating to Termination

of Pregnancy (TOP). A survey of 218 Irish General Practitioners (GP) found 97% GPs had a consultation specifically dealing with TOP, with 45% of GPs and GP Registrars (GPR) reporting a consultation within the past 6 months(Murphy et al., 2012). A similar study of obstetricians and gynaecologists (of whom 96% were Non-Consultant Hospital Doctors, or NCHDs) found 56% had been asked for information on abortion(Aitken et al., 2017). 38% referred a women to an information agency(Aitken et al., 2017).
No reason is given for referral, although one can hypothesise that a lack of education on abortion counselling among the NCHD's leaves them ill-equipped to deal with such situations.

Doctors and Medical Students are not properly informed

Surveys of doctors and medical students have highlighted a lack of knowledge about abortion care in Ireland. A survey of graduate and undergraduate medical students found that 25.7% of medical students were unaware of legislation allowing abortion in Ireland in instances where a woman's life is in danger(O'Grady et al., 2016). Among trainee obstetricians, 44% indicated uncertainty or unwillingness to certify eligibility for termination under the Protection of Life During Pregnancy Act, which is a requirement of obstetricians in Ireland(Aitken et al., 2017). The aforementioned survey of GPs and GPRs indicated concerns about the psychological trauma of having termination, something which, at the time, had no strong basis beyond anecdotal evidence(Murphy et al., 2012). It has since been proven that having a termination results in equal or improved psychological outcomes when compared to being forced to carry an unwanted pregnancy(Biggs et al., 2017). Together, these examples indicate a failure of the Irish Medical Education System to prepare doctors to deal with TOP. The need for education on TOP is widely accepted 54% of obstetric and gynaecology NCHDs working in Irish hospitals indicated they would be interested in training in abortion services as part of their curriculum(Aitken et al., 2017). Among Medical Students, there is widespread consensus that abortion training should be included as part of formal teaching. A study carried out on students at the University of Limerick found 95.2% of medical students believed abortion education should be offered on curricula(Fitzgerald et al., 2014). The most recent evaluation of attitudes of medical students on abortion found 92% support abortion in certain circumstances, with 56.6% indicating they would be willing to perform TOP in their future practice(O'Grady et al., 2016). Students from North America, where abortion is much more accessible, are more willing to perform TOPs should they be legally permitted(Fitzgerald et al., 2014). Given Ireland's large international intake as reported on multiple surveys (see (Boyle et al., 2013; Fitzgerald et al., 2014; Gouda et al., 2015) for examples), students from countries such as Singapore, Canada, the United States and the United Kingdom may be at a disadvantage when working in more liberal healthcare systems abroad, with less knowledge on TOP than their peers.

Irish Guidelines fail to address the issue

There are a number of instances in which anecdotal evidence influences doctors and policy makers in Ireland. Information in contravention with current evidence surrounding medical abortion has been published by the Health Service Executive (HSE) Crisis Pregnancy Program (CPP), and despite academic criticism, remains accessible on line at the time of writing (April 2017) (Sheldon, 2016). The errors, and their impact, will be discussed in detail a later section of this paper.

While this article will examine guidelines and legislation dictating what may or may not be said in a consultation room later, it should be noted that, in the past, individuals have conducted 'sting operations'

on pregnancy counselling services(O'Doherty, 2012; Sheldon, 2016). It is important that doctors are well informed of their obligations in relation to Medical Council Guidelines and Irish Legislation. The remainder of this article will look at abortion care as it is relevant to medical students and doctors in Ireland, and how MSFC addresses this.

Pre-Abortion Consultations

Irish Medical Council Guidelines (2009) sets out the responsibilities of medical practitioners in Ireland regarding abortion care. They state "It is lawful to provide information in Ireland subject to strict conditions, however it is not lawful to promote or advocate an abortion in such cases"(Irish Medical Council, 2007). Guidelines stipulate there is a "Duty to provide care, support and follow up for women who have an abortion"(Irish Medical Council, 2007). Conditions mentioned are elaborated in more detail in the Irish College of General Practitioners (ICGP) Crisis Pregnancy Management Guide(Ni Riain, 2013). These guidelines are specifically designed for General Practitioners. They clarify abortion counselling and aftercare within the Irish legal framework. This paper will now look at what it is legal and illegal to say in a consultation, and what services are available to women who have a termination. For those wishing to find out more on their responsibilities and restrictions in a consultation on TOP, the ICGP guidelines are a very good resource.

Discussing options

Where a woman requests information on abortion, there is a legal obligation on doctors to discuss all options in a non-directive manner(Regulation of Information, 1995). These include parenting, adoption, and specialist counselling. Current Irish Guidelines indicate that women who are certain of their decision "should not be subject to compulsory counselling"(Ni Riain, 2013). Should a woman decide to pursue counselling, it can be obtained free of charge, and locations and descriptions are found at www.positiveoptions.ie(Ni Riain, 2013).

Suggesting services

Paradoxically, while services have developed around abortion care, and one can discuss abortion providers abroad, it is illegal for a healthcare worker to directly refer a patient to such a service. Patients should be advised to request a copy of their medical records, and healthcare workers may suggest services which a patient can contact(Regulation of Information, 1995). There are two organisations which provide TOP in the United Kingdom, and offer care tailored to the needs of Irish people. They are the British Pregnancy Access Service (www.bpas.ie), and the Marie Stopes Clinic (www.mariestopes.org.uk). The Abortion Support Network (www.asn.org.uk) is an organisation which provides financial advice and assistance to Irish women who may struggle to pay for a TOP overseas.

Abortion through Online Telemedicine Services

Illegal medical termination in Ireland is becoming increasingly common. Between 2010 and 2015, there was an increase in the number of women who accessed online telemedicine services to procure abortifacients(Aiken et al., 2016). Organisations such as Women Helping Women (WHW) and Women On Web (WOW) recognise that Ireland's policy of exporting abortion care abroad discriminates against people of limited means or restricted visa status(Sheldon, 2016).

