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Erasmus Journal of Medicine: independent scientific journal

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Colofon

Erasmus Journal of Medicine is a scientific magazine by and for students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the students' organization of Erasmus MC).
The journal will appear twice a year. It will be published on paper (2500 copies) and on the EJM website (www.erasmusjournalofmedicine.nl).
The main purpose of the journal is to stimulate Erasmus MC medical students to read and write about medical scientific subjects, early in their career. A secondary purpose is to make the results of excellent student-driven research known to others. The journal contains papers describing original research (Full articles), systematic reviews (Reviews), summaries of recently conducted studies (Extended abstracts), short descriptions of research projects looking for students to participate (Research News), opinion papers written by students (Opinions), editorial comments and letters to the editor.
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Foreword

Publish or perish

The pressure put on researchers to publish articles in scientific journals is high. 'Publish or perish' is the ironic expression often heard. In order to further your scientific career publishing articles is vital, preferably in high impact factor journals, journals from which the number of citations to articles by peers is higher than average.
The peer reviewed articles system used by journals is therefore not only a good method of assessing the quality of scientific research systematically, but it also serves as a motivation for ambitious researchers to continue to work very hard. This is a welcome support for deans, who are responsible for the quantity and quality of the scientific output of their institutes.
Nevertheless, this reasoning has come under increasing pressure over the past decades. The success of researchers and professors is no longer being exclusively judged by their scientific merits based on the weight their articles carry in the peer review system. Researchers are increasingly also becoming entrepreneurs who need to raise external funds for their research. Professors are increasingly becoming managers, responsible for facilitating and coordinating this fundraising. All this within a context in which there has been a general increase in the call for social responsibility. We expect researchers nowadays to be able to hold a lively conversation in a talk show such as DWDD.

In addition to scientific research, patient care and education are 'equally important' core tasks that also continually need attention at Erasmus MC. Particularly education requires a great effort by the dean in motivating scientific researchers to invest sufficient time in this. The rewards for this core task (in terms of student satisfaction and professional education of a new generation of physicians and researchers) are less measurable and also take much longer than the academic recognition associated with a scientific publication.
Much is asked of researchers to combine all these tasks and at the same time work on their scientific career. "The number of tasks is constantly increasing but nothing is ever crossed out on the list", the people around me sometimes sigh. And this is indeed often the case. At Erasmus MC we aim to impart skills in young people enabling them to meet these expectations as well as possible. Part of scientific education is learning to read, publish and review scientific articles. Erasmus Journal of Medicine offers the opportunity to do this.

Certainly highly recommended!

Prof. Huibert A.P. Pols, Dean and Vice Chairman of the Board of Directors Erasmus MC

Erasmus Journal of Medicine 3rd issue

The third issue of the Erasmus Journal of Medicine is a fact. Looking back at the first and second issue we can't be anything but proud.

Large numbers of manuscripts are submitted and send trough a system that functions as on professional level. The members of the editorial board are becoming more aware of their individual tasks and greater plans are made for the future of the Erasmus Journal of Medicine.

This, however, does not mean that we are fully developed. Although evolution has taken a fast left turn and made us student editors from 'just' medical students into part of a well functioning editorial machine, there is still a lot that needs to be done.

For this, we need the help of all medical students at the Erasmus MC medical Center, because you make this journal into a success by sending in quality manuscripts and reading the work of your fellow medical students. But let us not forget all the others who read it.

Our aims are unchanged. We want to publish a high quality medical journal, by students, for students (and the rest of the employees at the Erasmus MC Medical Center).

'Enjoy the read.' We look forward to your contributions!

Denise van der Linde
Mostafa Mokhles
Maartje van der Schaaf
Thomas Thijs
Medical students, Erasmus MC University Medical Center Rotterdam, the Netherlands

Erasmus Journal Of Medicine

Image from Myrte Maessen & Beatrice van der Matten, Correlation between prenatal test results and fetal autopsy findings, this journal, page 18

Marfan syndrome: wait for aortic dissection or not?

Marfan syndrome (MFS) is one of the most common inherited connective tissue disorders with a reported incidence around 1 in 5000 individuals. There is a wide range of clinical severity. The disease typically manifests itself in cardiovascular, ocular and musculoskeletal abnormalities. Progressive aortic dilatation is one of the most important manifestations of MFS, since this could lead to the very dangerous complication of aortic dissection. Mortality of acute dissection is high and consequently MFS patients have a short untreated life expectancy of 32 years from birth onward.

The article by Jelle Bousema and Birgit Lavrijssen focuses on the very interesting question whether elective surgical valve-sparing aortic root replacement improves life expectancy without too many complications. The rationale behind this therapy is very logical: why wait for dissection if you could electively replace the dilated part of the aorta? However, like always, it is not as simple as it sounds.

The results of this systematic review suggest that elective root replacement improves life expectancy in MFS with an acceptable complication rate. However, how could we determine whether a treatment is working? The tricky thing is always to find a correct, unbiased comparison for the outcome. The golden standard or in other words the peak of the "evidence pyramid" is of course the randomized controlled clinical trial (RCT). But is this always possible? The answer is of course, as you would expect, NO. Most clinicians and patients will be rigidly opposed to participating in a trial that compares this treatment with no treatment. A trial design that compares direct elective surgery with postponed surgery (for example 5 years) could be helpful, and could be ethical, as most physicians will be in doubt about the proper timing of the treatment. Still, the comparison between the two treatment strategies would require prolonged follow-up, which will hamper feasibility. So, we are stuck with observational studies without control groups that claim that surgery improves survival, because in the 1970's life expectancy was 32 years and nowadays life expectancy for MFS is around 70 years. This conclusion however is strongly biased by the fact that life expectancy 40 years ago was per definition shorter than nowadays, by patient selection and confounding factors. For example bèta-blockade was also introduced for prevention of aneurysm progression and medical care in general has improved.

But since an RCT is not feasible and observational studies are biased, what is left? I think that we can reasonably conclude that evidence suggests that life expectancy is prolonged, but if we want to prove efficacy of valve sparing aortic root replacement and be able to predict which patients will benefit, we need relevant prediction and simulation models, that can be used to compare treatment with no treatment to estimate (quality adjusted) life expectancy for MFS patients. Perhaps a challenge for you as current medical students in the future?

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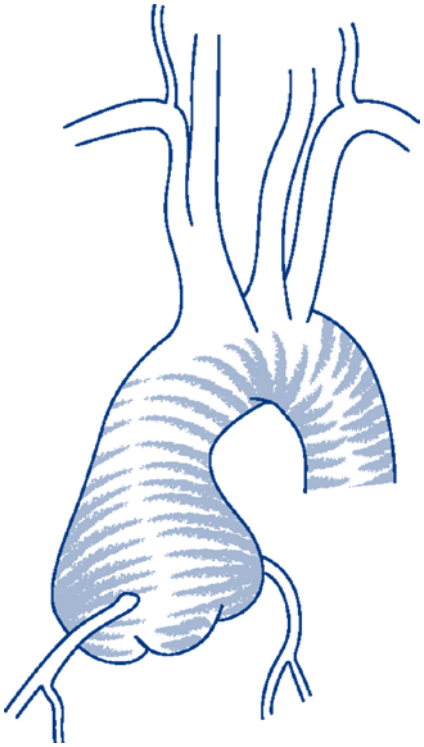

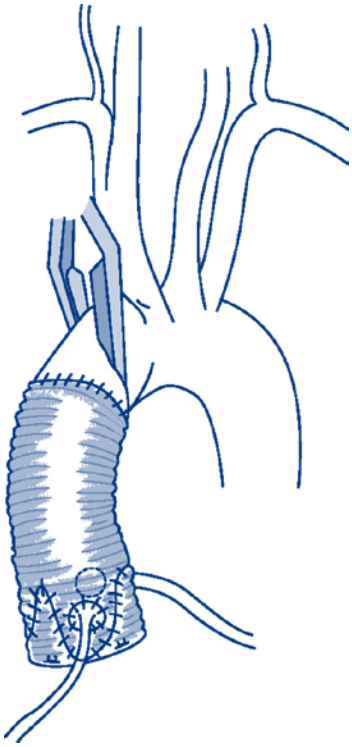

Splanchnic Vein Thrombosis unravelled or the quest for the missing link?

The most common presentations of venous thrombosis are deep vein thrombosis (DVT) of the lower extremity and pulmonary embolism. Splanchnic vein thrombosis (SVT) is an infrequent thrombotic disorder.

The causes of venous thrombosis can be divided into two groups: hereditary and acquired. Hereditary causes are for instance Factor V Leiden mutation, Protein S deficiency and Antithrombin deficiency. Acquired causes include malignancy, pregnancy and nephrotic syndrome. An underlying myeloproliferative disorder (MPD), especially polycythemia vera (PV) or essential thrombocythemia (ET), is also a risk factor for thrombosis. Considering large selected studies, prevalence rates for major thrombosis, at time of diagnosis, range from approximately 34 to 39% for PV and 10 to 29% for ET; the corresponding figures for thrombosis at follow-up are approximately 8 to 19% for PV and 8 to 31% for ET. [1]

Both PV and ET are strongly associated with a point mutation in JAK2. [2] JAK2 is a tyrosine kinase responsible for signal transduction by the erythropoietin, thrombopoietin, and granulocyte macrophage colony-stimulating factor receptors in hematopoietic cells, as well as for signal transduction by many cytokine receptors. It this way, it can be regarded a gain of function mutation. A substantial proportion of patients with SVT can be recognized as carriers of the JAK2 V617F mutation even in the absence of overt signs of CMD. [3]

In this issue of the journal Smalberg et al show that besides aquired point mutations in JAK2, also the germline JAK2 46/1 haplotype is associated with the occurrence of SVT. [4] Recent studies have convincingly shown a clear association between JAK2 46/1 haplotype and the acquisition of the JAK2 V617F mutation.[5] One therefore would expect that the patients with SVT and the JAK2 46/1 haplotype would be positive for the JAK2 V617F mutation as well. Indeed, this was the case in a number of patients. However, they were also able to show the JAK2 46/1 haplotype to be a risk factor in patients with MPD not carrying this specific mutation. In SVT patients without MPD, JAK2 46/1 haplotype was not a risk factor. Neither has there been found an association between this haplotype and DVT in patient with the specific JAK2 mutation. [6] Apparently, the haplotype alone is not sufficient. This study, therefore, calls for the identification of the factor responsible for the increased risk: the quest for the missing link.

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3. *De Stefano V, Fiorini A, Rossi E, et al. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. J Thromb Haemost 2007;5:708-14.*
4. *Smalberg JH, Koehler E, Darwish Murad S, et al. The JAK2 46/1 haplotype in Budd-Chiari syndrome and portal vein thrombosis. Blood 2011;117:3968-73.*
5. *Jones AV, Chase A, Silver RT, et al. JAK2 haplotype is a major risk factor for the development of myeloproliferative neoplasms. Nat Genet 2009;41:446-9.*
6. *Trifa AP, Crisan S, Popp RA, Cucuianu A, Buzoianu AD. JAK2 46/1 haplotype seems not to be associated with lower limb deep venous thrombosis. Blood Cells Mol Dis 2010;45:199-200.*

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How to become successful in scientific writing...

The Erasmus Journal of Medicine (EJM) is a peer-reviewed scientific journal. Its editorial board follows the international guidelines for journals and scientific publication. Therefore, the EJM is in many ways comparable with other international scientific journals. However, a major difference between EJM and other scientific journals is that the EJM is dedicated purely to medical students' research.

Since many habits are established during the medical education, we believe that it is important for you as a medical student to start publishing your research already in the starting phase of your medical education. However, young scientists often encounter major obstacles in publishing their first scientific paper because of the limited prior knowledge they have on how to publish in scientific journals. The EJM provides a platform to publish your scientific products and to gain experience with the steps that are to be taken in order to publish the results of a scientific research. Since the EJM is dedicated to students' research, the review process is slightly different from other international scientific journals.

We will help you ...

In contrast to other journals, EJM assists you during the entire process from submission to publication. The editors and reviewers provide extensive feedback during several revision rounds in order to help you improve the quality of the paper. Our Editorial Assistant, Petra Erkens calls you on your mobile phone to remind you of deadlines and help you to comply with author instructions. Personal meetings are sometimes arranged between members of the editorial board and student authors of manuscripts that need to be resubmitted, in order to discuss the reviewers' and editors' comments. Manuscripts submitted to EJM are, therefore, rarely rejected. Currently, the acceptance rate of EJM is as high as 80%. Furthermore, EJM provides the students extensive support in structuring and English editing of their manuscript, by making use of the expertise of mr Ed Hull and mr Charles Frink, both seasoned medical editors. After the paper is accepted for publication, Ed Hull helps you to get the storyline right, and after that mr Charles Frink helps you to get your English style and grammar up to the standards of an international English scientific paper. We are very grateful for their continuing efforts. We are sure that you will use the knowledge and experience you will acquire in this process to your benefit during your entire scientific career.

A summary of the submission procedure is published on page 46.

Looking back

The price you have to pay as a novice scientific writer for all this is relatively small. You will suffer a few minor blows to your ego, when you are confronted with the mildly put critique of editors and reviewers, but you will get used to that. After one or two review rounds, when your paper is accepted for publication, you will have to gear up and meet the English language editors. But after that the reward is large: a scientific publication in an international journal on premium glossy paper, of which you can really be proud. We hope that one day, when you are at the top of a gratifying academic career, you will be able to say "it all started with a publication in the Erasmus Journal of Medicine".

The Editorial Board of EJM cordially invites all Erasmus MC students to use this opportunity to get acquainted with scientific publishing and to submit your manuscript to EJM.

Mostafa Mokhles
Diederik Dippel

The efficacy of bone marrow transplantation in children with Niemann-Pick disease.

A systematic review

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Introduction: **Niemann-Pick disease is a group of disorders involving lysosomal accumulation of sphingomyelin and cholesterol due to deficiency of the enzyme acid sphingomyelenase (ASM). The main clinical features are hepatosplenomegaly, developmental delay, feeding difficulties, failure to thrive, hypotonia and deterioration of hearing and vision. This systematic review addressed the following question: is bone marrow transplantation an effective treatment for children with Niemann-Pick disease? Mortality among NPD patients is high and chances of recovery are low. Therefore, it is important to evaluate the current state of therapy for this disease.**
Methods: **I searched the Pubmed database on January 4, 2010 using a combination of the MESH terms Niemann-Pick disease 'and' bone marrow transplantation. The eligibility criteria included: English publications. Animal model studies and the adult form of NPD were excluded. To answer the main question of this review, the Acid Sphingomyelinase levels in leucocytes in all cases were compared before and after grafting, and the state of hepatosplenomegaly before and after grafting were compared.**
Results: **Five publications (follow up of cases) met the eligibility criteria. The NPD type B gave the most promising results, with decreased hepatosplenomegaly and increased ASM levels in the leucocytes. Increased ASM levels were seen in almost all cases, which is promising. But neurological deterioration, if present, was irreversible.**
Discussion: **BMT resulted in improvement after grafting and therefore appears to be an effective treatment for this disease. However, the limited number of publications precludes a definitive answer to my research question.**

Abbreviation

NPD	**Niemann-Pick disease**
BMT	**bone marrow transplantation**
BMA	**bone marrow aspirate**
ASM	**acid sphingomyelinase**

Background

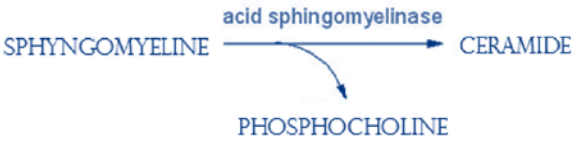
Niemann-Pick disease (NPD) comprises a clinically heterogenous group of disorders involving lysosomal accumulation of sphingomyelin and cholesterol [1]. Clinical features of this disease include hepatosplenomegaly, developmental delay, feeding difficulties, failure to thrive, hypotonia, deterioration of hearing and vision, and in 50% of the cases, the macula shows 'cherry red spots' [2]. Mortality is high among NPD patients and chances of recovery are low. Therefore, the current state of treatment is important to evaluate. Bone marrow transplantation, also known as Hematopoietic Progenitor Cell transplantation (HPC), is being widely studied as a treatment for NPD. A few cases of the Niemann-Pick disease treated with bone marrow transplantation were reported. The follow up of these patients could help to determine the efficacy of bone marrow transplantation in Niemann-Pick disease. Therefore the main question of this systematic review was: is bone marrow transplantation an effective treatment for children with Niemann-Pick disease?

There are three variants of Niemann-Pick disease, NPD A, B and C. The A and B variants are both characterized by a primary deficiency of enzyme Acid Spingomyelenase (ASM) and the resultant accumulation of sphingomyelin (see Figure 1) [3,4]. Under normal conditions, ASM is mainly found in lysosomes, where it participates in membrane degradation and turnover [2, 3]. In NPD A, characterized by a severe deficiency of ASM, the breakdown of sphingomyelin into ceramide and phosphorylcholine is impaired, resulting in excessive accumulation of sphingomyelin in all phagocytic cells and in the neurons. Spleen, liver, bone marrow, lymph nodes and lungs are the organs most affected, because of their high content of phagocytic cells. The central nervous system, including the spinal cord and ganglia, is also affected. Death occurs within the first 3 years [4].

NPD B variant is an autosomal recessive lysosomal storage disorder [5] presenting with organomegaly, but with few or no neurological symptoms [4,6]. NPD C variant is an autosomal recessive storage lipidosis in which fibroblasts exhibit a unique biochemical lesion characterized by delayed and impaired homeostatic responses to exogenous low-density lipoprotein (LDL) cholesterol loading, with lysosomal accumulations of unesterified cholesterol [7]. However, NPD C is quite distinct at the biochemical and molecular levels and is more common than NPD A and B.

Animal studies of bone marrow transplants (ASM 'knockout' mouse models) have shown promising results. ASM knockout mice that received bone marrow transplants showed a decreased accumulation of sphingomyelin and cholesterol quantitatively in their spleen. Sphingomyelin deposit in the bone marrow was also reduced histochemically. However, neurological manifestations were not reduced by the bone marrow graft [8]. Bone marrow transplantation recently reached the clinical phase in treatment of NPD.

Figure 1 - Function of the enzyme ASM



Methods

Search strategy

I searched the electronic database PUBMED using the combination of MESH terms Niemann-Pick disease AND bone marrow transplantation.

Inclusion criteria

- Published in English
- Fully-published (i.e., not in abstract form)
- Study included the infantile form of Niemann-Pick disease.
- Study included cases with Niemann-Pick disease and the results of bone marrow transplantation as a therapy.
- Cases of bone marrow transplantation performed on humans with Niemann-Pick disease.
- Complete follow up of cases with Niemann-Pick disease.
- Report characteristics: Report Engraftment BMT, ASM levels, state of liver, spleen and brains.

Exclusion criteria

- Study concerned the adult form of NPD (this form has a completely different pathology).
- Study concerned mouse models of transplantation or other animal studies.
- Study did not concern bone marrow transplantation

Study selection and quality assessment

The studies were reported cases, with complete follow up of patients. Data collection was provided by an independent reviewer, without any benefit of the results of this research.

Results

Overall, 5 publications (follow up of cases) met the criteria and were included in the study. Figure 2 outlines the flow of studies through the review process.

With the MESH terms Niemann-Pick disease AND bone marrow transplantation 19 results were found in the Pubmed Database with the limit English. Within these 19, based on title, 7 articles were based on animal studies, which were then excluded; 4 articles were not based on bone marrow transplantation, which were also excluded. Of remaining 8 articles, one had been published twice. Therefore, 7 articles remained for full-text screening.

Figure 2 - Flow of studies to final number of eligible studies

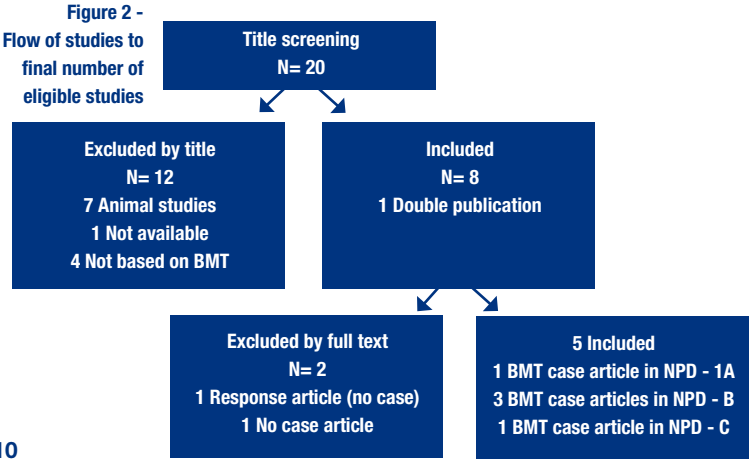


Table 1 - Study characteristics

Article	NPD Type	Clinical features
Bayever et al (1992) [1]	1A	Hepatosplenomegaly
	UMH	Developmental delay, poor weight gain, failure to thrive
		Mildly hypotonic and depressed reflexes
		Ophtalmologic examination: 'cherry red' spots on the retina
Bayever et al (1992) [1]	1A	Hepatosplenomegaly
	CHO	Feeding problems, poor weight gain and failure to thrive
	P	
	B	Mildly hypotonic and depressed reflexes
Vellodi et al (1987) [10] & Victor et al (2003) [6]		Hepatosplenomegaly
		Febrile convulsive
		ASM levels in leucocytes 0.44 (normal 0.75-3.5 nm/mg/hr)
		Chest radiographs: diffuse interstitial infiltrate in the lungs
		Liver biopsies: extensive accumulation of sphingomyelin in hepatocytes and Kupffer cells with early nodule formation
		Raised liver enzymes
Schneiderman et al (2007) [5]	B	Splenomegaly, thrombocytopeny
		ASM levels in peripheral leucocytes 0.24
		Chest radiographs: increased reticular and nodular interstitial markings
		Skinbiopt: Cultured fibroblasts
		BMA: Multiple sea blue histiocytes
		Ophtalmologic examination: 'cherry red' spots on both fundi
Hsu et al (1999) [7]	C	Hepatosplenomegaly (and neonatal hyperbilirubinemia)
		Neurological: developmental delay, mild mental retardation, dysarthria, ataxia, dysmetria, bilateral lower extremity spasticity
		ASM levels 40% of normal level
		Repeated lower respiratory tract infections
		Bone Marrow and liver biopsies: abundant foamy lipid-filled macrophages

After full-text screening, 2 more articles were excluded. One article [9] was a response to another article, and one article [3] was not a case, but a review about Niemann-Pick therapy, which was also excluded. In the end, 5 articles met the inclusion criteria and were included in this systematic review. (See flow chart)

Niemann-Pick disease type-A (also called type 1A) [1]

In Bayever et al. 2 cases of Niemann-Pick disease type 1A which had undergone BMT were reported. One case underwent the transplant in the University of Minnesota Hospital (UMH) and the other case underwent the transplant at the Children's Hospital of Philadelphia (CHOP).

With 3 months the UMH patient was observed to have developmental delay, feeding problems and poor weight gain. (See Table 1 for the expanded clinical features) At the age of 10 months this patient was referred for BMT. Before BMT the ASM leucocytes were below the normal ranges, and after BMT the ASM leucocytes were around 2.98 ±0.25 nm/hr/mg and stabilized (Table 4).

The CHOP patient also presented with feeding problems and poor weight gain at the age of 3 months (see Table 1 for the expanded clinical features). At the age of 4 months, the patient was referred for BMT. Like the UMH patient, the CHOP patient showed the

Table 2 - Study characteristics

First author (Year)	NPD Type	Diagnosis age Months)	BMT Age (Months)	ASM leucocytes Nm/h/mg *	Liver palpability	Spleen palpability
Bayever et al (1992) UMH	1A	3	10	Low	Increased	Increased
Bayever et al (1992) CHOP	1A	Birth	4	Low	Increased	Increased
Vellodi et al (1987) & Victor et al (2003)	B	8	38	0.44	12 cm below RCM**	14 cm below LCM***
Schneiderman et al (2007)	B	6	18	0.24		
Hsu et al (1999)	C		28	40 % of normal level	3 cm below RCM**	8 cm below LCM***

* Normal ASM levels in leucocytes are: 0.75-3.5 nm/mg/hr (5)

** Right Costal Margin *** Left Costal margin

Table 3 - Post BMT state of cases

First author (Year)	NPD Type	Engraft-ment BMT	Liver & spleen size	ASM leucocytes Nm/h/mg (Table 4)	Brain	Survival
Bayever et al (1992) UMH	1A	Yes, evidence	Increased	Normal (2.98 ± 0.25)	Deterioration	2 years
Bayever et al (1992) CHOP	1A	Yes, evidence	Increased	Normal (2.98 ± 0.25)	Deterioration	2 years
Vellodi et al (1987)	B	Yes, evidence	-	3.5	Normal	(not remark-ed)
Victor et al (2003)	B	Yes, evidence	Reduction	Increase followed by reduction	Late deterioration	16 years
Schneiderman et al (2007)	B	Yes, second evidence	Improve with weight gain	Increased -	Lansky score 80	11 years
Hsu et al (1999)	C	Yes, evidence	Impalpable after 6 months		Deterioration	-

same normal and stabilized ranges of ASM leucocytes (Table 4) after BMT.

In both patients before the bone marrow transplant, conditioning was carried out with Busulphan and Cyclophosphamide. Both patients also showed evidence of engraftment within 2 months of the BMT, with normal ASM levels.

BMT in Niemann-Pick disease Type A resulted in increased ASM levels in leucocytes. However, in both patients the neurological detoriation continued and the spleen and liver continued to increase in size. The bone marrow in both patients showed a decreasing number of storage cells. Bone marrow transplantation did not result in improvement of the disease, and both patients with NPD type A died 2 years after BMT.

Niemann-Pick disease type B [5, 6, 10]

The first reported case was from Vellodi et al. [10], where allogenic bone marrow transplantation was carried out on a 3-year-old girl with Niemann-Pick disease type B. She had a low level of sphingomyelinase activity in her leucocytes (0.44 nmol/h/mg table 1) and no obvious neurological impairment. At the time of transplantation, she was 3 years and 2 months old. The patient was developmentally normal for her age, but had slightly raised liver enzyme activities and extensive accumulation of sphingomyelin in the hepatocytes. For the detailed clinical features, see Table 1 (Vellodi et al.).

Before the bone marrow transplant, conditioning was carried out with Busulphan and Cyclophosphamide.

Success was confirmed with male chromosomes in the bone marrow (from her brother, the BMT donor) and with the rising levels of leucocyte sphingomyelinase activity on the 26th day after grafting. Before BMT, the ASM leucocytes were 0.44 nm/hr/mg. After BMT, this value rose to about 3.5 nm/hr/mg and stabilized. (see Table 4)

The 16 year follow up of Victor et al. [6] is based on the same patient reported in the article of Vellodi et al. Victor et al. reported a late neurological deterioration, and after 47 months, ASM levels decreased.

Schneiderman et al. [5], reported a case of an 18–month-old girl with NPD Type B who was treated 12 years ago with the bone marrow transplantation. At the age of 6 months the patient was referred due to persisting hepatosplenomegaly. This patient had mild thrombocytopenia, and bone marrow aspirate revealed the presence of multiple sea blue histiocytes, typical for storage diseases. See Table 1 for expanded clinical features of this case. Neurologically, this patient was in normal condition, but because of the persisting organomegaly and thrombocytopenia, a BMT was scheduled.

Pre-BMT, conditioning was carried out with thiotepa and cyclophosphamide. Autologous recovery was observed, so the BMT was repeated 7 months later. Successful engraftment was achieved at that time. Pre-BMT, the ASM levels in the leucocytes were 0.24 nm/hr/ mg. Post-BMT levels were 2.29nm/hr/mg on day 54 and 3.34 nm/hr/mg day 439 (see Table 4). Post-BMT, neurological detoriation appeared and slowly continued. The patient is now 13 years old and she has no thrombocytopenia. The patient is attending school full time and her grades are normal for her age.

In both patients with NPD type B, no obvious neurological impairment was observed pre-BMT, but their liver and spleen were enlarged. Post-BMT, both patients showed increased ASM levels in leucocytes. Although late neurological deterioration was present, these patients were able to live a normal lifestyle. In one case hepatosplenomegaly decreased, and in the other case it slowly increased. (See Tables 2 and 3)

Niemann-Pick disease type C [7]

Hsu et al. reported the case of a girl 3 years and 5 months old with Niemann-Pick disease Type C.

At the age of 14 months the patient was referred for investiga-

tion of repeated lower respiratory tract infections, developmental delay and persistent hepatosplenomegaly. Palpability of liver and spleen before transplantation were respectively 3 cm below right costal margin and 8 cm below left costal margin. See Table 1 for the expanded clinical features.

Pre-BMT conditioning was carried out with Busulphan and Cyclophosphamide. Successful engraftment was confirmed with evidence of male chromosomes (from her brother, the BMT donor). Pre-BMT, the ASM leucocytes were 40% of the normal ranges, but post-BMT values were not reported (see Table 4). Neurological detoriation continued post-BMT. The liver and spleen were reduced from pre-BMT sizes of 3 cm (liver) and 8 cm (spleen) below costal margin to both impalpable (see Tables 2 and 3). Survival in years for this case was not reported.

The patients with the different types of NPD all showed increased ASM levels in leucocytes, but they also showed graft-versus-host disease (GVHD). In NPD A and C, neurological deterioration continued after BMT, and in NPD B the neurological deterioration continued slowly or stopped.

Discussion

The results of my literature review suggest that bone marrow transplantation is effective in children with Niemann-Pick disease, especially in type B. This efficacy is probably due to the lack of neurological involvement in type B [11]. Therefore, Niemann-Pick disease type B with low liver involvement is a good candidate for bone marrow transplantation.

The lack of evidence in the other types of Niemann-Pick disease could be due to the neurological involvement, which is irreversible. Studies with mice models showed that the neurological involvement (if present) could be reduced if BMT is performed early. The study of Victor et al. [6] implies that BMT does not reduce neurological manifestations in humans with NPD because only a small number of bone marrow derived cells can cross the blood-brain barrier. Neurological detoriation is less in mice models, which could be due to the fact that the blood-brain barrier in mice does not close until one week after birth, in contrast to humans where it forms before birth.

Although all human case studies and bone marrow transplantation dependent cases found in the PUBMED database were included in this article without selection bias, publication bias was possible because only a few cases were reported of children with Niemann-Pick disease where BMT was performed.

Another limitation of the present study was the absence of a second reviewer.

Conclusion

Overall, these results indicate that BMT can be effective for patients with Niemann-Pick disease. If not treated, the mortality of young patients is very high, with accelerated neurological detoriation and hepatosplenomegaly. Therefore, BMT is a good option, even considering the high mortality of the intervention itself. This study implies that the survival is higher with BMT relative to survival without treatment.

Controlled trials are needed to provide clear evidence about this intervention. If possible, future studies should investigate a way to make BMT cells cross the blood-brain barrier. This could be needed to stop or prevent neurological deterioration. Further studies of treatments for this disease are necessary. Postnatal screening methods in high risk families could also be a point of attention.

Acknowledgement

I would like to thank Dr. PW Moorman for giving me useful feedback.

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The Best Postoperative Analgesia following Total Knee Arthroplasty.

A Systematic Review

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Objective: **Our objective was to determine whether Ropivacaine or Bupivacaine, and whether the addition of a Sciatic nerve block to a Femoral nerve block in total knee replacement-patients, provides better postoperative analgesia, resulting in lower morphine consumption and lower visual analogue scale pain scores (VAS-scores) in patients.**
Methods: **We searched the National Library of Medicine's Pubmed database on the 28th of January, 2011.**
Results: **The addition of a sciatic nerve block to a femoral nerve block provides lower postoperative visual analogue scale (VAS)- scores and lower morphine consumption in patients undergoing total knee replacement. The comparison between Rupivacaine and Bupivacaine did not provide clear results on postoperative morphine consumption. However we did find some conclusive results regarding VAS scores and sensory/motor block recovery.**
Conclusion: **Adding a sciatic nerve block to a femoral nerve block provides better postoperative analgesia for patients undergoing total knee replacement. Regarding the difference between the analgesic effects of Ropivacaine and Bupivacaine; according to our study, there is no distinct difference between the two substances.**

Introduction

Total knee replacement (TKR) is associated with severe postoperative pain. This postoperative pain is difficult to treat with oral analgesics; as they cause adverse endocrine, metabolic, and inflammatory responses[1]. Femoral nerve block (FNB) significantly improves postoperative analgesia compared with systemic opioid therapy, at least during the first 24 hours after TKR[2].
This makes femoral nerve block a well-accepted technique for regional analgesia after total-knee replacement. A block of the sciatic nerve, which innervates the thigh and the entire lower leg, is often combined with a femoral nerve block. However, the question remains if the addition of a sciatic nerve block leads to lower postoperative morphine consumption and lower visual analogue scale scores in patients.
Bupivacaine and Ropivacaine are both used in nerve blocks. Our aim was therefore to answer the following two questions:
1) Does Bupivacaine, which is more commonly used, provide less postoperative morphine use?
2) Does Bupivacaine result in lower pain scores than the newer analgesic Ropivacaine?

Methods

We performed two searches. First, to compare a femoral nerve block and a combined femoral-sciatic nerve block after a total knee replacement, we searched the Pubmed database using the following Mesh-terms.
"Arthroplasty, Replacement, Knee"[Mesh] AND "Nerve Block"[Mesh] AND "Femoral Nerve"[Mesh] AND "Sciatic Nerve"[Mesh].
Inclusion-criteria: A comparison between a femoral nerve block and a combined femoral-sciatic nerve block, pain scores as result, full text publication freely available at ErasmusMC.
Second, to compare a peripheral nerve block with Ropivacaine or Bupivacaine after a total knee replacement, we used the following Mesh-terms to search the Nation Library of Medicine's Pubmed-database.
"Arthroplasty, Replacement, Knee"[Mesh] AND "Nerve Block"[Mesh] AND "Ropivacaine "[Substance Name] AND "Bupivacaine"[Mesh].
Inclusion-criteria: A comparison between Ropivacaine and Bupivacaine, pain scores as result, full text publication freely available at ErasmusMC.
We noticed that not all publications were provided with Mesh terms for VAS scores, therefore we used the VAS scores as inclusion criteria.
We set the following limits for both searches: Randomized Controlled Trial, English, published between 1995-01-01 and 2011-28-01.