Abortion through online providers is becoming more frequent

In a 2010 survey, 11% of GPs in Ireland indicated that the use of illegal abortifacients had been brought to their attention(Murphy et al., 2012). In the same year, 548 women in Ireland and Northern Ireland had an online consultation with the only large scale online provider of abortifacients at the time, Women On

Web(Aiken et al., 2016). In 2016, this number accessing online consultations about TOP was estimated to be in excess of 2,000, showing a substantial increase in demand(Sheldon, 2016). We therefore assume that this has become a more frequent issue in consultation.

Providing an abortion outside the Irish legal framework is punishable by up to a 14 year prison sentence, which discourages Irish Doctors from providing advice to women who opt for a TOP through online services such as WOW and WHW(Aitken et al., 2017). It is illegal to supply prescription only medicine by mail order, so organisations such as WHW and WOW do not ship directly to the Republic of Ireland(Ni Riain, 2013; Sheldon, 2016). It should be noted that, in refusing to ship directly to Ireland, these organisations operate in full compliance with legislation(Sheldon, 2016). Health care professional who give information on how to obtain and use medications such as misoprostol "walk a fine line to avoid charges of aiding, abetting, counselling or procuring commission of criminal activities"(Sheldon, 2016).

Advice provided by Government Organisations is flawed

Previously, this article mentioned errors in advice distributed in Irish Guidance. The information provided by the HSE Crisis Pregnancy Programme (CPP) website, www.abortionaftercare.ie, is one such example. Errors in this document include claiming that medical abortion is less effective in patients who are pregnant with twins, something which is contradicted by current best evidence("Abortion Aftercare," 2017; Hayes et al., 2011). This resource also indicates that medical abortion may not work after 9 weeks, in contravention with the Royal College of Obstetrics and Gynaecologists Evidence-Based Clinical Guidelines, which indicates that, while prescribing and route of administration may differ depending on the gestation, medical abortion is safe up to 23 weeks, although from 13 weeks, 9.4% of cases require subsequent surgical evacuation, and from 10-13 weeks there is an increased rate of complication("The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No.7)," "The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No.7)," 2011). From 9-10 weeks, there is evidence that the procedure used by Women on Web (see (Aiken et al., 2016; Gomperts et al., 2008)) is suitable, with only a slightly higher rate of failure in the 9-10 week cohort compared to 0-9 weeks, and no increase in requirement for hospital admission or blood transfusion(Bracken et al., 2014). Therefore, it can be deduced that the HSE Crisis Pregnancy Programme guidance on the issue of telemedicine is not up to date with current best practice, and should be avoided by clinicians and individuals.

Other guidelines, such as the ICGP Crisis Pregnancy Management Guide, do not provide information on the medical management of abortion through in-absentia services, focusing instead on the legal aspects of the practice(Ni Riain, 2013). As such, there is no definitive resource, which takes into account the nuances of Irish medical practice, and which deals with telemedical TOP in an evidence based manner.

Women accessing TOP services online are not adequately supported

The advent of abortion facilities through telemedicine, and the failure of Irish organisations and government bodies to deal with this new phenomenon, has left Irish women in an odd and unfortunate position. Someone may find themselves unable to access TOP overseas, and will turn to online providers. Interviews with counsellors at the Irish Family Planning Association mention instances where women bring abortifacient pills to a counselling sessions(Sheldon, 2016). Counsellors are limited to saying such pills should always be taken under medical supervision(Sheldon, 2016). Consultations with doctors may yield similar

results, and government information online is unreliable. Women in such a situation are underserved.

The demographic of women accessing TOP online implies, in many cases, an already disadvantaged background. Reasons for requesting online abortion services include financial difficulty (43.5%) and a desire to finish school (14.8%)(Aiken et al., 2016). 24.3% of women report not having family support, and 34.6% had difficulty affording the donation of €70 that covers the costs of the service provided(Aiken et al., 2016). There is a significant association between lack of emotional and social support, and lack of economic resources(Aiken et al., 2016). These figures show that disadvantaged Irish women are more likely to access TOP through online services, and have fewer supports in doing so.

The limited capacity of counsellors and healthcare workers to assist women seeking TOP through online services, in addition to the disadvantaged demographic of this population, contributes to class discrimination in healthcare. The legislation which restricts clinicians from providing information to women in these situations was developed in an era before telemedicine(Sheldon, 2016). However, the example given of state sponsored misinformation shows the negligent approach taken by the Irish Heath Service. An educational and harm reduction strategy is needed to deal with this issue.

Aftercare

Women who have had a termination in the UK will receive a high quality of care, which may include counselling, information on possible side effects, Rhesus status, VTE risk assessment, advice on cytology screening, STI screening and treatment, and advice on contraception(Ni Riain, 2013). It should be assumed that women who have received abortifacient medication online have not had the same quality of care. Complications of medical abortion include severe bleeding, uterine rupture, cervical trauma, procedure failure and post-abortion infection(Ni Riain, 2013).

Counselling services are available free of charge, although it should be noted that women who report negative feelings (feelings of loss, guilt, sorrow, disappointment or low feelings) are in a minority compared to the majority of women who report positive feelings (relief, satisfaction, happiness) following a TOP through telemedicine services(Aiken et al., 2016). Concerns that travelling abroad for TOP has a negative impact on a woman's health have been expressed by the medical community(Murphy, M. 2012). Indeed, 90% of NCHD obstetricians have provided follow up care to women who have accessed abortion services abroad, so these concerns are likely based on interactions, rather than assumptions(Aitken et al., 2017). More data on the comparative needs of women following a TOP abroad versus through on-line services is needed.

Medical Students For Choice

Medical Students for Choice (MSFC) was founded in 1993 by students at the University of California in San Francisco, owing to concern at the lack of abortion and contraception education being taught formally(Medical Students For Choice Headquarter 2017). MSFC's first European Chapter was founded in Trinity College Dublin in 2010, with activists reaching out to other colleges in Ireland (Obara, 2012). There are now MSFC Chapters in 5 Irish Universities(Personal Communication, 2017). MSFC offers reproductive education through local, student lead activities, and through clinical experience.

MSFC Trinity hosted a number of events in the past year, including a workshop on Intra Uterine Device (IUD) insertion, a video screening, participation in the annual March For and a Journal Club. One of the best attended events hosted was a talk from Susan Yanow, the founding director of the Abortion Access

Project, and consultant to a number of organisations providing essential medicines to women, such as WHW. She gave an interactive talk on how medical abortions are performed from the view point of an online consultation. The workshop helped to address some of the educational needs outlined in this article, and students who attend are better placed to understand the needs of women in Ireland.

Reproductive Health Electives (2-4 weeks) and Observership (1-2 weeks) can very easily be organised through MSFC, who provide funding up to 1,000 US Dollars to students. The organisation puts students in contact with Doctors, Hospitals and Clinics, and Students from Trinity have, in the past, undertaken placements with groups such as the British Pregnancy Access Service, Bellevue Hospital New York, and Woman's College Hospital and Mount Sinai Hospital Toronto. MSFC Trinity regularly hosts an Electives Evening. Details are outlined at www.msfc.org.

Conclusion

Irish and NCHDs agree there is a need for abortion training in Ireland as part of core curricula. Inadequacies in pre-existing knowledge among these groups, and flaws in guidance offered by government organisations add to the concern that Irish women are not able to access reliable, accurate information through which they can make well informed decisions.

The expanding role of MSFC in Ireland reflects a growing desire within medical students to better understand the often complex issue. Further, this paper highlighted concern that services provided abroad, or online, cannot support women to the same extent as local health care providers.

"We can't replace local health care. You can give information, you can give pills, you can trust women to do it themselves but, if there is a problem, you need the local clinic to assess the situation" —Rebecca Gomperts, WOW (Sheldon, 2016)

While Irish legislation restricts provision of safe abortion care, physicians who are well informed can improve the safety of TOP. Misunderstanding of legislation is a major barrier to this safer care, and it must be addressed through harm reduction strategies and through education.

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Conflict of Interest Statement

The author is a Student Leader for MSFC, and current Co-Auditor of the Trinity Chapter of MSFC Ireland. MSFC provides financial support to MSFC Trinity College Dublin to host events. The author has not received payment from MSFC for any activity, including the writing of this article.

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Refugee aid is not supererogatory: A cosmopolitan Rawlsian framework for thinking about human rights, health and our obligations to refugees

Evan Hurley O'Dwyer

Few issues in world affairs kindle as much argument as the normative question of the just way to handle refugees. The question of how far our obligations to refugees extend evokes fundamental questions about the nature and purpose of citizenship, borders and the nation-state. In this essay an ethical framework will be outlined for thinking about human rights, health and our obligations to refugees.

Michael Walzer, the liberal communitarian philosopher, discussed obligations to refugees in Spheres of Justice (Walzer, 1983). His argument is the conventional nationalist argument favouring restrictive immigration policies. Walzer argues in favour of Westphalian sovereignty, with each country having the ultimate right to exclude whomever it wants. A similar viewpoint holds that helping refugees is a supererogatory act. Supererogation is a technical term covering the class of actions that are morally good but not strictly necessary. Many people view admitting refugees as a charity act – it goes "beyond the call of duty," as there are no moral obligations that compel a state to aid non-citizens.

This view was criticized by the utilitarian philosopher Peter Singer, who argued that wealthy nations should admit many more refugees than they currently do (Singer, 1988). Given the short nature of this essay there will be no digression on the utilitarian challenge to today's refugee policy. This essay advocates for a cosmopolitan extension of the framework for national distributive justice outlined by John Rawls in A Theory of Justice. This framework naturally leads to questions about human rights, health and our obligations to refugees.

Rawls's theory of distributive justice followed Rousseau, Hobbes, Locke and Kant by resting its foundations on a social contract. Rawls's theory concentrated on the ideal organization of a nation-state and its institutions. Rawls asked us to imagine ourselves in a so-called "original position" – a hypothetical "state of nature" (Rawls, 1971). Members of the original position are behind a "veil of ignorance," preventing them from knowing certain details about themselves, such as their race, sex, intelligence, strength, and social class. According to Rawls, ignorance of these details leads to principles that are fair to everyone. If an individual is unaware of how she will end up in her own conceived society, she is unlikely to privilege any one class of people, and would instead develop a scheme of justice that treats all fairly.

Rawls argued that people in the original position would choose two specific principles. Rawls's first principle states that "each person is to have an equal right to

the most extensive basic liberty compatible with a similar liberty for others". These basic liberties of citizens include the liberty to vote, to run for office, freedom of speech, liberty of conscience, and freedom of personal property. Rawls's second principle of justice states that social and economic inequalities must be arranged so that (a) "they are to be of the greatest benefit to the least-advantaged members of society" (the difference or "minimax" principle) and (b) "offices and positions must be open to everyone under conditions of fair equality and of opportunity." Rawls viewed (b) as being lexically prior to (a), however it is the difference principle which Rawls is most famous for. He asserted that inequalities in the distribution of primary social goods are permissible only if they benefit the least well-off members of society.

Rawls rejected the idea of moral desert and rejected basing distributive shares on morally arbitrary contingencies. He maintained that success-determining factors are often the result of a natural lottery (for example, the family one is born into). While Rawls opposed the idea of moral desert he allowed for socially legitimate expectations. For example, a doctor or a business owner may be entitled to a high salary, so long as this incentive benefits society, specifically those who are worst off. (Sandel, 2009)

If we wish to develop the notion of a human right, we must expand Rawls's theory. In A Theory of Justice, Rawls was solely concerned with the organization of the nation-state. It was not until decades later in The Law of Peoples that Rawls attempted to address international justice (Rawls, 1993). Rawls's extension of his own theory to the international sphere was heavily criticized by his own supporters, including German philosopher Thomas Pogge, as having "no egalitarian principle" (Pogge, 1994). This essay advocates a cosmopolitan extension of Rawls's theory, with each human a citizen of humanity in a global original position (GOP) with members behind a veil of ignorance. Any rights agreed upon in the GOP would be universal.