Results

Our first Pubmed search produced 11 publications, of which 4 were included based upon inclusion criteria (Table 1). Our second Pubmed search produced 6 publications, of which 2 were included based upon inclusion criteria. Later a third publication was added, which we found in the references of a meta-analysis.[8].(Table 2). Both searches were performed on the 28th of January.

The addition of a Sciatic nerve block

In all publications (Table 1), the addition of a sciatic nerve block (SNB) to a femoral nerve block (FNB), resulting in a combined femoral-sciatic nerve block (FSNB), was associated with less postoperative pain in patients.
The publications of Allen et al., Hunt et al. and Pham Dang et al. all showed significant lower postoperative pain scores in the FSNB group compared to the FNB group (Allen et al. $P<0.05$, Hunt et al. $P<0.05$ and Pham Dang et al. $P<0.0001$). However, the first two publications reported that this difference disappeared after a

Table 1 - Summary and results of included publications (part 1)

Reference	Journal	Comparison	# pt.	Outcomes	Results
Allen et al., 1998	Anesthesia and Analgesia	FNB, FNB + SNB	36	VAS, morphine consumption, nausea, pruritus, sedation, patient satisfaction	The FSNB group had lower pain scores than the FNB group until POD 1 (PM)
Hunt et al., 2009	The Journal of Arthroplasty	FNB, FNB + SNB	88	VAS, morphine consumption	The FSNB group had lower pain scores on the day of surgery but there was no difference on POD 1 and 2
					The FSNB group used significantly less PCA morphine
		FNB, FNB + SNB		VAS, morphine consumption,	compared to the FNB and control group.
Pham Dang et al., 2005	Regional Anesthesia and Pain Medicine		28	amplitude of knee flexion, occurrence of postoperative nausea and vomiting	Pain scores at rest were significantly higher in the FNB group compared to the FSNB group.
					This difference disappeared after 36 hours after surgery.
					The FSNB group consumed 81% less morphine compared to the FNB group.
Morin et al., 2005	Regional Anesthesia and Pain Medicine	FNB, FNB + SNB, PNB	90	Morphine consumption, pain scores, maximal bending and extending of the knee, walking distance	Postoperative morphine consumption during 48 hours was significantly lower in the FSNB group than in the FNB group.
					Postoperative pain scores were not different.

Table 2 - Summary and results of included publications (part 2)

Reference	Journal	Comparison	# pt.	Outcomes	Medication dosage	Results
de Lima e Souza et al., 2008	Journal of Clinical Anesthesia	Ropivacaine, Bupivacaine	90	Pain scores, morphine use, sensory/motor block recovery	Bupivacaine 40 mL 0.25% Ropivacaine 40 mL 0.25%	No significant difference in morphine use and pain scores.
						Significantly more patients remained with a nerve block at T3* in the Bupivacaine group (respectively P=0.013 and P=0.015)
Beaulieu et al., 2006	Anesthesia and Analgesia	Ropivacaine, Bupivacaine	46	Pain scores, morphine use, sensory/motor block recovery	Bupivacaine 40 mL 0.5% Ropivacaine 40 mL 0.5%	Morphine use was significantly higher at 24h in the Ropivacaine group (P<0.05)
						Pain scores were significantly higher at 7, 8 and 10h in the Bupivacaine group (P<0.05) and at 28h in the Ropivacaine group (P<0.05).
						The Bupivacaine group showed significantly slower motor block recovery between 12 and 20h and a significantly slower sensory block recovery between 24 and 28h.
McNamee et al., 2001	ACTA Anesthesiologica Scandinavica	Ropivacaine, Bupivacaine	75	Pain scores, morphine use, motor block recovery	Bupivacaine 1 mg * kg-1 (mean weight 77.0 kg) Ropivacaine 1mg * kg-1 (mean weight 80.5 kg)	No significant difference in morphine use and in nerve block recovery.
						Pain scores between 24 and 28h were significantly higher in the Ropivacaine group (P<0.05)

*T3= 10-24h after operation.

period of 24 hours. Pham Dang et al., however, reported that this difference remained until 36 hours after surgery.
The morphine consumption in the publications of Hunt et al., Pham Dang et al. and Morin et al. all proved to be significantly lower in the FSNB group than in the FNB group (Hunt et al. P<0.05, Pham Dang et al. P<0.003 and Morin et al. P<0.05).

Ropivacaine versus Bupivacaine

All the publications we included compared Ropivacaine and Bupivacaine, but they differed in concentration and dosage of analgesics. Nonetheless, the concentration and dosage within each publication did not vary (Table 2).
In the publications we reviewed regarding the first question (Table 2), a comparison between Ropivacaine and Bupivacaine, we did not see a clear difference in the morphine consumption. Only Beaulieu et al. showed a significant difference at 1 of the 12 time points studied (P<0.05).
Regarding the pain scores, we found more conclusive results. Both Beaulieu et al. and McNamee et al. showed significantly higher pain scores around 28h after surgery for the patients treated with Ropivacaine compared to Bupivacaine. (Beaulieu et al. P<0.05 and McNamee et al. P<0.05)

Both de Lima e Souza et al. and Beaulieu et al. found a significantly lower motor block recovery after 10 to 24h in the Bupivacaine group (Lima e Souza et al. P=0.015 and Beaulieu et al. P<0.05).

The same results were found regarding the sensory block recovery. (10 to 24h for de Lima e Souza et al. and 24 to 28h for Beaulieu et al.) (Lima e Souza et al. P=0.013 and Beaulieu et al. P<0.05).

Discussion/Conclusions

The addition of a Sciatic nerve block

We conclude that the addition of a Sciatic nerve block to a Femoral nerve block provides better analgesia after total knee replacement, resulting in lower postoperative morphine use and lower VAS-scores. This conclusion is based upon the fact that 3 out of 3 publications which measured postoperative pain demonstrated significantly lower VAS- scores in the FSNB group. Also, 3 out of 4 publications presented significantly lower postoperative morphine consumption in the FSNB group.

Ropivacaine versus Bupivacaine
We conclude that Ropivacaine provides slightly better analgesia compared to Bupivacaine, merely because of the shorter recovery time. In the Ropivacaine group only 1 out of 3 publications reported a significant increase in postoperative morphine consumption. Regarding the sensory/motor block recovery, 2 out of 3 publications presented a significantly slower recovery in the Bupivacaine group.

Clinical use
Based upon our conclusions, we advise adding a Sciatic nerve block to a Femoral nerve block as a standard for all postoperative analgesia treatments regarding total knee replacement.

Concerning the Ropivacaine versus Bupivacaine, we recommend that clinicians use whichever of these two drugs substances that the hospital has the most experience with, until there is sufficient evidence to choose one above the other.

Limitations of this study
All publications that we reviewed had patient groups with mean ages between 55 and 77 years. Therefore, these results may not be applicable for patients outside this range. Also, the number of patients used for each publication was limited, ranging from 28 to 90 patients.

Suggestions for future research
More studies comparing Ropivacaine with Bupivacaine with larger patient groups might give a more conclusive result. Also, the side-effects of both analgesics should be monitored and compared, something which was lacking in all publications we reviewed.

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Review

The efficacy of ECT in the treatment of schizophrenia.

A Systematic Review

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Objective: **Schizophrenia is a disabling mental illness. Because medication is not always effective, electroconvulsive therapy (ECT) could also have a place in the treatment of this disorder. To gain insight into the efficacy of ECT, we addressed the following question: What is the efficacy of ECT compared to sham-ECT in patients with schizophrenia?**
Methods: **We searched MEDLINE/PubMed for double-blind randomized controlled trials that compared ECT with sham-ECT in patients with schizophrenia using objective outcome measures.**
Results: **We found 6 RCTs, and all trials reported a trend of decreased disease severity in both ECT and sham-ECT. Four trials reported a significantly larger decrease in the ECT group compared to sham-ECT group. No significant superiority of ECT was demonstrated after follow-up.**
Conclusions: **We found evidence for the efficacy of ECT compared to sham-ECT in schizophrenia. This effect, however, seems to diminish over time. This also means that the reduction in symptom severity after ECT is in part a placebo effect.**

Introduction

Background

Schizophrenia is a serious mental illness and one of the world's top ten causes of long-term disability[1]. The most important symptoms of schizophrenia can be categorized as either a positive symptom, like psychosis, or a negative symptom, like apathy, withdrawal and cognitive impairment. The prevalence of schizophrenia in western civilization is about 1%, and the onset of the disease is usually between the ages of 16 and 30 [1]. Antipsychotic medication has been used as first-line treatment in schizophrenia since the 1950s. Prior to the emergence of antipsychotics, electroconvulsive therapy (ECT) without anesthesia was widely used. ECT induces a seizure for therapeutic purposes: an electrical current is administered to the brain via electrodes applied to the scalp [2]. Muscle relaxants were not available at that time, so side effects of ECT included fractures of the spine and extremities due to the vigorous muscular contractions that occur during the generalized seizure. Because of those side effects and the emerging alternative of antipsychotic medication, this therapy fell out of favor.

Antipsychotic medication is, however, not always an effective therapy and, once again, there is discussion about whether electroconvulsive therapy has a place in the treatment of schizophrenia [3]. Nowadays, to induce sedation and avoid the abovementioned adverse side effects, anesthetics and muscle relaxants are given during the procedure [2].To study the efficacy of ECT, the treatment can be compared with a placebo treatment. The placebo condition is called "sham-ECT", where the patient is anesthetized and the electrodes are connected to the scalp, but no electric current is administered and therefore no convulsion is generated.
In a 2005 Cochrane review, the effectiveness of ECT in schizophrenia was investigated. A short-term effect was observed, but a long-term effect was not found. Hence ECT was recommended only when an acute improvement was indicated. In this Cochrane review, results of studies comparing ECT with sham-ECT and results of studies comparing ECT with placebo pills were all taken together. Therefore, the placebo effect of ECT could not be judged objectively: ECT has to be compared to sham-ECT to rate the placebo effect [2].

Study objective

In this review, ECT was compared to sham-ECT and its placebo effect in patients with schizophrenia. Therefore, we addressed the following question: What is the efficacy of ECT compared to sham-ECT in patients with schizophrenia?

Methods

Search strategies

We conducted a search on January 12th 2011 using MEDLINE/PubMed for English-language only using the following phrase: "Schizophrenia"[Mesh] AND "Electroconvulsive Therapy"[Mesh] AND ("sham"[all fields] OR "placebo"[all fields] OR "simulated"[all fields] OR "control"[all fields]) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND English[lang]). A second search was conducted using the same key words in free text form instead of MeSH. Reviews, letters, abstracts, editorials and practice guidelines were excluded from search. Furthermore, we checked references of included papers by hand, for other relevant RCTs, to ascertain completeness of search results.

Selection criteria and quality assessment

Only randomized, placebo-controlled, human trials were included. Relevant trials included those that compared the efficacy of ECT with sham-ECT and where patients had been diagnosed with schizophrenia prior to trial. We only included trials using objective outcome measures, which were measured at baseline as well as during and/or post-trial.

General assessment of the methodological quality of the trials was conducted using the following criteria: randomization, blinding, comparability of the patients who were allocated to the ECT group and the patients who were allocated to the sham ECT group at baseline, proportion of patients who completed follow-up,

analysis conducted in the same group of randomization and equal treatment of ECT group and control group apart from intervention. Overall methodological quality of the trials was assessed using the abovementioned general criteria and some specific criteria that were particularly important for our own analysis: schizophrenia diagnostic criteria, ECT method, number of ECT treatments, duration of illness prior to trial, medication used during the treatment period and equality of the medication in the ECT group and the sham group.

Data extraction

We independently extracted trials identified by the electronic search and assessed them for relevance. Arising disagreements were resolved by consensus. For each report, the following information was extracted: study type, study objective, sample size, controls, duration of illness, treatment duration and objective outcome measures.

Analysis

To analyze the extracted trials, we searched for one or more comparable outcome measures that were used in all of the included trials. If too much diversity between trials was found, analysis was conducted using conclusions concerning the efficacy of ECT instead of different values in outcome measures.

Results

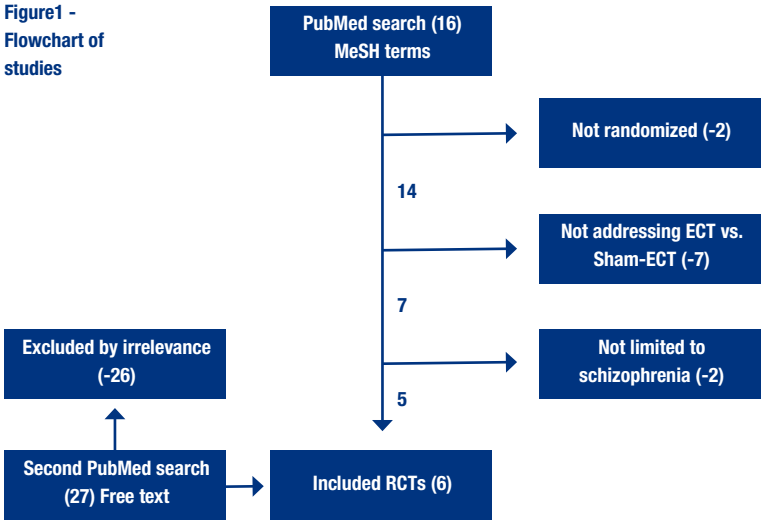
Included Trials

Our electronic search yielded 16 studies that were potentially relevant to this review. Of these, 11 did not meet inclusion/exclusion criteria; two studies were not randomized, seven studies did not asses the efficacy of ECT compared with sham-ECT and two did not primarily focus on the efficacy of ECT in patients who suffer from schizophrenia. The second search using free terms to assure completeness yielded only one new study that met the inclusion criteria, and a reference check of included articles yielded no new eligible studies. Consequently, 6 RCTs in total were included and analyzed in this review [Figure 1].

Trial characteristics

We analyzed six double-blinded, placebo-controlled (sham-ECT), randomized trials published between 1980 and 2003. Trial periods ranged from 4 to 18 weeks [Table 1]. We observed a considerable variation in duration of illness, type and dosage of antipsychotic medication used, duration of follow-up and objective outcome measures that were used in the RCTs. In total, 132 patients with

Figure1 - Flowchart of studies



schizophrenia who received either ECT (n = 69) or sham-ECT (n = 63) were included in these trials. All six RCTs used a parallel design where group allocation was executed using randomization. One of these trials used the Montgomery Asberg Schizophrenia Scale (MASS), the Visual Analogue scale: Global Psychopathology (V/A:GP), the Visual Analogue scale: Depression (V/A:D) and the Hamilton Depression Rating Scale (HDRS) to asses symptom severity. One trial used the Comprehensive Psychiatric Rating Scale (CPRS) and one trial used the Katz Adjustment Scale (KAS) as an objective outcome measure [Table 1]. In four trials, the Brief Psychiatric Rating Scale (BPRS)[11] was used for measuring symptom severity, and three of these trials also administered the Clinical Global Impression Scale (CGIS). We considered the comparability of outcome measures insufficient to do a quantitative analysis of the results.

Table 1 - Study characteristics

Study	Study type	Sample size ECT	Sample size control	Duration of illness before trial (months)	Number of ECT's in trial	Medication (mg/day)	Follow-up (weeks)	Objective outcome measures (* = primary outcome scale)
Taylor (1980) [4]	Double-blind RCT	10	10	> 6	8 -12	Chlorpromazine (300), Trifluoperazine (15)	16	CPRS, GP*
Brandon (1985) [3]	Double-blind RCT	9	8	-	8	None	28	MASS*, HDRS, V/A:G, V/A:D
Abraham (1987) [5]	Double-blind RCT	11	11	< 24	8	Trifluoperazine (20)	26	BPRS*, CGIS
Sarkar (1994) [6]	Double-blind RCT	15	15	< 6	6	Haloperidol (15)	24	BPRS*, KAS
Ukpong (2002) [7]	Double-blind RCT	9	7	-	6	Chlorpromazine (300)	20	SANS, BPRS*, CGIS
Goswami (2003) [8]	Double-blind RCT	15	10	> 60	6	Chlorpromazine (1000)	-	BPRS*, CGIS

Qualitative analysis

Compared to baseline, all six trials reported a decrease in disease severity in one or more of the outcome measures, in both real ECT and sham-ECT. Of these, four trials also reported a statistically significant larger improvement in disease severity after treatment in the real ECT group compared to sham [Table 2]. However no significant superiority of real ECT was demonstrated after follow-up.

Discussion

Interpretation of results

Relative to sham-ECT, ECT appears to more effectively reduce symptom severity in schizophrenia. The results indicated better efficacy of ECT compared to sham-ECT, because in four of six RCTs we found a significant larger decrease in symptom severity in the ECT group compared to sham-ECT directly after treatment. These findings are in line with the Cochrane Database review[2]. No evidence was found proving the superiority of ECT over sham-ECT after follow-up, because the rate of improvement decreased, and lasting improvement of symptom severity was found in the sham-ECT group as well. This improvement did not significantly differ from final improvement in the real ECT group.

We conclude that the efficacy of real ECT is present initially but seems to diminish over time. Taking into account the improvement that was seen in the sham-ECT group, we can conclude that the effectiveness of real ECT is partially due to the placebo effect and not solely caused by the convulsions generated in ECT. The effect caused by convulsions is superior to the placebo effect in alleviating symptoms severity, but is only present shortly after treatment. This means that we found evidence that ECT may have a place in the treatment of schizophrenia, but more research on efficacy of long-term maintenance ECT in schizophrenia is indicated in order to achieve a persisting decrease in symptom severity.

Limitations and representativeness

Although we only selected randomized, placebo-controlled, trials that compared the efficacy of ECT with sham-ECT in schizophrenia, there were several differences between the RCTs. First of all, no objective outcome measures were used in some of the trials, and not all trials reported raw data. This meant that we could not do a quantitative analysis of the results. In order to make quantitative comparisons between trials possible, we could have transformed each outcome scale to a 0-100% scale and expressed differences as percentage difference. A drawback to this approach would be that different scales may not represent entirely similar outcomes. Ideally, we would need the distribution of scores in each trial to corroborate this approach. These were not always available. However, this should not compromise our conclusions about the placebo affect, since no objective outcome measure quantifies the placebo effect, and we focused on the significant differences in outcome between trial groups, no matter which outcome measures were used.

Secondly, due to changes over time in the diagnostic criteria for schizophrenia, there are small differences in the inclusion criteria between the older and newer trials [3,4,5,9].

Thirdly, duration of illness prior to trial may have affected trial outcomes as well. Three of the trials showed a duration of illness of either less than 6 months or unknown [3,6,7].

Fourthly, the different types of medication and dosage might have influenced trial outcomes [10]. However, we considered comparability sufficient for this review. All but one trial used comparable medication, and despite the fact that in this one aberrant trial no medication was used at all, no significant difference in outcome was found in comparison with the other trials. Moreover, there were no concrete indications that the difference in medication affected the results of the initial trials [3].

Finally, no follow-up data were measured in one of the trials and therefore long term efficacy of ECT in this trial could not be taken into account in our conclusions [8].

Another limitation was that the number of patients in the trials was relatively low. This was not due to drop-out, but due to the fact that it is very hard to include schizophrenic patients in placebo controlled trials and especially in ECT trials.

Table 2 - Qualitative analysis of symptom severity on primary outcome scale

Study	Primary outcome variable	ECT: baseline (SD)	Sham-ECT: baseline (SD)	ECT: end of treatment (SD)	Sham-ECT: end of treatment (SD)	Difference in improvement: ECT - Sham [end of ECT] (p-value)	ECT: end of follow-up (SD)	Sham-ECT: end of follow-up (SD)	Difference in improvement: ECT – Sham [end of follow-up] (p-value)
Taylor	Clinical GP	6.5	6.4	1.6	3.7	2.1	1.8	2.2	-1.7
(1980) [4]		(0.2)	(0.2)	(0.4)	(0.5)	(p=0.04)	(0.6)	(0.4)	(NS)
Brandon	MASS	9	12	3	9	6	3	4	-5
(1985) [3]		(1.3)	(1.6)	(1.2)	(1.8)	(p=0.05)	(1.1)	(1.3)	(NS)
Abraham	BPRS	22.36	22.09	10.54	17.09	6.55	5.36	10.36	-1.55
(1987) [5]		(4.80)	(6.07)	(4.33)	(7.79)	(p=0.05)	(3.58)	(9.02)	(NS)
Sarkar	BPRS	24.6	28.0	6.6	6.1	-3.9	1.8	3.6	2.3
(1994) [6]		(7.3)	(7.8)	(9.7)	(6.3)	(NS)	(2.1)	(3.9)	(NS)
Ukpong	BPRS	22.33	19.43	3.67	4.14	3.37	1.00	1.29	1.29
(2002) [7]		(7.83)	(7.28)	(4.21)	(3.85)	(NS)	(3.00)	(3.42)	(NS)
Goswami	BPRS	55	50.1	44	40.4	9.7	-	-	-
(2003) [8]		(7.2)	(3.9)	(7.6)	(10)	(p=0.002)			

Suggestions for future research

Despite the fact that the results showed an initial decrease in disease severity and therefore an indication of the efficacy of ECT, this effect seems to fade over time. Hence more research is needed to address whether a persisting decrease in disease severity can be achieved using ECT. It would also be interesting to investigate how ECT decreases symptoms on a biological level, although such a study would be challenging. This review merely addressed the question of whether ECT is an effective therapy compared to placebo in schizophrenia, without taking possible side effect into account.

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Review

Is there a clonal relationship between leukemic cells and bone marrow mesenchymal stem cells?

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Abstract

Despite risk-adapted therapy, 20% of children with acute lymphoblastic leukemia (ALL) do not respond well to chemotherapy. One theory states that the interaction between the leukemic cells (LCs) and the mesenchymal stem cells (MSCs) plays an important role in the pathogenesis of leukemia. Recent studies have shown that the MSCs might contain the same aberration as the ones that are found in leukemic cells.

In this systematic review we compared six articles to determine if aberrations found in the LCs might also be present in MSCs and whether this shows evidence for a possible clonal relationship. Overall four articles did not detect a possible clonal relationship between the LCs and MSCs. The remaining two articles reported a clonal relationship between the LCs and BM-MSCs. To assess whether aberrations similar to those found in LCs are also present in the MSCs and to show evidence that no contamination took place, FISH, immunophenotyping and V(D)J rearrangements were performed by the researchers of the above mentioned articles.

Despite their contradictory conclusions based on the V(D)J rearrangements, the two articles both indicated that there is a possible clonal relationship between MSCs and LCs. Based on this evidence, we do not think that MSCs play a crucial role in the pathogenesis of leukemia, but it is likely that a clonal relationship is present in one specific type of leukemia, MLL-AF4, which arises in utero. This conclusion must be qualified because it is still unknown whether MSCs are V(D)J positive or not. This makes contamination hard to rule out.

The best way to provide evidence for a clonal relationship between MSCs and LCs would be by dual detection. The dual detection marker would contain the 'fusion gene' and a marker for ALL (CD19) or MSCs (CD105). By means of this dual detection it can be shown that the aberration would either be in ALL cells, in MSCs, or in both. This would provide conclusive evidence for contamination.

Introduction

In the Netherlands about 530 children are diagnosed with cancer every year. Nearly one-third of these children are diagnosed with leukemia, mainly acute lymphoblastic leukemia (ALL). Although the survival rates of childhood cancer are increasing because of better and more intensive treatment and genetic knowledge, 30% of the children diagnosed with cancer still die [1].The prognosis depends on cytogenetic abnormalities and response to therapy. Therapy can be adjusted to specific, individual variables, such as age, type of malignancy, stage and presence of cytogenetic abnormalities. However, despite this risk-adapted therapy, 20% of children with ALL do not respond well to chemotherapy. Currently, this resistance or bad response to chemotherapy cannot be explained.

One theory states that the interaction between the leukemic cells (LCs) and the mesenchymal stem cells (MSCs) may contribute to the resistance or bad response to chemotherapy. Mesenchymal stem cells are derived from the mesenchym, which is a particular form of undifferentiated connective tissue located in the primitive embryo. These stem cells are multipotent, which means that they are able to differentiate into several lineages of both mesodermal and non-mesodermal tissue, such as osteocytes, adipocytes, chondrocytes, myocytes, cardiomyocytes, fibroblasts, myofibroblasts, epithelial cells and neurons [2-4]. Together with the hematopoietic stem cells (HSC) and the endothelial stem cells (ESC), the MSCs form the progenitor cells in the bone marrow (BM). They can stimulate and differentiate the blood cells in the bone marrow due to the production of growth factors and cytokines [4]. Because of their differentiation capacity, MSCs are generally known from their target in tissue regeneration fields [2]. However, the roll of the MSCs in the development and progression of leukemia is still unknown. Recent studies have shown that the MSCs might contain the same mutations as the ones that are found in leukemic cells [5-8][11][12]. This could be evidence for a possible clonal relationship between MSCs and LCs, which means that the cells descend from a genetic-identical precursor cell. If the mesenchymal stem cells indeed play a crucial role in the pathogenesis of leukemia patients, this could be a promising new target for therapy. In addition, the presence of mutations in mesenchymal stem cells might explain why some patients do not respond well to chemotherapy.

Several articles reported on the contribution of the mesenchym to the pathogenesis of leukemia due to its possible clonal relationship, but their results are contradictory. The main question we addressed in our study was: is there a clonal relationship between LCs and BM-MSCs based on possible identical aberrations?

Methods

On December 14, 2010 we searched the electronic database PubMed using the following search terms: 'Mesenchymal stem cells [MAJR] AND leukemia [MeSH] AND (translocation OR chromosomal aberration OR fusion gene)'. To prevent bias, we read the articles independently. The exclusion criteria used for this systematic review were the following: the articles had to be published or written in English and they had to compare the aberrations found in the LCs with the BM-MSCs.

Results

Our Pubmed search produced eight articles. After applying our exclusion criteria, six articles remained for our systematic review on the correlation between the aberrations found in LCs and possibly in BM-MSCs. These articles all concerned patient studies (Table 1).

In total there were four studies that did not detect a possible clonal relationship between the LCs and MSCs. In other words, they did not detect that these cells descended from a genetically identical precursor cell. These articles were: Wöhrer et al. [5], Zhao et al. [6], Jootar et al. [7] and Carrara et al. [8]. Their total patient population consisted of 62 chronic myeloid leukemia (CML) patients.

The bone marrow MSCs of these 62 CML patients were isolated by either using the Ficoll-Hypaque density gradient or the Ficoll-Paque Plus gradient. This density-gradient can be used to separate cells from other elements in the blood. After this selection, the mesenchymal stem cells were screened for the BCR-ABL1 aberration. The BCR-ABL1 aberration plays a central role in the pathogenesis of CML [9][10].

Differentiation assays verified whether the isolated cells were in fact stem cells. A differentiation assay can be used to prove the multipotency of the stem cells, by showing the differentiation in for example osteoblasts or adipocytes. On all cell samples FISH and immunophenotyping were performed. Most cell samples consisted out of MSCs. It is very important to rule out whether these samples were contaminated by other cells such as LCs. If the used samples were not pure cell samples unreliable results may be presented due to this contamination. The FISH technique is useful for identifying chromosomal abnormalities, such as the BCR-ABL fusion gene. A fusion gene is formed from two separate genes.

Table 1 - Overview of study characteristics

	Publication date	Journal	Population	Characteristics of the patients
Wöhrer et al.	2007	Anticancer Research	8	CML
Zhao et al.	2005	Leukemia Research	28	CML
Jootar et al.	2006	Leukemia Research	11	CML
Carrara et al.	2006	Brazilian Journal of Medical and Biological Research	15	CML
Menendez et al.	2009	Journal of Experimental Medicine	38	ALL
Shalapour et al.	2009	Journal of Molecular Medicine	49	ALL

To characterize the cells, immunophenotyping can be done. This is a technique to distinguish cells by using antibodies against specific cluster of markers (CD). Cluster of markers are present on the cell. By using a combination of antibodies, cells can be characterized

Three of the four studies did not show a clonal relationship between the LCs and MSCs: no aberrations were found in the MSCs. The fourth article, Wöhrer et al., did find an aberration in the MSCs: by means of immunophenotyping they showed that this was due to contamination, meaning that no aberration was present in the MSCs (after immunophenotyping the 'MSC' cells were CD45 positive; CD45 is a hematopoietic marker).

On the other hand, the remaining two articles, Menendez et al. [11] and Shalapour et al. [12], did find a clonal relationship between the LCs and BM-MSCs. These studies concerned a patient population of 87 ALL patients. The BM-MSCs of these patients were screened for multiple aberrations that were found in the LCs. The isolation of BM-MSCs took place with the use of Ficoll-Hypaque density gradient or the Ficoll-Paque Plus gradient. For all isolated cells, a differentiation assay was made to validate the stem cells. In addition, FISH, immunophenotyping and V(D)J rearrangements were performed to assess whether aberrations were present in the MSCs (Table 2). V(D)J rearrangement is a random genetic recombination between variable, diverse and joining gene segments, taking place in the early stages of B- and T-cells.

Table 2 - Analysis and outcome measures of the study

	FISH	Cut-off value for FISH normal BM	MSC fraction: Immuno phenotyping for ALL markers	V(D)J rearrangement of MSCs similar to that of ALL?	Differentiation assays	Conclusion
Wöhrer et al.	YES	-	YES, CD45 +	-	YES	Contamination
Zhao et al.	-	-	NO	-	YES	No translocation present in BM MSC
Jootar et al.	YES	≥3%	NO	-	YES	No translocation present in BM MSC
Carrara et al.	YES	-	NO	-	YES	No translocation present in BM MSC
Menendez et al.	YES	-	NO, majority neg. but pos. cells present	NO	YES	4 MSC samples found positive for MLL-AF4
Shalapour et al.	YES	6%	NO	YES, 2 positive samples	YES	10 of 49 samples found positive for TEL-AML1, E2A-PBX1 or MLL rearrangements

Discussion/conclusion

In total, two out of six articles found a possible clonal relationship between the MSCs and LCs. The third article, Wöhrer et al., found positive results, but showed that this was due to contamination, since the samples turned out to be positive for CD45.

To show evidence for a clonal relationship, Menendez et al. and Shalapour et al. used several techniques. Both studies used FISH to determine a possible clonal relationship between LCs and MSCs. Menendez et al. found that the corresponding leukemic fusion gene could not be detected in the MSCs of the patients carrying TEL-AML1, BCR-ABL, AML1-ETO, MLL-AF9, MLL-AF10, MLL-ENL or hyperdiploidy. However, they detected 6.8±1.7% positivity in the MLL-AF4 infant B-ALL patients. They concluded that this was evidence for the fusion gene being present in the MSCs of the MLL-AF4 patients. This type of aberration is very specific and the fact that it only occurred as the MLL-AF4 mutation, is a strong indication for a clonal relationship. Still, this remains uncertain because the result (6.8±1.7%) could be due to false-positivity. The validity of their techniques is therefore questionalble.

In contrast to Menendez et al., Shalapour et al. determined the cut-off value (6%) for FISH in normal bone marrow, which was determined with the use of MSCs from healthy donors. They included 49 patients with the most common chromosomal translocations in children with ALL: TEL-AML1, E2A-PBX1 and MLL rearrangements. They found that the MSCs of 10 of these 49 patients showed one of the three translocations with a positivity between 10% and 54%, depending on the patients and the time point of analysis. These 10 patients were included in the study. They were able to retrieve MSCs with a specific translocation from these 10 patients, even when the patients were in remission and LCs were not present in the BM. This is a very strong indication for a clonal relationship.

The FISH test does not provide evidence that contamination has not taken place. If contamination did take place, the same FISH results would be present (Figure 1). In order to show evidence that no contamination had taken place, both Menendez et al. and Shalapour et al. performed monoclonal Ig gene rearrangements. Analyzing the Ig gene rearrangements provides information about the clonal origin of the disease.

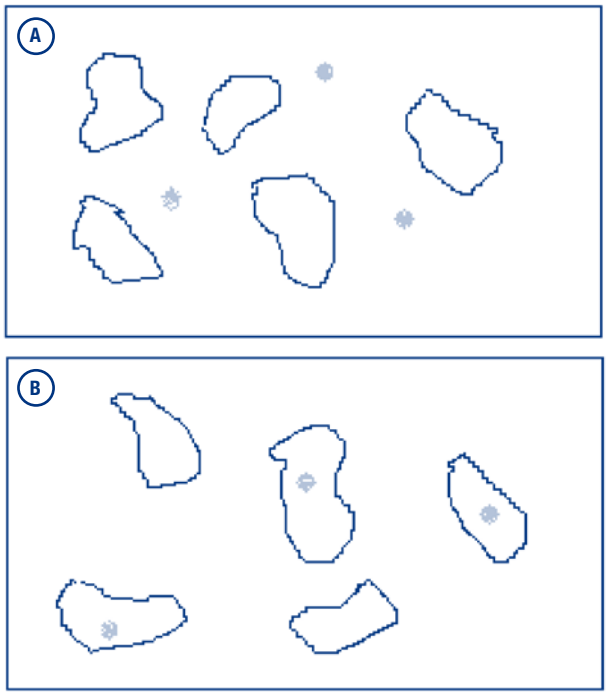
Menendez et al. performed monoclonal Ig gene rearrangements in only 3 patients. They characterized the rearrangements in the MLL-AF4 leukemic blasts. After this was done, they searched for the presence of these specific rearrangements in the MSCs. Using this technique they provided evidence for the absence of V(D)J rearrangements in the MSCs, although their results were negative. Based on this outcome, they concluded that no contamination of their MSCs samples had taken place. They concluded that this was evidence for an early developmental relationship between MSCs and the leukemic blasts.