There are two ways members in the GOP might argue for including reasonable healthcare as a universal right. One argument suggests that healthcare is a primary social good, which would make its distribution subject to the difference principle. Any distributive scheme would be arranged to maximize the share of the least well-off. Another Rawlsian approach to healthcare has been advocated by Norman Daniels; "The most promising strategy for extending Rawls's theory simply includes health-care institutions and practices among the basic institutions involved in providing for fair equality of opportunity" (Daniels, 1985). He argues that there is a special connection between normal human functioning and the range of opportunities open to an individual. It has long been shown that there are social determinants of health (Marmot, 2005). It is thus reasonable that members of the GOP would enshrine fair access to reasonable healthcare as a right. Any rational agent would want guaranteed access to healthcare when the veil of ignorance is lifted.

The question remains of what special refugee rights members of the GOP would

agree on. University of Toronto Professor Joseph Carens made a strong philosophical argument that a Rawlsian society would have open borders (Carens, 1987). However, even without this politically controversial assumption, there are strong arguments in favour of an egalitarian way of handling refugees. At the very least, members of the global original position would rationally agree to certain refugee rights such as non-refoulement and would provide for a global institution which would safeguard the rights of refugees.

A potential criticism of the global extension of the original position is that it would undermine the sovereignty of the nation-state. To an extent this is true, however if we accept the legitimacy of the human rights movement, we accept the possibility of universal human rights which no nation-state may violate. These rights create positive and negative duties that citizens and states must abide by. The rules that would be envisaged in the GOP would act as a basic set of principles – within a state additional principles may be formed, however they must not conflict with the universal set. Similarly, being part of a nation state may give extra entitlements to a citizen – one could view a state as a mutual benefits social club. However, the fact that a citizen has special duties to other citizens in the same nation-state does not abrogate her general duty to uphold human rights in a global setting. The argument that one cannot attempt to help refugees "because we must help our own first" is an example of this fallacy.

What prescriptive conclusions can be gained from the Rawlsian approach? First, an institution such as the UN can act as one of the cosmopolitan institutions that would be set up in the global original position. To a certain extent it already plays this role, having managed to convince the majority of countries in the world to sign up to The Universal Declaration of Human Rights. The Rawlsian framework can make sense of the role of the UN, the WHO and the UNHCR in international justice and can guide decision-making. International practices may be examined through the veil of ignorance to determine their legitimacy. There is much evidence that human rights of refugees are systematically overlooked. The nationalistic idea that citizens have no duty to help outsiders is a modern equivalent of feudal privilege and has left refugees with no safeguard when their own country fails to protect rights. When people speak of the "European refugee crisis", they mean a crisis for Europe, as opposed to for refugees themselves. International policy in general is aimed at curtailing the spontaneous arrival of legitimate asylum seekers and refugees. Lebanon, which has a population of less than 6 million, has over 1 million registered (and an estimated .5 million unregistered) Syrian refugees. The US, which has a population of 320 million, has pledged to take in a mere 10,000 Syrian refugees. The EU, which has a population of 742.5 million, has had close to 800,000 asylum applications from Syrian refugees since April 2011 (UNHCR, 2016). Wealthy nations are neglecting their responsibility to contribute their fair share – instead, the burden falls on countries like Lebanon and Jordan, which are less wealthy than the US and EU. The refugee crisis is a problem which knows no borders. As such, an egalitarian solution to the problem must

rely on a cosmopolitan formulation of justice, where a nation-state's distance from refugees in need does not negate the duty to protect the human rights of refugees.

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Ask for Help: An Exploration of Factors that Inhibit and Influence the Health- and Help-Seeking Behaviour (HSB) of Post-Natal Women Experiencing Morbidities.

Fatimah Alaya

Morbidities affecting women in the post-natal period, alongside their health help-seeking behaviour, has been explored by national and international studies. This literature review focuses on exploring the factors that inhibit and support health- and help-seeking behaviour of post-natal women experiencing two of the six most common morbidities, postpartum depression and intimate partner violence.

Introduction

Pregnancy, birth and the post-natal period are milestones in the life of a woman and her partner (Gaskin, 2004; NMBI, 2015). Although this milestone can be joyous, fulfilling and life transitioning, some women experience health problems, known as maternal morbidities, and the true burden of these morbidities is still unknown (WHO, 2013). Despite the realities of maternal mortality, and the risks involved during the post-natal period, many women can experience morbidities and these issues are not readily addressed by healthcare professionals (Brown and Lumley, 1998; Thompson et al., 2002; Begley et al., 2013). The post-natal period encompasses the time from the birth of a baby up to six weeks post-birth (Marchant, 2009). Women can experience many types of morbidities during this period, including urinary-faecal incontinence (Mason et al., 2001; Takaoka, 2013), pelvic girdle pain (Albert et al., 2002; Wu et al., 2004), sexual function and dysfunction (East et al., 2012), post-partum depression (ACOG, 2008; Pieta et al., 2014) and intimate partner violence (IPV), all having an impact on a woman's physical and psychological post-natal health (Groves et al., 2015).

Health-seeking behaviour (HSB), is a woman's conscious decision to access help to improve her level of health and wellbeing (NANDA, 1990). This is a decision initiated by a pregnant woman experiencing a physical or psychological complication that affects her personal ability to carry out daily and personal functions (Cornally and McCarthy, 2011). HSB should facilitate a healthcare professional, the midwife, GP, or other medical healthcare professional, to detect, screen and reduce the complications experienced by post-natal women (NMBI, 2015). Furthermore, the behaviours implicit in the act of seeking help can also promote a strong healthcare-woman relationship, in particular between midwife and woman.

Nationally, 16.8% of first time mothers in Ireland often experience back pain, 17.7% suffered from depression and anxiety within three-months of delivery, 54.8% experienced urinary incontinence with exercise and 14.4% experienced moderate faecal incontinence at three-months post-natal (Begley et al.,2013). These national statistics identified a high prevalence of post-natal morbidities in an Irish cohort. International figures also identified such a high prevalence with 46.6% of French women and 53.4% of Italian women experiencing post-natal morbidities (Saurel-Cubizolles et al., 2000).

Consequences of some of the morbidities highlighted included minor outcomes such as sleep disturbance and depressive symptoms (Goyal et al., 2007). Major

far-reaching outcomes included excessive smoking, alcoholism, increased risk of experiencing IPV, and consequences for the child including the efficacy of breastfeeding (Chee et al., 2007).

Healthcare professionals, specifically midwives, are women's advocates by actively engaging in health promotion and education to empower women (NMBI, 2015). This empowerment is key to increasing a woman's self-confidence and involvement in their care. Seeking information and help to gain better care and improve health care. This requires the midwife to engage and gain insight into the wellbeing of the woman. Similarly, women should be encouraged to interact with health professionals. Such interactions can lead to women seeking help and improving their health status, when experiencing physical or psychological complications during pregnancy and the post-natal period (NMBI, 2015).

Method

A scope search was initially conducted. Three focused key terms were identified: behaviour, morbidity and post-natal. A list of free text terms were developed for each term, followed by search strings, via electronic databases, accessed via TCD Library and included: PubMed, CINAHL, PsychINFO and Maternity and Infant Care (MIDIRS Online). Additionally, manual searches via: WHO, HSE, NHS, NICE, RCOG and the Cochrane Database. Grey literature was also reviewed.

The inclusion criteria included qualitative and quantitative research pertaining to pregnant women, HSB, morbidities and the post-natal period. Publication dates extended from present day to the previous twenty years to include seminal studies. Filters were applied, English language and full texts, noted as the most effective.

Initially 8,253 articles were retrieved. Duplicates, filters and examination of titles and abstracts reduced the findings to 101 articles. An annotated bibliography was conducted for each of the 101 articles. Additionally, a simple appraisal tool reduced the results to 56, emerging as directly relevant to the three key terms, review question and used to construct this literature review

Results

One of the main inhibitors to HSB emerged as the nature of the professional relationship, more specifically the midwife-woman relationship, with focus on the exchange of information and stigma.

Firstly, the midwife-woman relationship was one of the most common factors in reviewing inhibitors of HSB. Women often felt disappointed, frustrated and humiliated following interactions with healthcare professionals, expressing that they felt discouraged from seeking information and fully engaging in HSB. A lack of sufficient time and appearing unapproachable by healthcare providers resulted in many women feeling patronised, or felt a sense of disinterest towards their complications, and this inhibited HSB (Beck, 1993; Thom, 2003).

Secondly, the exchange of information was another influence limiting HSB. Midwives did not prepare, educate or impart sufficient information to women. Instead, women sought help from female relatives and friends who had similar delivery experiences, rather than turning to a midwife, or other health professional in the obstetric and gynaecological service. The female relatives and friends often misinformed women, by claiming that experiencing complications was inevitably a consequence of their delivery with no real available treatment options (Buurman and Lagro-Janssen, 2013; Dennis and Chung-Lee, 2006).

Finally, the issue of stigma was prevalent across the literature review. Women felt stigmatised as a result of feeling different to other women with similar experiences

(Goffman, 1963), resulting in them revealing, hiding or disregarding their morbidity (Cramer, 1999).

From the review of the literature three substantial results emerged as important areas to direct healthcare attention on to improve HSB:

1.The importance of women engaging in HSB to reduce and limit stress levels associated with post-natal complications (Robb et al., 2013)
2.The importance of midwives identifying the presence of stress which can be a trigger to facilitate better HSB (Joachim and Acorn., 2000)
3.Introduce social support to increase HSB (Cramer, 1999)

One of the strongest facilitators of HSB included sources and types of support. Razurel and Kaiser (2015) developed a scale to investigate who women sought help from healthcare professionals, focusing on the relation of satisfaction with social support and the women's post-natal health. Five main sources were identified and each was associated with a different form of support: from the spouse, woman's mother, family, friends, and professionals. The scale identified that:

-Women engaging in HSB with their spouse experienced less psychological disorders
-Women engaging in HSB and seeking support from their own mothers, benefited their psychological health and parental self-efficacy
-Family and friends were regarded by women as a source of social support, reducing vulnerability and increasing self-efficacy
-Women heavily rely on the expertise and knowledge from healthcare professionals, and specifically rely on the midwifery service;
-Engaging in HSB with a midwife increases the positive psychological experience of pregnancy for women and enhances the development of their parental self-efficacy.

Furthermore, the scale reinforced that professional support was deemed as an integral point of reference for women, as it increased positive psychology and the development of parental self-efficacy (Razurel and Kaiser, 2015).

Recommendations

The literature review identified that healthcare professionals in the obstetric and gynecological services, such as midwives, can lack the appropriate knowledge regarding HSB and the range of complications experienced by women in the post-natal period. Clinically, improvements can be made, including:

-Establishing and facilitating study days for healthcare professionals, obstetricians at all levels of training, midwives, and student midwives in relation to maternal health and morbidity and HSB.
-Using surveys or investigative scales that can be distributed to women to establish their HSB during the prenatal, delivery and post-natal period.
-Including the topic of HSB into policies and guidelines to ensure well-rounded care and better medical guidance and midwifery practice is in place.

Incorporating the woman's support network into pregnancy and post-natal education will reinforce the primary evidence based, best care, and education provided by the obstetric team, and in particular the service provided by the midwife. Doing so will increase the likelihood of standardising the information being shared, and therefore reduce discrepancy, distrust, and enhance women's engagement in HSB.

HSB is a novel and relatively underdeveloped research area, although it is a subtype of general 'sickness beahaviour' (Cornally and McCarthy, 2011). Further qualitative research is suggested to gain a deeper understanding into how women decide to reach out for help and engage in HSB, and explore how to best facilitate and encourage the midwife-woman

relationship to achieve better HSB.