Shalapour et al. found a 99.9% and 28% positivity for leukemia specific V(D)J gene rearrangements in the MSCs of two patients. They interpreted the presence of the V(D)J rearrangements as evidence for possible clonal relationship between LCs and MSCs, suggesting that MSCs are involved in the pathogenesis and/or pathophysiology of childhood ALL.

Despite these contradictory conclusions based on the V(D)J rearrangements, they both drew the same conclusion: there is a possible clonal relationship between MSCs and LCs.

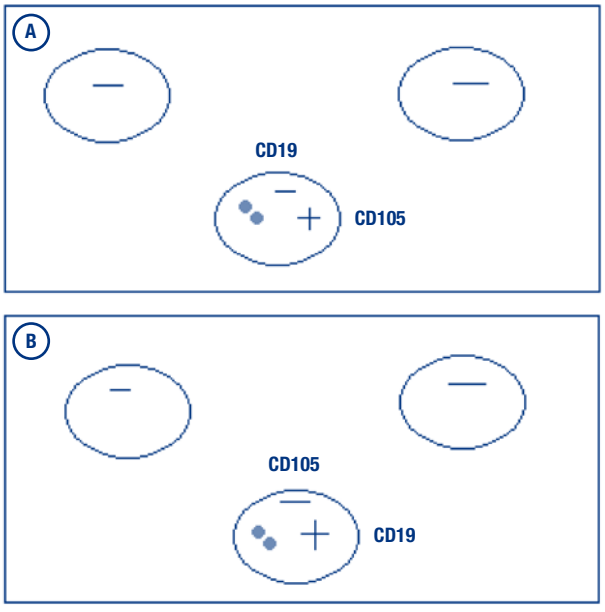
Based on the evidence provided by Wöhrer et al., Zhao et al., Jootar et al. and Carrara et al., we conclude that MSCs no not play a crucial role in the pathogenesis of leukemia. However, it is likely that a clonal relationship is present in one specific type of leukemia: MLL-AF4. We base this assertion on the evidence provided by Menendez et al. and the fact that this is a type of leukemia which arises in utero [13]. Due to this early development of leukemia, MSCs might contribute substantially to the pathogenesis of leukemia.

Figure1 - Evidence of contamination?



A. Three signals, ALL-cell derived, contamination of MSCs
B. Three signals, MSC derived only

Figure 2 – Recommendation



A: Positive for CD105, negative for CD19; No contamination ⇨ Mesenchymal stem cell
B: Positive for CD19, negative for CD105; Contamination proved ⇨ Leukemic Cell

Limitations and recommendation for future research

There were two limitations to our study that should be acknowledged. First of all, few articles have been published about a possible clonal relationship between the LCs and MSCs. Therefore, we only included six articles in our systematic review. Secondly, it remains very difficult to rule out contamination. The best way to provide evidence for a clonal relationship between MSCs and LCs would be by dual detection.

The dual detection marker would contain the 'fusion gene' and a marker for ALL (CD19) or MSCs (CD105) (Figure 2). By means of this dual detection, researchers can determine whether the aberration is located in ALL cells, in MSCs, or in both. This would provide conclusive evidence for contamination.

Overall the best option would be to continue research. Greater knowledge might lead to better therapeutic options and better understanding of the disease and its relapse.

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Review

The best surgical approach for treating multinodular goiter.
A systematic review

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Abstract

Objective: **To compare the effectiveness and complications of total thyroidectomy/near total thyroidectomy with subtotal thyroidectomy/bilateral subtotal thyroidectomy/Dunhill operation when treating benign multinodular goiter.**
Methods: **We systematically reviewed all available medical literature published since 2008.**
Results: **The four articles reporting recurrence of multinodular goiter all showed a significantly lower recurrence after total thyroidectomy. Two articles reported that a reoperation was required more often after bilateral subtotal thyroidectomy compared to total thyroidectomy. However, one of these articles reported no significant difference in reoperation frequency when comparing Dunhill operation and total thyroidectomy. Complications such as nervus laryngeus recurrence injury and hypoparathyroidism or hypocalcaemia were significantly higher in total thyroidectomy in two and three articles respectively. However, nervus laryngeus recurrence injury was significantly lower when total thyroidectomy was compared to reoperations.**
Conclusions: **Total thyroidectomy appears to be the most appropriate and effective surgical procedure for multinodular goiter.**

Introduction

Multinodular goiter (MNG) is a common condition, especially in elderly women. The prevalence of MNG is particularly high in regions with iodine deficiency, where it occurs at a younger age. Surgical treatment can consist of total thyroidectomy (TT), near total thyroidectomy (NTT), subtotal thyroidectomy (STT) and Dunhill operation (DO).

Besides surgery, radioiodine therapy is an attractive alternative, as it does not require hospitalization [1,2]. Another new treatment is the combination of subtotal thyroidectomy with prophylactic levothyroxine [3]. Although these non-surgical techniques have shown promising results, for large goiters and cases in which malignancy cannot be ruled out, surgical therapy remains the best treatment [4].

In 2008 Agarwal et al. stated that total thyroidectomy is a safe option in the hands of expert surgeons, and that near-total thyroidectomy is a similarly effective but safer option [5]. Although subtotal thyroidectomy is marginally safer than total thyroidectomy, it may leave undetected thyroid cancers in place. The authors concluded that total thyroidectomy is the procedure of choice for the surgical management of benign multinodular goiter. Recently, more articles have been published on this topic, and techniques such as the use of an ultrasonic dissector have been introduced [6,7]. An update on the topic is therefore needed. Based on the statements of Agarwal et al. and newly published articles, our study reviewed literature published after Agarwal et al. to test the current hypothesis that total thyroidectomy is the best choice for MNG.

This evidence-based review aims at studying the available data about the appropriateness and safety of total thyroidectomy and subtotal thyroidectomy. In this review, we addressed the following research questions. (1) Which type of surgery minimizes recurrence and reoperation for multinodular goiter and is thus the most effective? (2) Which type of surgery leads to fewer complications (defined as injury of the nervus laryngeus recurrens and hypoparathyroidism)?

Methods

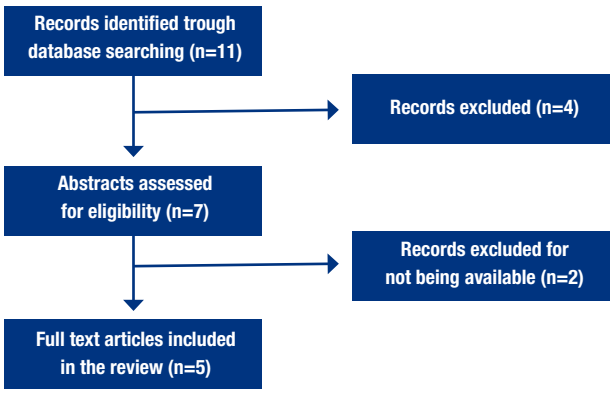
The National Library of Medicine's PubMed database was searched for articles written in English between 01-01-2008 and January 2011. The search was limited to Clinical Trials, Comparative Studies, Controlled Clinical Trials and Randomized Controlled Trials. In our search strategy we used both MeSh terms and text words:
1. Goiter/surgery [MAJR] AND Multinodular [All fields].
2. Goiter, nodular/surgery [MAJR].

We included only articles that were written in English, that compared total Thyroidectomy to other surgical techniques and that were available to the Erasmus Medical Center. Total thyroidectomy was compared to subtotal thyroidectomy and near total thyroidectomy based on various outcomes. Primary outcomes were defined as prevalence of recurrence or completion thyroidectomy. Secondary outcomes were defined as incidence of complications (morbidity).

Results

Our search resulted in eleven articles, of which five were included in this review (Fig. 1). Three articles were excluded because they did not compare any surgical techniques. One article was excluded because it did not compare total thyroidectomy to subtotal thyroidectomy. Another two articles were not discussed in this review because they were not available to the Erasmus Medical Center.

Figure 1 - Flow diagram of study selection



Most articles were retrospective cohort studies or non-randomized controlled trials, one study was a randomized controlled trial. Four articles described recurrence of multinodular goiter after surgery, and all showed a significantly lower recurrence in TT [8,9,10,11].

Three studies reported on reoperation rates [8,9,12]. These articles showed that reoperation was required significantly less often in TT when compared to STT or hemitotal thyroidectomy (HT). However Barczyński et al. also reported that there was no significant difference in reoperation when comparing TT and DO. These results are shown in Table 2.

Five studies also reported morbidity such as hypoparathyroidism, sometimes reported as hypocalcemia, and nervus laryngeus recurrens injury [8,9,10,11,12]. These complications were significantly higher in three studies when performing TT. However one article showed that TT had fewer complications compared to reoperation of STT and HT. Three articles found no differences in complications when comparing TT to STT. These results are shown in Table 3.

Table 1 - Studies

Study	Study Design	Measurements	Year	N	Country
Barczynski et al. [8]	Randomized Clinical Trial	Comparing TT, DO and BST* for prevalence of recurrent goiter and need for reoperation.	2010	600	Poland
Tezelman et al. [9]	Non-Randomized Controlled Trial	Comparing TT and BST for completion thyroidectomy and complications.	2008	2592	Turkey
Vaiman et al. [10]	Retrospective Cohort Study	Comparing TT, STT and NTT for the incidence of complications.	2008	6223	Israel, Russia
Vaiman et al. [12]	Retrospective Cohort Study	Comparing primary TT and STT for complications and comparing TT/ST to completed thyroidectomy.	2008	7123	Israel, Russia
Yang et al. [11]	Non-Randomized Controlled Trial	Comparing TT/NTT and STT for recurrent goiter and complications.	2008	346	China

* BST = bilateral subtotal thyroidectomy

Table 2 - Primary Outcomes

Study	Recurrence of MNG	Results (%)	P-value	Reoperation	Results (%)	P-value
Barczynski et al.	TT vs. BST	0.52 vs. 11.58	< 0.001	TT vs. BST	0.52 vs. 3.68	0.03
	TT vs. DO	0.52 vs. 4.71	< 0.01	TT vs. DO	0.52 vs. 1.57	n.s.*
Tezelman et al.	TT vs. BST	0 vs. 7.1	0.007	TT vs. BST	0 vs. 2.24	0.007
Vaiman et al. [10]	TT vs. NTT + STT**	0 vs. 20.5	<0.05	-	-	-
Vaiman et al. [12]	-	-	-	TT vs. STT	0 vs. 16.5	-
	-	-	-	TT vs. HT	0 vs. 18.5	-
Yang et al.	TT vs. STT	0 vs. 6.70	< 0.05	-	-	-

* Not significant, ** Recurrence in TT, NT and STT: 0%, 5.9% and 21.5% respectively.

Table 3 - Secondary Outcomes

Study	Surgical Techniques	N. Laryngeus recurrens injury	Hypoparathyroidism
Barczynski et al.	TT vs. BST*	5.49% vs. 2.1%, p = 0.007	10.99% vs. 2.1%, p <0.001
	TT vs. DO*	5.49% vs. 4.23%, n.s.	10.99% vs. 4.23%, p = 0.007
Tezelman et al.	TT vs. BST*	n.s.***	8.4% vs. 1.42%, p<0.001
Vaiman et al. [10]	TT vs. NTT**	1.4% vs. 1.2%, n.s.	2% vs. 1.9%, n.s.
	TT vs. STT**	1.4% vs. 1.1%, n.s.	2% vs. 2%, n.s.
Vaiman et al. [12]	TT vs. STT**	1.4% vs. 1.2%, n.s.	3.5% vs 2.5%, n.s.
	TT vs. Reoperation**	1.4% vs. 3%, p<0.05	3.5% vs. 5.9%, p<0.1
Yang et al.	TT vs. STT*	1.89% vs. 1.68%, p=0.48	6.92% vs. 5.03%, p=0.16

* Transient Nervus Laryngeus recurrens injury and transient hypoparathyroidism.
** Permanent Nervus Laryngeus recurrens injury and permanent hypoparathyroidism.
*** Not significant

Discussion

Our review suggests that TT minimizes recurrence and reoperation for multinodular goiter and is therefore a more effective operation technique. Recurrence of goiter after surgery was significantly lower after TT. The study of Lehwald et al., which was excluded from the results because it did not compare TT and STT, also confirms these results: after STT more recurrent nodules were reported [13]. Furthermore, Lehwald et al. compared function preserving (FP) surgery to standard radical surgery (STR). They defined FP as a unilateral resection or less then subtotal thyroidectomy with a remnant of > 4 ml. STR was defined as all surgery leaving a remnant volume of < 4 ml or NTT with a remnant of < 1 ml. Their conclusion was that there is a significantly higher risk of recurrent nodules after FP (18.6%) than after STR (2.5%).

Our review does not lead to a conclusive answer to our 2nd research question regarding complications. Reoperation rates were, as to be expected, significantly lower after TT. However the morbidity was higher after performing TT. Complications such as the risk of nervus laryngeus recurrens injury were increased. In STT, the surgeon does not come near the nerve but in TT the entire tissue of the thyroid gland is removed. For the same reason, the risk of hypoparathyroidism would also be increased because the parathyroid glands are at risk due to the complete removal. Although there were more complications in TT, reoperation after STT raised the rate of morbidity even higher. Reoperation rates after STT range from 3.68% to 16.5% (Table 2). This indicates that TT is the best choice for MNG.

However, new techniques such as postoperative levothyroxine therapy seem to reduce recurrence rates in the other thyroid lobe after partial resection of the thyroid gland, as described in a recent study [3]. Kaniuka et al. described how iodine treatment of MNG might be a good alternative to surgery [1]. But not all new techniques have shown promising results. For example, the use of a ultrasonic dissector does not seem to influence complication rates, as reported in two studies [6,7].

Limitations

There are some drawbacks to this review. Only one study was a randomized controlled trial and it is very possible that in the other studies there was a high rate of confounding by indication. Also, some studies were not performed in the western world, so compliance rates of patients taking medication may be lower, thus raising recurrence rates after STT.

Drawing conclusions based on the study of Agarwal et al. and these recently published articles is difficult, since the hospitals studied could differ in terms of their surgical expertise and therefore differ in complication rates.

Conclusion

TT seems to be the best choice for MNG despite the higher rate of complications. More comparative trials should be carried out, especially to validate and compare new techniques, for instance combining STT and postoperative prophylactic levothyroxine.

While many surgeons still perform sub-total thyroidectomy, total thyroidectomy seems the best overall option, but new techniques like the use of iodine and prophylactic postoperative levothyroxine raise new questions. These new techniques should be compared to TT as to see if recurrence and complication rates after reoperation can be lowered.

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Preventive aortic root replacement in Marfan syndrome

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Summary

Objective: **To give an overview of the short and long term results of preventive aortic root replacement in patients with Marfan syndrome (MFS).**
Methods: PubMed was searched on January 18th 2010 looking for papers on preventive aortic root replacement in MFS patients. Two authors screened the studies separately, using the same inclusion and exclusion criteria.
Results: Seven studies were included in this review. Overall 1645 patients were analysed, with a mean follow-up duration of 10.8 years. Average 30-day mortality was 1.9 % in elective surgery, and 8.4% in urgent surgery. Late mortality occurred in 16.8% of the patients. Endocarditis developed in 4.5% of the patients.
Conclusion: **Preventive aortic root replacement significantly improves life expectancy in Marfan patients.**

Introduction

Marfan Syndrome (MFS) is the result of a fibrillin-1 deficiency and has multisystemic manifestations, which typically involve the skeletal, cardiovascular and ocular systems [1].
Some examples of the most associated features with Marfan syndrome are occular lens dislocation, aortic valve prolapse, and aortic dilatation [2].

Dilatation of the aortic root exists in about 75-85% of the patients with Marfan syndrome [3].This includes dilatation of the aortic sinuses and annulus in addition to
the ascending aorta, leading to aortic valve insufficiency. If left untreated there is a high risk of death due to dissection or rupture of the aorta or heart failure resulting from severe aortic regurgitation [4].

Cardiovascular complications are primarily responsible for a reduced life expectancy and occur in more than 95% of adults with MFS. Without surgical treatment, the life expectancy of patients with MFS is 32 years. In 93% of the cases, cardiovascular complications are the cause of death [5].
Operative therapy of aortic aneurysms and dissections is still a challenging surgical intervention and is associated with a high postoperative mortality [6]. By improving operative therapy, the incidence of postoperative mortality and morbidity should decline [7].

Aortic root replacement (ARR) is a method introduced by Bentall and De Bono, which uses a composite mechanical valve conduit. It has long been considered the 'gold-standard' treatment. However, complications related to long-term anticoagulation are present in a significant number of patients. Therefore, a valve-sparing aortic root replacement (VSRR) was introduced. This technique preserves native valves and thereby avoids the disadvantages of a mechanical valve conduit and the complication of anticoagulation [8].

Endocarditis remains the most common late complication after aortic root replacement. Endocarditis is an infection of the endocardial surface of the heart and may include one or more heart valves, the mural endocardium, or a septal defect. It may occur as a result of turbulence or trauma to the endothelial surface of the heart, which makes the heart vulnerable for bacteria and infective endocarditis develops [9].

To prevent this, patients receive prophylactic antibiotic treatment and the use of homograft root replacement is preferable. [10] Despite these measures, it is not always possible to prevent endocarditis. In this review we look at late endocarditis, defined as endocarditis developed later than 60 days after aortic root replacement.

The aim of this review was to give an overview of the short and long term results of preventive aortic root replacement in patients with Marfan syndrome. Our primary endpoints were survival, both early and late survival, and occurrence of endocarditis.

Methods

On January 18th 2011 we conducted a literature search of all articles indexed in Pubmed with the following search terms: marfan syndrome/surgery"[Mesh] AND "epidemiologic studies"[Mesh] AND ("aorta/surgery"[Majr] OR "aortic aneurysm, thoracic/surgery"[Majr]). We only included studies in English on preventive aortic root surgery in Marfan patients with a follow-up duration longer than 5 years. In this review we focus on the mortality and risk for endocarditis after surgery. Studies where free full text was not available for students of the Erasmus MC online in PubMed were excluded. Studies involving only acute operations, external root replacement or which did not describe mortality/survival or endocarditis were excluded. Two authors searched independently and achieved consensus about the 7 articles included. Figure 1 shows the selection process during this systematic literature review.

Any death within 30 days after aortic surgery was considered to be an early death. We analyzed the early mortality by adding up the number of participants of all studies, and dividing this number by the total number of early deaths. We divided early mortality in early mortality after elective surgery and early mortality after urgent surgery. Average results are calculated by the authors with data from the included articles.

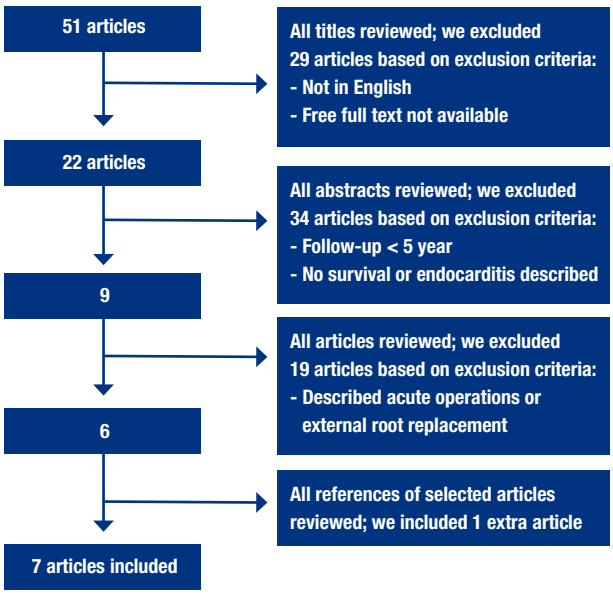

Figure 1 - Flow chart representing the selection of studies during the literature

Results

A total of 51 articles were identified, of which 7 articles were included (Figure 1). Overall, 1645 patients were analysed with a mean follow-up time of 10.8 years. Table 1 provides an overview of the publications obtained by the systematic review. In this review we focus on the mortality and risk for endocarditis after surgery. Results of the studies are showed in table 2.

30-day mortality

Table 2 gives an overview of the 30-day mortality of the various studies. The results are split into elective and urgent surgery. We calculated the 30-day mortality for all the studies together. A total of 1317 patients had elective surgery and 288 patients had urgent surgery. In both groups there were 22 deaths within 30 days.

Late mortality

Late mortality was defined differently in each article, so we give an overview of the late mortality results. Coselli JS et al[5] presents two late deaths for a long-term survival rate of 96.2%. Cameron DE et al[11] present 74 late deaths among the 370 patients who survived more than 30 days after surgery. Iguchi A et al[12] present four late deaths, at 2, 14, 24 and 27 months after the aortic root operation. Gott VL, Cameron DE et al[13] describe 43 late deaths. Alexiou C et al[14] present 15 late deaths. Gott VL, Greene PS et al[15] present 15 late deaths. Gott VL, Gillinov AM et al [16] present 28 late deaths. Table 3 provides an overview of the long-term mortality results.

Late endocarditis

Cameron DE et al [11] present 18 cases (4.8%) of endocarditis from the 370 aortic root replacement operation survivors. Gott VL, Cameron DE et al[13] show 11 patients (4%) with endocarditis from 271 root replacement operation survivors. Gott VL, Greene PS et al [15] present 24 patients (3.6%) who developed late endocarditis. Gott VL, Gillinov AM et al [16] present 14 (5.5%) of the 256 hospital survivors with late endocarditis.

Discussion

Preventive aortic root replacement significantly improves life expectancy in patients with Marfan syndrome. The average age of the patients at the time of surgery was 35.8 years. Cardiovascular complications in Marfan patients mainly occur at this age. By using preventive surgery, these complications can be avoided. Without surgery Marfan patients have a life expectancy of 32 years [5]. Our late mortality results suggest that surgery increases the life expectancy of Marfan patients. The results show a lower 30-day mortality rate in elective surgery compared to urgent surgery. This can be explained by the fact that the pre-operative situation of the patient is worse in urgent surgery. Furthermore, urgent surgery is a more difficult procedure for the surgeon.

Long-term survival confirms the improvement in life expectancy. Without surgery, 93% of Marfan syndrome patients die at a young age due to cardiovascular complications [5]. Preventive surgery increases survival, even 20 years postoperatively. The risk of developing endocarditis is relatively low compared with the advantages of the operation.

All included articles were published in peer-reviewed magazines. In- and exclusion were not exactly the same in all articles so the patient characteristics of the studies were not exactly the same. Despite that difference the results of the studies could be compared.

The authors recommend a study with a large number of patients, all selected by the same in- and exclusion criteria. Preferably, this study should make use of only one surgical technique (VSSR or ARR). By doing this, the outcomes can be compared better. A prospective randomized controlled trial studying the outcome between preventive aortic root surgery and for example sham surgery or conservative treatment with urgent surgery when that is necessary would be impossible, because to deprive Marfan patients from such a potentially lifesaving procedure as preventive aortic root replacement would be unethical.

Table 1 - Overview of publications included in the analysis

First author	Study country	Year of publi-cation	Operative period	No of patients	Type of surgery	Urgent surgery (%)	Mean follow-up (years)	Mean age (years)
Coselli JS [5]	United States	1995	1989-1994	69	ARR	NR	10	39.4
Cameron DE[11]	United States	2009	1976-2006	373	ARR / VSRR	8.3	20	32.9
Iguchi A [12]	Japan	2005	1985-2002	22	ARR	NR	6.9	31
Gott VL,Cameron DE[13	US / Europe	2002	1976-2000	271	ARR / VSRR	13.3	20	33
Alexiou C [14]	England	2001	1972-1998	65	ARR	41.5	8	41.7
Gott VL, Greene PS[15]	United States	1999	1968-1996	675	ARR	17.3	6.7	34
Gott VL,Gillinov AM[16]	United States	2001	1976-1993	170	ARR	NR	4	38.3
Average	-	-	-	-	-	20.1	10.8	35.8

VSRR, Valve-Sparing Root Replacement; ARR, Aorta Root Replacement; NR, not reported

Table 2

	30-day mortality			
First author	**Preventive (%)**	**Urgent (%)**	**Late mortality* (%)**	**Endocarditis** (%)**
Coselli JS [5]	1.4	NR	2.9	NR
Cameron DE[11]	0	4.4	19.8	4.8
Iguchi A [12]	0	NR	18.2	NR
Gott VL,Cameron DE[13]	0	5.6	15.9	4.0
Alexiou C [14]	2.6	11.1	23.0	NR
Gott VL, Greene PS[15]	1.5	12.5	21.3	3.6
Gott VL,Gillinov AM[16]	7.6	NR	16.5	5.5

VSRR, Valve-Sparing Root Replacement; ARR, Aorta Root Replacement; NR, not reported

* Late mortality: from 30 days after surgery till end of follow-up

** Endocarditis: from 30 days after surgery till end of follow-up

Table 3 - Study outcomes late mortality

	Late mortality			
First author	**5 year**	**10 years**	**15 years**	**20 years**
Coselli JS [5]	3.8%	NR	NR	NR
Cameron DE[11]	8.1 %	14.5%	19.0%	24.4%
Iguchi A [12]	9.8%	25.6%	NR	NR
Gott VL,Cameron DE[13]	11.0%	19.0%	24.0%	33.0%
Alexiou C [14]	14.5%	27.3%	NR	NR
Gott VL, Greene PS[15]	16.0%	25.0%	NR	41.0%
Gott VL,Gillinov AM[16]	18.0%	27.0%	33.0%	NR

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Review

Ethnic Disparities in Mental Health Service Use and Unmet Mental Health Need Among Children in the USA

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Summary

Objective: **Early detection and treatment of emotional and behavioral problems among children has a positive effect on their future development, well-being and health. However, children from different ethnic backgrounds who need mental health care do not all receive equal mental health services. The aim of this systematic review is to describe the ethnic disparities in mental health service use among children (2-12) in the United States.**

Methods: **We conducted a systematic search of the PubMed database for studies on mental health service use and unmet need for these services among children aged 2-12, from different ethnic groups in the USA. We compared Caucasian children to Afro-American and Hispanic children.**

Results: **Four studies met our inclusion criteria. Three publications indicated that Hispanic children received relatively fewer mental health services than Caucasian children. Two publications indicated that this was also the case for Afro-American children. In unadjusted analyses, Hispanic children had more unmet need for mental health services than Caucasian children in 2 of 3 publications. After adjusting for factors such as demographics, socioeconomic status and severity of the mental health problems, 1 study showed this result, another study showed the opposite. Afro-American-Caucasian disparities existed in unmet needs for mental health services in 2 of 3 publications in the unadjusted odds ratios. After adjustment, Afro-American-Caucasian disparities remained significant in 1 study.**

Conclusions: **These results show ethnic disparities in mental health service use among children in the USA, and suggest there are also ethnic disparities in unmet need.**

Introduction

Research has shown that early detection and treatment of emotional and behavioral problems among children has a positive effect on their future development, well-being and health [1]. It is estimated that one in five children have mental problems, such as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD) and depression [2]. To receive adequate therapy, those children must find their way into mental health services. Prior research found that the rate of mental health service use for children is low and that most children who need mental health treatment do not receive any services [3].
Studies on adult and adolescent populations strongly suggest that ethnic disparities in mental health service use exist even after controlling for the effects of social-economical-status and access to care. These findings have been noted for a range of medical disorders [4,7].

Studies in the UK have reported ethnic-related disparities in mental health service use [4]. Goodman et al. reported greater unmet mental health care needs among children from India, Pakistan, Bangladesh and South Asia compared to Caucasian children, whereas the evidence of greater unmet needs among Afro-American African and Afro-American Caribbean children was sparse and inconsistent [4].

We expect that ethnic-related disparities also exist in the United States, but due to a different ethnic mixture, the results from research in the UK are not all applicable to the United States. If we can determine the extent to which ethnic related mental health care disparities exist among children in the United States, then effective interventions might be developed. The focus of this review is on ethnic disparities in unmet need for mental health treatment in children in the United States. To our knowledge, this is the first systematic review about ethnic mental health care disparities among children in the United States.

The aim of our systematic review was to address the following research question. Are there ethnic-related disparities in mental health service use and unmet need for these services among children (2-12 years) in the United States?

Methods

Search strategy

We searched the PubMed electronic database for English-language articles published from the beginning of this database to January 20, 2011 using the following Medical Subject Headings (MeSH): Healthcare Disparities, Mental Health Services and Ethnic Groups. The search was limited to articles about preschool children (aged 2-5 years) and children between 6 and 12 years of age. The reference lists of identified articles were also examined for additional studies missed by the PubMed search.

Study selection and data extraction

Two independent reviewers (SB and IMM) identified potentially eligible articles by screening the titles and abstracts of the search

result. To be eligible, studies had to include the following: 1) children aged 2-12 years, sampled from the general population or from mental health clinics serving the general population (i.e. excluding selected groups such as foster children or children in secure forensic units); 2) a report of children who needed mental health services, who used mental health services and who did not; 3) at least two specified ethnic groups or one minority group compared to all other children in the sample or a comparable general population sample; and 4) study populations located in the United States. In the event of uncertainty about study eligibility based on abstracts alone, the reviewers examined the full text of articles.

The exclusion criteria were as follows: 1) review as publication type; and 2) articles that were not freely available online or available online for Erasmus MC or in the paper collection of the Erasmus MC library.

The primary outcome measure of interest was the association of unmet need for mental health services with ethnicity. First we compared the rates of mental health service use by children from different ethnic groups. Then we compared the unadjusted and the adjusted odds of having unmet need for mental health services from Afro-American and Hispanic children with those of Caucasian children. Adjustments were made for factors such as demographics, socioeconomic status, and severity of the mental health problems (see footnote of Table 4 for more details).

Results

Description of studies

Our PubMed search produced 11 publications. After applying the exclusion criteria 2 eligible articles remained [8,9]. Two additional references were identified in the reference lists that met all inclusion criteria and were subsequently included in the review [10,11]. The included studies are described in Table 1.

All of the included studies were observational studies and had been published since 2002. Three studies examined the use of mental health services of ethnic groups relative to the Caucasian population [8,10,11], and three studies examined the rates of unmet need for these services among different ethnic groups [8,9,10]. Although not specified in our inclusion criteria, all 4 studies included a Caucasian, Afro-American and Hispanic sample. This allowed us to have a single strategy for combining information across studies, by always comparing the results for each minority ethnic group (Afro-American or Hispanic) to the Caucasian sample. Two studies also included a group categorized as 'other' [8,10].

Mental health service use

Three studies reported on mental health service use among Caucasian, Afro-American and Hispanic children (Table 2). In two of these studies, Afro-American children received fewer mental health services than Caucasian children did [8,10], but in one of these studies this significant difference was found in only one of three data sets [10]. In another study, Afro-American children were less likely than Caucasian to get treatment for depression, but not for any condition overall [11]. The results of 3 studies indicated that Hispanic children received fewer mental health services than Caucasian children [8,10,11].

Table 1 - Details of included studies

Study reference	Setting, date	Study design: study population	Ethnic groups
Coker et al., 2009 [8]	United States, 2004-2006	Cross-sectional analysis (N=5,147)	Caucasian, Afro-American, Hispanic and 'other' fifth graders (10/11 years old)
Kataoka et al., 2002 [10]	United States, 1996-1998	Cross-sectional analysis of three nationally representative household surveys in the USA: 1) the	Caucasian, Afro-American, Hispanic and 'other' children (aged 3-17 years old)
Ngui et al., 2007 [9]	United States, 2000-2002	National Survey of American Families (N=28,867), 2) the National Health Interview Survey (N=11,017), and 3) the Community Tracking Survey (N=8,852)	Caucasian, Afro-American and Hispanic children under 18 years
Zimmerman, 2005 [11]	United States, 2000	A cross-sectional analysis (N=7,660) Cohort study (N=2,487)	Caucasian, Afro-American and Latino children aged 7-14 years old

Table 2 - Mental health service use among children from different ethnic groups

Study reference	Mental health service use	Ethnic disparities in mental health service use
Coker et al., 2009 [8]	9.0% of fifth graders had ever used mental health services in their lives	Unadjusted analyses – ever use of mental health services: Caucasian 14%, Afro-American 6%, Hispanic 8% (p<0.001).
Kataoka et al., 2002 [10]	6.0-7.5% of USA children received mental health service in a 12-month period	Unadjusted analyses - one of three data sets showed significantly lower rates of mental health service use in ethnic minority groups: - survey 1) Caucasian 6.4%, Afro-American 6.1%, Hispanic 4.4% (no significant differences) - survey 2) Caucasian 7.2%, Afro-American 4.9%, Hispanic 3.9% (p<0.001) - survey 3) Caucasian 8.1%, Afro-American 6.7%, Hispanic 5.8% (no significant differences)
Ngui et al., 2007 [9]	NA	NA
Zimmerman, 2005 [11]	6.17% of children had seen a specialty mental health service use provider in the previous two years	Adjusted analyses - Latino children are significantly (p<0.05) less likely to get any treatment than Caucasian children; OR 0.33. Afro-American children are less likely than Caucasian children to get treatment for depression; OR 0.14–0.28 (p<0.05), but not for any condition overall; OR 1.07.

Abbreviations: NA, not available; OR, odds ratio.