Conclusion

When post-natal women who experience morbidities engage in HSB, it increases the likelihood of improving their level of physical and psychological wellbeing and health (Robb et al., 2013). HSB by a patient is often the first step where a health professional can identify an issue, and initiate and deliver care. Hence, the successful identification of HSB when it presents to a healthcare profession is integral for healthcare delivery (NMBI, 2015). The importance of communication and education within HSB has been highlighted by this review, furthermore they are strongly applicable to medical and midwifery students when transitioning through electives, rotations and their senior careers, as it ensures the delivery of high quality care that is truly person centred. In particular, the importance and relevance here should be made to medical students who are entering their OBGYN rotation, midwifery students and interns, as their increased patient contact will lend to the higher likelihood of women engaging in HSB. By incorporating, facilitating and having an in-depth knowledge of HSB, the healthcare professional-patient relationship can be strengthened, increasing the likelihood of women engaging with health professionals, especially midwives, in a meaningful way, and this can have benefits that reach across institutions and society, psychosocially, physiologically, as well as financially (Razurel and Kaiser, 2015) .

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Bone Remodelling in Space: A Review

Connor Keller and Shane Arsenault

Alzheimer's disease is the most common neurodegenerative disease in the world. Despite years of intense research, its pathogenesis remains quite controversial. Many different explanations have been proposed to describe its onset, the most established of which is the β-amyloid hypothesis. This hypothesis proposes that the disease is primarily caused by the formation of β-amyloid plaques in the brain. The presence of these plaques, it is suggested, ultimately leads to neuroinflammation, tau aggregation and, eventually, neuronal death and the often-cited neurocognitive sequelae observed in Alzheimer's patients. However, recent evidence suggests neuroinflammation may in fact be a root cause of the disease as opposed to acting as an eventual or coincidental manifestation. More specifically, it has been found that the activation of inflammasomes in microglia (the brains immune cells) contributes to the production of proinflammatory cytokines which then potentiates the neuroinflammatory response, with other downstream affects including increased β-amyloid plaque build-up, tau aggregation and a loss in cognitive function. Therefore, more and more studies are suggesting that neuroinflammation - and particularly the inflammasome - could be targeted therapeutically to prevent and treat Alzheimer's disease in patients.

Introduction

The homeostatic maintenance of human bone is an important process for conditions amenable to survival. Bone provides the skeleton for muscle attachment and support which enables motion as well as providing protection for vital organs such as the brain and heart. Bone also plays a necessary role in other basic homeostatic functions including maintaining constant levels of density and inorganic calcium. For example, human long bone must be preserved at around 60% inorganic calcium to maintain structural integrity while the ossicles of the middle ear must be kept at around 90% to allow for auditory proficiency (Seeman, 2006). Circulating calcium is also required in functional homeostasis as it is a central component in neurotransmitter release, muscle contraction and as a second messenger in cell signalling.

Considering the importance of bone in the maintenance of human physiology, it would follow logically that preserving adequate bone density and inorganic calcium levels would be critical in maintaining homeostasis during space flight. Understanding changes in bone mass and bone quality in the unique microgravity of the space environment is the first step to defining an osteoporosis risk, and establishing whether an intervention is required to mitigate that risk. This paper will examine the basics of bone remodelling and structural maintenance before delving into the past and current literature in homeostatic control of bone density in space.

Regulation of Bone Remodelling

To provide context for the review of bone density maintenance in space flight, we must look at what factors regulate physiological homeostasis. This centers around the balance between parathyroid hormone (PTH), activated 1,25-dihydroxycholecaliferol (1,25-(OH2)D3) and calcitonin. The parathyroid gland, specifically the chief cells, release PTH in response to a decrease in circulating plasma calcium levels. This increase in PTH is sensed in bone via the vascular network of the bone matrix, enabling upregulation of osteoclast activity. Osteoclasts mediate the breakdown of bone by carbonic anhydrase which causes an increase in circulating calcium levels by mobilizing calcium previously stored in bone.

The mechanism for this upregulation lacks a distinct physiological receptor which actively upregulates osteoclasts. Instead, osteoblasts secrete RANK-ligand, which in turn activates osteoclasts. PTH further increases circulating calcium by increasing reabsorption of calcium in the kidneys and increasing the secretion of phosphate in the urine. PTH also increases the conversion of

inactive Vitamin D to the active metabolite 1,25-(OH2)D3. Active 1,25-(OH2)D3 works similarly to PTH to increase serum calcium concentrations. Unlike PTH however, 1,25-(OH2)D3 exerts its influence by increasing the reabsorption of calcium in the kidney as well as increasing calcium absorption from the gut. Serum calcium self-regulates by decreasing levels of circulating PTH in a negative feedback loop.

Calcitonin disrupts osteoclast activity through binding and disabling osteoclast receptors that would normally recognize RANK-L for activation. This decreases calcium release and stabilizes bone density.

It is the combination of the aforementioned three factors, as well as peripheral influence by oestrogen, thyroid hormones and glucocorticoids, which allows the human body to maintain a delicate balance between trabecular and cortical bone turnover and serum calcium levels.

Bone Cell Types and Normal Bone Remodelling

In normal bone remodelling, a balance between bone resorption and bone formation is regulated and maintained to ensure there is no significant net changes in bone mass, and consequently, mechanical strength (Feng & McDonald, 2011). An imbalance between bone resorption and bone formation may occur under certain pathological conditions or in the absence of mechanical stimulation, leading to abnormal bone remodelling and the development of bone disorders.

There are two major types of bone in the human body; cortical and trabecular bone. Cortical bone provides mechanical support and leverage functions and protects vital organs, whereas trabecular bone provides strength, and is the major site of bone remodelling. Old or damaged bone is removed by osteoclasts, then replaced by new bone formed by osteoblasts at a rate of 25% turnover in trabecular bone and 3% in cortical bone annually (Clark, 2008). Bone composition is approximately 10% cells, 60% inorganic mineral crystals, and 30% organic matrix (Seeman & Delmas, 2006). Hydroxyapatite composes the majority of the inorganic mineral crystals and type one collagen represents approximately 88% of the organic matrix, while other non-collagenous proteins comprise approximately 10% and lipids and glycosaminoglycans the remaining 1-2% (Feng & McDonald, 2011).