Table 3 - Unadjusted odds ratios of unmet need for mental health services

Ethnic group	OR (95% CI) Coker et al., 2009[a] [8]	OR (95% CI) Kataoka et al., 2002 [10]	OR (95% CI) Ngui et al., 2007 [9]	OR (95% CI) Zimmerman, 2005 [11]
Caucasian	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	NA
Afro-American	ADHD 0.3 (0.2-0.4)*	0.85 (0.54-1.33)	1.80 (1.30–2.51)*	NA
	ODD 0.5 (0.3-0.8)*			
	CD 0.3 (0.2-0.6)*			
	Depression 0.3 (0.1-0.7)*			
Hispanic	ADHD 0.4 (0.2-0.6)*	2.29 (1.41-3.73)*	0.90 (0.62–1.30)	NA
	ODD 0.5 (0.2-0.9)*			
	CD 0.5 (0.2-0.9)*			
	Depression 0.4 (0.1-1.0)*			

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CD, conduct disorder; CI, confidence interval; ODD, oppositional defiant disorder; OR, odds ratio; NA, not available.
*p<0.05.
[a] Coker et al., 2009: only the unadjusted odds ratios of mental health service utilization for children with symptoms of 1 of 4 of the most common psychiatric diagnoses in children (ADHD, ODD, CD, and depression) were available, not for the 4 diagnoses together [8]. The odds ratios indicate having symptoms of a mental health condition and receiving mental health services, which is met need instead of unmet need; smaller odds ratios indicate more unmet need [8].

Unmet need for mental health services

Three studies reported unadjusted rates of unmet mental health need (Table 3). All these studies measured use and need of mental health services by parental reports [8,9,10]. In one study, the presence of parent-reported symptoms of four of the most common psychiatric diagnoses in children above a specific cutoff value was compared with a parent report of mental health service use [8]. Another study based 'need' on a parent-reported screening measure that estimated need for a clinical evaluation, and compared this need with adult respondent reported use of any mental health services of their child [10]. Ngui et al. did a survey of children with special health care needs and their use of mental health services, reported by their parents [9].

Kataoka et al. found that Hispanic children had more unmet need than Caucasian children (odds ratio=2.29) [10]. Coker et al. found significant differences in unadjusted odds ratios; compared to Caucasian children, fewer Hispanic children with symptoms of ADHD, ODD, CD and depression had ever utilized services [8]. Another study (in unadjusted analyses) found Afro-American-Caucasian disparities in unmet mental health needs [9]. Coker et al. found significant differences in unadjusted odds ratios; fewer Afro-American children with symptoms of ADHD, ODD, CD, and depression had ever utilized mental health services compared to Caucasian children [8]. Although Zimmerman examined a subsample of children with high values of symptom variables and their treatment probability, these results were not reported [11].

Three of the included studies reported adjusted odds ratios of unmet mental health need (Table 4). Adjustment was made for factors such as demographics, socioeconomic status, and severity of the mental health problems (see footnote of Table 4 for more details). All these studies found a significant difference in odds ratios of unmet need, comparing Afro-American or Hispanic with Caucasian children. In one of these studies, Hispanic children with mental health problems had greater adjusted odds of having unmet need than Caucasian children after adjusting for other demographic factors and parent characteristics [10]. However, another study showed reduced adjusted odds of unmet mental health needs among Hispanics [9]. After adjustment, Coker et al. found bigger and insignificant odds ratios of met need for Hispanic children compared to Caucasian children with symptoms of ADHD, ODD, CD and depression [8]. After adjusting for relevant covariates, Ngui et al reported that the odds ratio of unmet mental health needs was smaller and insignificant for Afro-American compared to Caucasian children [9]. However, Coker et al. found that the differences for Afro-American children compared with Caucasian children with symptoms of ADHD, ODD, CD, and depression remained significant [8].

Table 4 - Adjusted [a,b,c] odds ratios of unmet need for mental health services

Ethnic group	OR (95% CI) Coker et al., 2009[a] [8]	OR (95% CI) Kataoka et al., 2002[b] [10]	OR (95% CI) Ngui et al., 2007[c] [9]	OR (95% CI) Zimmerman, 2005 [11]
Caucasian	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	NA
Afro-American	ADHD 0.3 (0.2-0.5)*	1.28 (0.9-1.83)	1.39 (0.99–1.94)	NA
	ODD 0.4 (0.2-0.7)*			
	CD 0.4 (0.2-0.8)*			
	Depression 0.2 (0.1-0.6)*			
Hispanic	ADHD 0.7 (0.3-1.5)	2.66 (1.45-4.91)*	0.62 (0.40–0.96)*	NA
	ODD 0.5 (0.2-1.2)			
	CD 0.8 (0.3-2.1)			
	Depression 1.4 (0.5-4.7)			

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CD, conduct disorder; CI, confidence interval; ODD, oppositional defiant disorder; OR, odds ratio; NA, not available.
*p<0.05.
[a] Coker et al, 2009: in this study the odds ratios indicated having symptoms of a mental health condition (ADHD, ODD, CD, or depression) and receiving mental health services, which is met need instead of unmet need; smaller odds ratios indicate more unmet need [8]. Adjusted for child age, gender, and health insurance; parent age, educational attainment, English proficiency, social contacts or resources, and psychological distress; household composition and income; and study site [8].
[b] Kataoka et al., 2002: adjusted for variables listed in table and regional location, parental education, single-parent household, and parental mental health functioning as measured by the five-item Mental Health Inventory [10].
[c] Ngui et al., 2007: adjusted for child's age, gender, maternal education, poverty, number of children in household, residence, usual source of care, personal doctor or nurse, interview language, number of children with special health care needs in household, child's condition stability and condition severity [9].

Discussion

Our study shows that there are ethnic-related disparities in the use of mental health services among children in the United States; Afro-American and Hispanic children receive fewer mental health services than Caucasian children. The aim of this review was to describe the ethnic disparities in mental health service use and unmet mental health need among children (2-12 years) in the United States. We found ethnic disparities in mental health service use among children in the United States and in unmet need. Afro-American children received fewer mental health services than Caucasian children in 2 of 3 publications [8,10]. Another study found a similar result, but only for treatment of depression [11]. Hispanic children received less mental health services than Caucasian children in the three publications that reported mental health service utilization [8,10,11].

Next we described ethnic disparities in unmet need for mental health services. Our results were inconsistent. In the unadjusted ratios of unmet need for mental health services we found that Hispanic children had more unmet need than Caucasian children in 2 of 3 publications [8,10]. But after adjustment for factors such as demographics, socioeconomic status, and severity of the mental health problems, we found in one study that Hispanic children with mental health problems had greater odds of having unmet need than Caucasian children and one study that shows the opposite result [10,9]. We also found Afro-American-Caucasian disparities in unmet needs for mental health services in 2 of 3 publications in the unadjusted odds ratios [8,9]. After adjusting, Afro-American-Caucasian disparities stayed significant in only one study; a smaller proportion of Afro-American children with psychiatric symptoms received mental health services than Caucasian children with psychiatric symptoms, indicating more unmet need among Afro-American children [8].

Limitations

This review has several limitations. Our search may have missed publications on our subject. The Mesh-term 'Healthcare Disparities' is introduced in 2008. Therefore we also examined the reference lists of identified articles for additional studies missed by the PubMed search. We could have missed articles that were not in the reference lists of our included studies. Finally, we had a limited number of studies which we examined for ethnic disparities in unmet need for mental health services among children. Because these studied showed inconsistent results, we were unable to draw definitive conclusions. We were interested in children aged 2-12 years old. Because few studies were available on this subject with this age range, we also included studies with data-analyses on adolescents older than 12 years. These studies did not distinguish between children and adolescents. Therefore our results are not strictly applicable to children under 12 years of age.

The included studies also had limitations. All 4 studies included data from parental reports. Parental reports are subject to recall and reporting bias.

In all 4 studies homeless and institutionalized children were excluded. One study [9] also excluded recent immigrants. As a result of these limitations, the studies could underestimate the true prevalence of unmet needs and mental health service use.

In the studies we analyzed, there was lack of Hispanic, Afro-American and Caucasian subgroup data. Because these ethnic groups consist of many subgroups, more specified data about these particular groups is needed.

Conclusions

The results of this review raise questions about the magnitude of ethnic-related disparities in mental health service use among children in the United States and in unmet need. Although we were unable to draw definitive conclusions, the results provide a direction for further research. More data will be needed to provide consistent results to draw definitive conclusions about unmet need. There is also more specified data needed about different subgroups in ethnic groups. If the extent of ethnic-related mental health care disparities among children in the United States is determined, then effective interventions might be developed. These interventions should focus on children of ethnic groups who usually do not find their way to mental health services.

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Hepatitis B vaccination: effects of diminishing HBV immunity, nonresponse and a review of the vaccination protocol in the Netherlands

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Abstract

Around two billion people worldwide have a serologic indication of infection with hepatitis B virus (HBV). Vaccination is an effective way of preventing infection and spread of this disease. However, a small percentage of those vaccinated (vaccinees) do not respond to the vaccination. Also, immunity can decline in the years after the vaccination. These individuals appear to be at risk of HBV infection. We investigated recent innovations in HBV vaccines and came to the conclusion that the current Dutch vaccination protocol should be revised in order to protect vaccinees with diminishing immunity and non-responders.

Introduction

In 1883, almost 1300 ship workers were vaccinated against smallpox with a vaccine made from human lymph. About 15% of them fell ill with jaundice during the weeks following vaccination. Lurman [1] proved that contaminated lymph was the source of the epidemic, during which patients fell ill up to eight months later. This is thought to be the earliest recognition of the public health importance of hepatitis B virus (HBV) infection.

The etiology of this "serum hepatitis", as it was called, was not discovered until the 1960s. [2] According to the World Health Organization two billion people worldwide have serologic markers indicating current or past infection with HBV. Of this population, 360 million are chronically infected.

Vaccinating against HBV is an effective way of preventing infection and reducing the spread of the disease. The first vaccine was licensed in 1981 and is now one of the most widely used vaccines in the world. However, a small percentage of those vaccinated (vaccinees) do not respond to the vaccination. Also, several years after vaccination the immunity against HBV can decrease. Non-responders and vaccinees with diminished immunity are both at risk of HBV infection.

Vaccines are constantly being improved, which has resulted in 'third generation' HBV vaccines and several other innovations. The third generation vaccines are produced in mammalian cells, instead of yeast cells, and contain two more antigens that stimulate antibody production. These new vaccines might reduce the percentage of non-responders. This article describes hepatitis B and the vaccines that have been created to control it. Several alternative methods of vaccination and novel vaccines are discussed, which may be worth including in the standard vaccination protocol in the Netherlands.

Hepatitis B

Hepatitis B is caused by the Hepatitis B virus. The virus infects hepatocytes. During the acute infection it causes liver inflammation, jaundice and vomiting. Severe acute infections may cause fulminant liver infections and liver failure. Chronic infection with

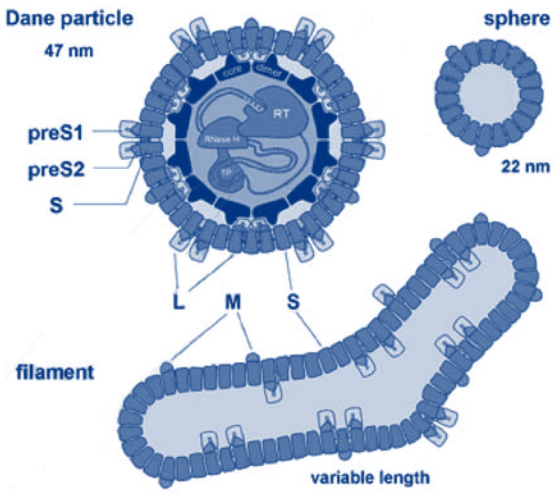

Figure 1 - Schematic structure of the hepatitis B virions. The Dane particle, the filamentous form and the sphere-shaped virion. The different antigens are shown (S, M, L for small, mid-sized and large antigens). Image source: University Heidelberg, Germany

HBV can cause liver cirrhosis and hepatocellular carcinoma [3]. The virus was identified in 1965 [2], when the major surface antigen (HBsAg) was discovered. This antigen is the major envelope protein of the virus and consists of three related envelope proteins (Figure 1) [4]. The major protein is the small HBs. This polypeptide is 226 amino acids (aa) in size and is present in a glycolysated and non-glycolysated form. The other two envelope proteins are mid-sized HBs protein, non-glycolysated HBs with an extra 55-aa residue, and the large HBs protein (similar to the mid-sized protein, but with an extra 199-aa residue). These three proteins covalently link to form the virus envelope [5].

Acute infection is diagnosed by measuring HBsAg and IgM antibodies against the core antigen of HBV (aHBcM) or IgM antibody alone. During the course of the infection antibodies against HBsAg (aHBs) are produced and HBsAg is cleared. Antibodies against the HBV e-antigen are also produced (aHBe), as well as IgG anti-bodies against the core antigen (aHBc) (Figure 2a) [6]. In some cases the patient is chronically infected by HBV (Figure 2b). The HBsAg persists for at least 6 months and the patient remains infectious. Chronically infected patients can be divided into two groups: those who have evidence of continuous viral replication and those in a non-replicative state. Chronic infection with Hepatitis B increases the risk of liver cirrhosis and hepatocellular carcinoma.

Vaccination against Hepatitis B

The first hepatitis B vaccine was produced in the 1970s by harvesting the HBsAg from the blood of hepatitis B carriers. Inactivation of these samples was accomplished by treating the samples with a combination of urea, pepsin, formaldehyde and heat. [7] The second generation hepatitis B vaccine was developed by using recombinant DNA techniques. The HBsAg was produced by using a HBV-transfected yeast *(Saccharomyces cerevisiae)* to express the hepatitis B antigen. The recommended immunization protocol for healthy individuals in the Netherlands is three doses of vaccine, administered intramuscularly, over a course of 6 months (at 0, 1 and 6 months). Efficacy of vaccination is determined by assessment of the level of antibodies to HBsAg. Some factors may indicate the need for different vaccination strategies, such as immunosuppression, chronic kidney disease or neonates born from HBsAg positive mothers. [8]

In 1997 the World Health Organization recommended that Hepatitis B vaccination should be integrated into national immunization programs in all countries. So far, this has been implemented in 168 countries. [9] The result of this worldwide implementation of hepatitis B vaccination is a reduction of acute and chronic hepatitis B infections. This effect is especially notable in highly endemic countries. For example, in Taiwan the HBsAg prevalence in children younger than 15 years of age decreased from 9.8% to 0.7%, and in Gambia it was reduced from 10% to 0.6%. Since the start of infant hepatitis B vaccination in Hawaii, the prevalence of HBsAg has been reduced by 97%. [9]

Hepatitis B vaccine non-responders

Most vaccines against hepatitis B use a single hepatitis B antigen. This antigen is the viral envelope protein: the hepatitis surface antigen. The vaccination response can be determined by measuring the concentration of antibodies against the HBsAg. Most patients produce a high concentration of antibodies. However, a small group of vaccinees (5-10%) [10, 11] produce no (<10 IU/mL) or suboptimal concentrations (10-100 IU/mL) of antibodies, which are known as non-responders and low-responders. These non- or low-responders have no protection against hepatitis B or are protected for only a few years. Contributing causes to the absence of or suboptimal response are genetic predisposition, immunosuppression, certain chronic illnesses (for example, HIV and AIDS, chronic kidney disease) and age. [10, 12]

The genetic predisposition of non-responders is currently being studied. The immune system is a vast and complex mechanism with numerous factors influencing the responses required to combat disease. The most obvious factor influencing the generation of antibodies against the hepatitis B vaccine are the Human Leukocyte Antigen-molecules (HLA). Antigens taken up by antigen presenting cells are presented to naive CD4+ T cells by binding the antigen to HLA-II. If the HLA-II molecule is somehow incapable