The bone remodelling process is carried out by the bone multicellular unit (BMU) and requires the action of four major types of bone cells; bone-lining cells, osteocytes, osteoblasts and osteoclasts. The bone-lining cells cover the inner endosteum of the bone and are thought to be quiescent osteoblasts, connected to active osteoblasts via adherens junctions (Clarke, 2008). Pluripotent stem cells give rise to the osteoprogenitor cells which in turn differentiate into osteoblasts, osteocytes and bone-lining cells. (Partridge, 2010). Osteocytes differentiate from osteoblasts and are embedded within the bone matrix during skeletal development or during previous cycles of bone remodelling. The osteocytes maintain their connection with each other and the bone surface via filopodial cellular processes, forming a syncytium.

The osteocyte functions as a mechanosensor, as fluid may flow in response to external forces in osteocytic canaliculi causing fluxes in calcium across filopodial gap junctions and transmitting information from the osteocyte to the osteoblasts (Clarke, 2008). Furthermore, osteoclasts, the bone-resorbing cell, are multinucleate giant cells which differentiate from mononuclear cells of the monocyte/macrophage lineage when stimulated by the monocyte/macrophage stimulating factor (M-CSF) and the receptor activator of nuclear factor kappaB (NF-kappaB) (Feng & McDonald, 2011).

The bone remodelling process involves four major distinct yet overlapping phases. The activation phase begins when mononuclear/macrophage osteoclast precursors lift the endosteum containing the bone-lining cells off the bone surface (Clarke, 2008). This is followed by the fusion of the mononuclear cells to form the multinucleated pre-osteoclasts. These pre-osteoclasts then bind to the bone matrix via interactions between integrin receptors in their cell membranes and RGD-containing peptides in the extracellular

matrix (ECM) proteins, forming annular sealing zones around the bone-resorbing compartments beneath the multinucleate pre-osteoclasts.

The second phase of the bone remodelling process is resorption. The formation, activation, and resorption of osteoclasts are regulated by the ratio of receptor activator of NF-kappaB ligand (RANK-L) to osteoprotegerin (OPG), and by the concentrations of a number of factors includingparathyroid hormone (PTH), vitamin D and calcitonin (Arfat et al, 2014). Furthermore, sclerostin (SOST) also stimulates osteoclasts, and antagonizes the action of Wnts and bone morphogenetic proteins (BMPs), providing a potential target for monoclonal antibodies in diminishing osteoclastic activity (Qin et al, 2015) . Mature osteoclasts secrete hydrogen ions via proton pumps and chlorine ion channels to lower the pH of the resorbing compartment to 4.5. These osteoclasts also secrete tartrate-resistant acid phosphatase, cathepsin K (serine protease), matrix metalloproteinase-9 (MMP-9), and gelatinase from lysosomes to digest the organic matrix, forming Howship's lacunae in trabecular bone, and Haversian canals in cortical bone (Clarke, 2008). This phase is completed by mononuclear cells, once the multinucleate osteoclasts have undergone apoptosis.

The third phase refers to the reversal compomentof bone remodelling. Coupling signals have been proposed to link tresorption to formation including transforming growth factor-beta (TGF-beta), insulin growth factor-1 (IGF-1), IGF-2, BMPs and fibroblast growth factor (FGF) (Hock et al, 2004). TGF-beta released from bone matrix decreases osteoclast resorption by inhibiting RANK-L in a fashion variant on the strain gradient in the lacunae (Smit et al, 2002, Smit et al, 2002). The strain gradient refers to how osteoclasts resorb cortical bone in a cutting cone, with strain increased behind the osteoclasts and reduced in front. In trabecular bone lacunae, the strain is highest at the base and lowest in the surrounding edges, with osteoclasts activated by reduced strain and osteoblasts by increased strain.

The final phase of the bone remodelling cycle is bone formation as osteoblasts synthesize new collagenous organic matrix, and regulate the mineralization of this matrix by releasing small membrane-bound matrix vesicles that concentrate calcium and phosphate and destroy mineralization inhibitors such as pyrophosphate (Anderson, 2003).

Spaceflight

The influence of spaceflight on the regulation of calcium has been a central point in understanding the effects of space travel on human physiology. The lack of gravity in space means loss of one of the most important aspects in regulating levels of bone density - mechanical resistance or loading on bone. This has been an area of discussion and research from before the first manned space flights. Despite being an area with high levels of interest, research and development have proved less fruitful than one might expect, due in large part to a poor sample size and the importance of maintaining safety standards on manned spaceflights.

Given that observations and measurements, as well as potential interventions can only accurately be measured during missions, there have been less innovations made despite the time course of spaceflight and bloom of technology in the intervening years. There have however, been a number of seminal studies and recently developed methods used to study microgravity conditions outside of spaceflight.

History of Research

The initial studies revolved around pre- and post-flight measurements of bone density in the heel and wrist on the Gemini and Apollo missions in the 1960's and 1970's (Smith et al, 2014). This proved, first and foremost, the ability of human beings to withstand microgravity while remaining compatible with life. It also demonstrated a loss in bone density, even over short flights of up to a maximum of fourteen days. The 1970's were rounded out by the Skylab studies in which three missions went up for up to a maximum of eighty-four days, providing data that suggested increased levels of calcium loss through faecal and urinary excretions during flight

(Whedon et al, 2006). Samples were frozen from this flight and upon subsequent analysis in the 1990's demonstrated bone resorption resulting in losses of calcium and bone density.

Advances continued during the era of the space shuttle, though the Columbia mission, on which a highly specialized calcium kinetics study was designed, was ultimately ill fated as it crashed on landing. The majority of information gleaned from shuttle era studies was similar to that of early flights, in that pre- and post- flight measurements made up the majority of data, providing a limited data-set with which to observe in-flight changes.

The advent of the space stations proved more fruitful in furthering our knowledge of bone remodelling in microgravity, as well as providing evidence for effective interventions. First iRED and then aRED (interim and advanced resistance exercise device, respectively) (Zwart, 2007, Smith et al, 2012, Smith et al, 2014) were premiered on the international space station. These technologies replaced simple treadmills and stationary bicycles in providing resistance based exercise options to astronauts with the aim of increasing new bone formation, balancing microgravity based losses. Ultimately it was the aRED that proved to be effective in increasing bone formation as it provides greater loading capacity, a wider variety of exercises designed to target sites which traditionally display the highest degrees of bone mass decline and can simulate the inertia associated with gravitational loading (Smith, 2012). At the same time as the introduction of the aRED however, dietary changes such as an increase in omega-3 polyunsaturated fatty acids and supplementation with vitamin D, both factors important in calcium homeostasis, were improved in these missions, possibly confounding the findings (Smith et al, 2014). Other important nutritional components which can affect the excretion of calcium include diets high in animal protein and potassium and diets with a high dietary sodium intake, which is typical to an astronaut diet, as both have been shown to increase urinary calcium excretion (Arfat et al, 2014).

Finally, pharmacological interventions have been proposed and tested as a preventative course inhibiting bone resorption. Bisphosphonates including oral alendronate, etidronate and intravenous zoledronic acid, the first line treatment for osteoporosis according to the 2012 NICE guidelines, have been considered and tested. Though results are confounded by the conversion from iRED to aRED in the target population and dietary advances, the studies seem to suggest that the effects are beneficial beyond exercise and that side effects are outweighed by these benefits (Smith et al, 2014). Testosterone supplements have also been mooted as a potential preventive agent, though no benefits have been shown either in bed-rest or extended spaceflight studies.

Effects of Microgravity on Bone Remodelling

Space and the simulated microgravity environment alters the cellular physiology of bone MSCs, osteoblasts, osteocytes and osteoclasts. MSC differentiation is redirected from osteogenesis to adipogenesis in those who have experienced a brain or spinal cord injury and subsequent withdrawal of mechanical loading on the bones (Arfat et al, 2014). This withdrawal of mechanical loading makes these injuries a convenient terrestrial model for research into unloading in spaceflight. Cytoskeletal changes affecting MSCs include alterations in the F-actin filaments that mimic those seen in cellular apoptosis. In addition to this, microgravity induced reduction in MSC differentiation to osteoblasts is mediated by a decrease in the mitogen-activated protein kinase (MAPK) pathway (Huang, 2009).

Microgravity-induced bone loss has been attributed to the reduced proliferation and differentiation of osteoblasts, as well as their decreased responsiveness to bone-related factors. Actual or simulated weightlessness disrupts osteoblast microfilaments, resulting in defective bone formation, and a decrease in the expression of the transcription factor alkaline phosphatase (ALP), which is important for osteoblast differentiation (Carmeliet et al, 1997). Regarding

the signalling pathways which affect osteoblast differentiation, integrin B1, a microgravity sensitive BMP2 regulator, causes inhibition of focal adhesion kinase (FAK) as well as ERK 1 and 2 activation when blocked by antibodies(Arfat et al, 2014). BMP2 is responsible for starting osteoblast cytoskeletal rearrangement during osteoblast induction, affecting osteoblast migration and adhesion (Huang, 2011). Osteocytes regulate bone resorption and formation in the context of both bone remodelling. Under normal gravity, mechanical loading can lead to strain and deformation of the bone matrix and disturb the interstitial fluid surrounding the lacunar-canalicular network of osteocytes. This fluid shear stress is one of the major mechanical stimuli acting on osteocytes.

In microgravity, there is an absence of mechanical loading, resulting in a dramatic reduction in fluid shear stress, and subsequent activation of the osteocytes and release of the physiologically important second messenger molecules. In addition to this, microgravity also induces alterations in the cytoskeletal architecture of the osteocytes and suppresses the gap junctions connecting these cells to one another (Di, 2011). Apoptosis of the osteocytes will negatively impact the bone remodelling events which maintain weakened bone. This loss detrimentally affects the areal bone mineral density (aBMD), the current standard in the measurement of bone density, by up to 10% according to Sibonga (2013). LeBlanc et al (2000) have reported aBMD losses of between 1-1.5% per month, exceeding the aBMD decline observed with primary osteoporosis in older individuals. When one considers the increased risks of mortality associated with osteoporotic fractures, this provides a very real marker for the requirement of management of aBMD decline. Lastly, osteoclast differentiation is enhanced in the microgravity environment, likely due at least in part to elevated levels of specific growth factors in pre-osteoclasts, possibly leading to an alteration in the RANKL:OPG ratio (Sambandam, 2010).

Concerns

Unfortunately, there remain a number of concerns with regards to the current breadth of research in bone remodelling during spaceflight. With the small number of missions and limited number of crew members on each mission it is difficult to produce satisfactory experimental design to confirm or update hypotheses.

Furthermore, due to the intense nature of spaceflight missions cannot be compromised to craft studies in which astronauts were exposed to different conditions or experimental measures. Safety requires that each are subjected to conditions which maximize their likelihood of returning home intact. Also due to the nature of the astronaut selection process it is impossible to truly randomize or control for a number of selection variables, ensuring that the studied sample is often quite homogenous.

With further regards to the safety concerns, the fact that diet, nutrition and pre-screenings have been improved has meant that any data gleaned from studies of exercise in the microgravity environment may have been altered by the dietary changes. Thus comparing missions or forms of exercise is difficult due to a high degree of variability in underlying conditions.

Conclusions

In summary, we see extraterrestrial research into bone resorption as a field which has made significant advances, but one which still invites discovery. While countermeasures have been derived, they remain imperfect, with room for improvements to aid in maintenance of skeletal integrity. Optimizing nutrition to aid in maintaining a healthy balance has also progressed, specifically in regulation of Calcium, Vitamin D and caloric intake, with enhanced Omega-3 polyunsaturated fatty acids. However, there remains significant room for an expansion of knowledge when considering the potential requirements of longer spaceflight missions currently under development.

Conflict of Interest

Neither author has any conflict of interest to declare.

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