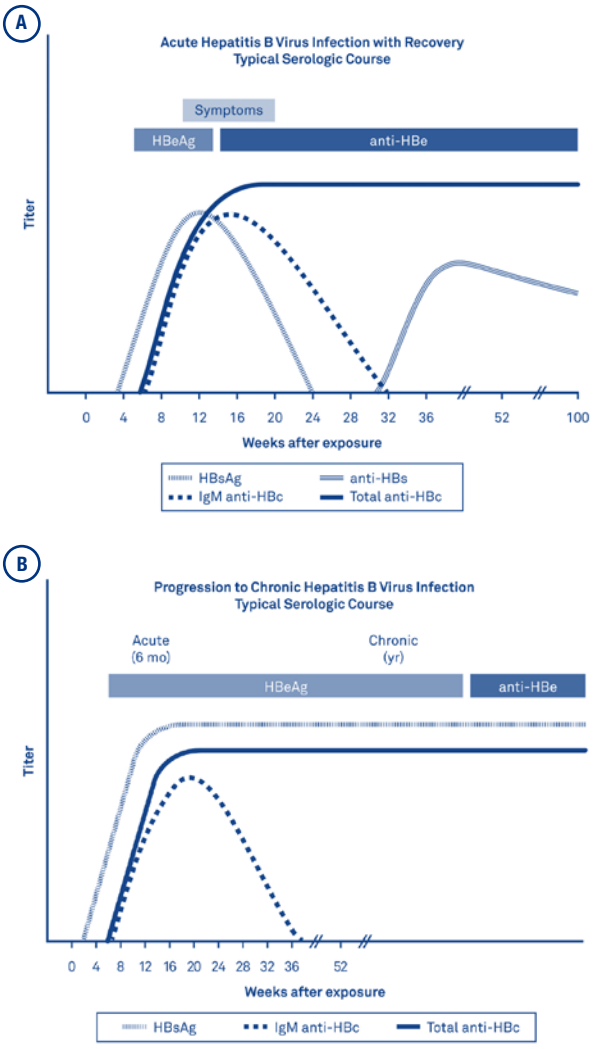

Figure 2 - Typical serologic courses of hepatitis B infection. (a) Typical course of an acute infection from which the patient fully recovers. (b) Typical course of an acute infection which develops into a chronic infection. Image source: Centers for Disease Control

of binding the HBsAg, the antigen cannot be presented to T cells and no immune response is generated. The incapability of binding HBsAg in HLA-II molecules may be caused by genetic variation or mutations which lead to an uncommon folding of the binding groove or different binding groups in the groove. Several studies suggest a link between a lack of long-term immunity and specific HLA haplotypes. Noh et al. [13] described the link between Celiac Disease and HBV vaccine non-responsiveness. Celiac Disease is linked with several HLA haplotypes, but most specifically with DQ2. [14] Gluten reactive T cells in the lamina propria have a cytokine profile dominated by a high production of IFNγ. Noh et al. postulated that the non-responsiveness to HBV vaccines of Celiac Disease patients is due to the suppression of the Th2 response and thus B cell differentiation due to the high production of IFNγ. However, after careful evaluation and investigation, Ertem et al. [11] suggested that compliance to a gluten free diet rather than the specific HLA alleles has a primary role in HBV vaccine responsiveness in Celiac Disease patients. Compliance to a gluten free diet resolves the active inflammation in the gut and lowers the levels of IFNγ. Poor responsiveness to the HBsAg vaccine is associated with the DR3 and/or DR7 alleles in Caucasian vaccinees. In Japanese subjects, the Bw54-DR4-DQW4 haplotype is associated with poor vaccine response. [15] In particular, hemodialysis patients fail to respond or develop low antibody levels. [16] Caillat et al. investigated the HLA class II alleles in hemodialyzed patients and showed that 44.5% of the poor responders were DR3 and DR14,

compared to 18.1% of DR1 or DR15 patients. Apparently, the composition of HLA class II partly determines the response to the HBV vaccine. Apart from HLA class II differences, several other factors may influence the immune response, such as defective antigen-presenting cell/T cell interactions and elimination of HBsAg-specific helper T cells during maturation. [15]

Currently, the efficacy of vaccination is only determined by assessing the level of antibodies to HBsAg. However, this approach does not take cellular immunity into account, which is also induced by vaccination and is important for the development of an adequate antibody response. Bauer and Jilg [17] reported a measurable response of HBsAg specific memory T and B cells in individuals with waned immunity. They described how HBsAg specific effector and memory T cells were isolated in patients who were successfully vaccinated in the past, but had no measurable levels of aHBs. The isolated T cells were then stimulated with HBsAg, and aHBs secretion was measured. This showed that all individuals possessed HBsAg-specific B cell memory. Non- or low-responders may have this cellular immunity as well, but fail to produce fully matured aHBs producing plasma cells.

Effects of diminishing immunity and vaccine non-response

The antibody levels of vaccinated individuals tends to wane during the years after vaccination. It has been estimated that 13% to 60% of initial responders lose their detectable antibodies against HBsAg (aHBs). [10] According to a recent report from Taiwan,15 years after successful vaccination, 30% of the vaccinated children had no detectable aHBs levels. In 33% of the vaccinated children, anti-HBcore was detectable, and 1 child had detectable levels of HBsAg. [18] A report from Alaska described a study of 841 patients, of which 84% were successfully vaccinated. During the years after vaccination, 16 patients were found to be infected with HBV (of which 6 tested positive for HBV DNA in serum). [19] Another study followed 635 successfully vaccinated patients for 5 years (a total of 773 patients were vaccinated). Of these 635, 27% lost their measurable aHBs, where 55 patients were infected by HBV and 8 of these were clinically important (characterized by elevation of liver enzymes and detection of HBsAg in serum) [20]. Interestingly, Shepard et al. [21] stated that they observed no clinical cases of hepatitis B in follow-up studies. They described the quick rise of aHBs after a booster has been given and hypothesized that this simulates the response which would occur after the individual has been exposed to HBV.

Currently, vaccination status is defined by the level of measured aHBs in blood. This approach does not include the cellular immunity, which contributes to the immune status of the vaccinee. Still, there are indications that a measurable aHBs level is an important factor in the immune status. However, this only refers to waning immunity, i.e., for individuals who have been previously vaccinated successfully. The fact that successfully vaccinated people still get infected with HBV after their immunity has waned indicates that aHBs plays an important role in the immunity against HBV. Hepatitis B vaccine non- or low-responders generate only very low or no aHBs levels. Unless other factors, like a cellular immune response, provide immunity during the first few years, it can be assumed that non- or low-responders are not protected against HBV. Some research has been done to try to discover whether individuals retain immunity after losing their measurable aHBs. Bauer and Jilg [17] described the measurable response of HBsAg specific memory T and B cells, which suggests that individuals do have a cellular memory response against the vaccine.

Alternative vaccination approaches

There are several possible ways of improving the vaccination response. The first approach is by varying the protocols and methods of vaccination using the traditional second generation vaccine. The second approach is by using novel vaccines, like the third generation vaccines. Several options are summarized below:

Alternative approaches using the existing vaccines:

- Double dose vaccination/combo vaccine. To try to improve the response of low- and non-responders using the traditional second generation vaccine, several options are available. Currently, the method of inducing the immune response of a non-responder in the Netherlands is by vaccinating with a double dose of a hepatitis A and B vaccine. By using a combo-vaccine, the immune response to the HBsAg is theoretically improved by the presence of hepatitis A antigens.
- Intradermal injection. Another approach using the second generation vaccine uses intradermal injection [22] instead of intramuscular injection. The skin (dermis and epidermis) are rich in dendritic cells and other antigen presenting cells which are capable of stimulating the immune system. Consequently, intradermal delivery of vaccines may improve the immune response compared to intramuscular delivery. Although a review conducted by the World Health Organization [23] concluded that intradermal delivery is not superior to intramuscular delivery, this method may improve the response in non- or low-responders.

By using novel vaccines, the response of non- or low-responders may be drastically improved:

- Multi HBs antigen vaccines. Traditional second generation hepatitis B vaccines contain only a single, clonal antigen: recombinant HBsAg. Non-response to this vaccine may be due to HLA-II molecules, which are unable to present that specific antigen. This may be circumvented by using a vaccine that contains several genetic variants of HBsAg. Several research projects have identified mutations in the neutralizing epitope of HBsAg [9, 24-28]. By using vaccines that contain these mutated HBsAg's, cross-reactivity of the generated antibodies against the HBsAg may be induced.
- HBsAg production in mammalian cells. The HBsAg in traditional vaccines is also produced by using transfected yeast-cells. The HBsAg produced in this way is non-glycolysated. A novel method of producing HBsAg is by using mammalian cells, which produce glycolysated antigens, and therefore use the same post-transcription mechanisms as in humans [29]. - Third generation vaccines. Third generation vaccines are vaccines that are produced in mammalian cells, but also contain two other antigens: preS1 and preS2. The antigen used in most vaccines is the small (S1) HBsAg. The residues of the mid-sized (preS1) and large (preS2) HBs proteins are not included in these vaccines. However, research has shown that these two residues appear to have an enhancing effect on the T cell recognition of the S1 HBsAg [29-32]. Rendi-Wagner et al. [33] described the high immunogenicity of the novel vaccines containing preS1 and preS2 next to the S1 HBsAg, which are produced in mammalian cells. Only two injections of this third generation vaccine is enough to elicit an immune response in about 80% of the non- or low-responders. Moreover, factors such as chronic illness and age tend to lower the response when using the traditional vaccine. The influence of these factors seems to be less when using the third generation vaccines.

Conclusion

Considering new developments regarding vaccine research, a revision of the vaccination protocol described by the Dutch government [8] is needed. The government protocol does not have recommendations if an individual is a true non-responder; it apparently assumes that any immunity (measurable aHBs) in the past guarantees lifelong immunity. The government protocol has not included third generation vaccines in its program, and thus non- and low-responders are potentially at risk of infection with hepatitis B.

Currently, the vaccination program for non- or low-responders consists of repeating the original schedule. If the vaccinee still has no response, the patient is vaccinated with a double dose of a combo vaccine for hepatitis A and B. That amounts to 9 vaccine injections and 3 aHBs measurements. If the third generation vaccine is used after the first failed vaccination attempt, it amounts to 6 vaccine injections and 2 aHBs measurements. This could be a more cost-effective method. In any case it is a less invasive procedure for the vaccinee, which may increase the likelihood of completing the vaccination schedule. An evaluation of the third generation hepatitis B vaccines would be valuable to Dutch healthcare, particularly regarding non- and low-responders to the hepatitis B single antigen vaccines who belong to high risk groups, such as medical personnel and family members of hepatitis B positive patients.

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Prenatal sex selection: a closed ethical discussion?

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Introduction

When in January 2010 it was rumored that the prenatal sex selection clinic in Utrecht wanted to reopen, the debate about gender selection in the media reopened as well.[1]. De clinic gives parents the option of choosing the sex of their unborn child. However in 1998 the clinic was ordered to be closed by the Minister of Health. As a result, many Dutch couples now go abroad for prenatal sex selection [1]. And although the debate received attention in the media, gender prenatal sex selection was not discussed as a political issue.

The Dutch population has not yet made up its mind about prenatal sex selection, but the prevailing social norm seems to be that as long as your baby is healthy, you should be grateful[2]. This implies that it is acceptable for parents to prefer a healthy child rather than a disabled one, but apparently it is not acceptable to speak about preferences for a male or female child.

In this paper I will first discuss the technique of prenatal sex selection. I will review the arguments for banning prenatal sex selection that were used by the Minister of Health. Finally I will discuss why parents might have a preference for the sex of their unborn children and what consequences it would have for parents, their children and society as a whole if prenatal sex selection were to be allowed.

The technique of prenatal sex selection

Although it is ethically controversial to select the sex of an unborn child, in recent years much research has been done on this topic. At the academic hospital in Maastricht, a procedure called pre-implantation diagnostics (PGD) is performed to prevent X-linked diseases, such as Duchenne and Becker muscular dystrophy [3]. However it can also be used for prenatal sex selection.

This technique is performed on throphoblasts that are created through in vitro fertilization. The diagnostic analysis that is carried out in order to determine the sex of the embryos is called FISH-labelling. The throphoblasts have to be spread out on a microscope slide. Subsequently they are hybridized to chromosome-specific DNA probes, which are labelled with different fluorescent markers [4]. The X chromosome is labelled with the SOX probe and the Y chromosome with the SGY probe. These probes consist of high repetitive DNA that is labelled directly with orange for the X-chromosomes and green for the Y-chromosomes [5]. The embryos with a green label will become males and the embryos with two orange labels will become females. The preferred sex can be selected and then implanted in the uterus.

Ethical aspects of gender selection

The prenatal sex selection clinic in Utrecht was founded more than 15 years ago. It was forced to close in 1998 by the Minister of Health, but since then has been providing information about sex selection to interested people [6]. Despite the belief of the founder that choosing the sex of an unborn child is a private matter, the Minister sent a letter to the Second Chamber of Parliament in 1995 explaining why she felt this was undesirable. She discussed several social consequences, such as demographic changes and inequality of men and women. She also presented ethical arguments concerning the "interest of the child, creating a slippery slope, freedom of choice and the instrumental aspect of sex selection" [7].

Recently, more research has been done on the societal effects of prenatal sex selection. The University of Groningen conducted research throughout Europe to determine whether parents would choose to have another child if they could select its sex. In terms of preferences and demographic consequences, the research showed that within Europe there is a general preference for a mixed composition of society. This means that parents in Europe generally have no clear preference for male or female children. In countries with a higher probability that the elderly will be poor, men prefer to have male children. In countries where women are disadvantaged, both men and women have a preference for male children [8]. However neither of these situations apply to the Netherlands. Combining that with the fact that only a small group is actively pursuing prenatal sex selection, it is unlikely that this will lead to major demographic shifts or to discrimination against men or women. Furthermore, I believe that parents are capable of making these kinds of decisions. For example, in the case of hermaphroditism or intersexuality, where the baby has both male and female biological characteristics, parents usually choose the gender of their child.

When discussing the interest of the child, the biggest concern of the Minister was that children will be reduced to an object to fulfill the wishes and desires of their parents. "We hereby might create an environment in which it is no longer objectionable to select children by means of technology"[7]. The Minister argued that if this environment threatened the general interest, she could choose to limit the reproductive choices of the parents [7].

On the other hand, the government does provide IVF treatments for couples that cannot become pregnant naturally, which is in fact a technology that is used to fulfill the wish of the parents to have children. Isn't the unborn child also being used as an instrument in this case? To take it even further, isn't the decision to have children always the fulfillment of the desire to make one's life complete? Perhaps parents that want to select the sex of their baby simply have a more specific preference that needs to be fulfilled in order for them to feel complete. Whereas other people are happy to have a healthy child, regardless of its sex, these parents want a girl instead of a boy (or the reverse).

Apparently, it is completely understandable in the Netherlands to lament a baby that is not entirely healthy, whereas it is absolutely unimaginable that you would be disappointed if you have a boy when you wanted a girl, for example. In England, however, there seems to be less of a taboo on this topic [2]. Although disappointment about the sex of your child is not yet a scientific or psychological term, parents, mainly mothers, talk about it on forums.

When some mothers are disappointed about the sex of their newborn, they experience this as the actual loss of a child, and they go through a period of grieving before they can even start

taking care of their baby. For some people, it is crucial to be able to choose the sex of their baby. For example, some mothers want to be able to do 'girly' things with their daughters, things they would never be able to do with boys, things that only mothers can understand because they are female. Therefore, these mothers will be better at raising a girl than a boy. This also applies to women who have miscarried a baby girl. These women feel guilty towards themselves and towards their partner for not being able to bring a healthy baby girl into the world. For them, this is a way to overcome that trauma, to give them the feeling that they are capable of giving birth to a healthy girl. Isn't that worth some consideration?

Conclusion

Prenatal sex selection is a controversial subject, and many people have rational or intuitive opinions on the matter. The question remains, however, whether prenatal sex selection will ever become a matter of political debate. I believe that something positive can certainly be said for prenatal sex selection. Some people have very strong and specific preferences, such as the sex of their child. If allowing prenatal sex selection is a way in which they can optimize their happiness, and others are not harmed by this, I see no reason why this technology should be banned. I believe the 1998 arguments of the Minister need to be updated, especially taking into account the Groningen research, which refutes the purported harms of prenatal sex selection. However, for now the Dutch taboo remains: if you are pregnant and you are asked whether you want a boy or a girl, the answer will still be: 'As long as it is healthy, we are happy'.

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Abstract

Prognostic Value of Major Extracranial Injury in Traumatic Brain Injury: An individual Patient Data Meta-analysis in 39,274 patients

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Introduction

Although major extracranial injury (MEI) is common in Traumatic Brain Injury (TBI) patients, its effect on outcome is controversial. We aimed to study the prognostic effect of MEI on mortality after TBI.

Methods

We included individual patients with TBI from three observational studies (EBIC, UK4 and TCDB, included in the IMPACT* database), one recent Randomized Controlled Trial (CRASH**), and one trauma registry (TARN***). MEI was defined as any extracranial injury with an Abbreviated Injury Score ≥ 3 or "requiring hospital admission on its own". We related MEI to mortality (14 day in TARN and 6 month in IMPACT and CRASH) with logistic regression analysis, adjusted for age, motor score and pupillary reactivity, stratified by brain injury severity (mild, moderate and severe TBI). We pooled the odds ratios in IMPACT and CRASH with random effect meta-analysis. To assess heterogeneity between CRASH and IMPACT we calculated the between-study variance τ^2 . We did not include TARN in the pooled analysis, because this study included patients who died before of shortly after admission. We also calculated partial R^2 statistics to indicate the amount of variance explained by MEI.

Results

We included 17,132 (44%) severe, 7,229 (18%) moderate, 14,909 (38%) mild TBI patients, 39,274 in total. Mortality was 25% and 32% had MEI. MEI was a strong prognostic factor for mortality in TARN, adjusted odds ratio (OR) and 95% confidence interval (95%CI) were 2.81 (2.44-3.23) in mild, 2.18 (1.80-2.65) in moderate and 2.14 (1.95-2.35) in severe TBI patients. The prognostic effect was smaller in IMPACT and CRASH with pooled adjusted ORs and 95%CIs of 2.14 (0.93-4.91) in mild, 1.46 (1.14-1.85) in moderate and 1.18 (1.03-1.55) in severe TBI patients (Figure 1). The between-study variances τ^2 and p-values for heterogeneity were 0.39 (p=0.02) for the mild, 0.11 (p=0.10) for the moderate and 0.0 (p=0.98) for the severe TBI studies. The prognostic value of MEI in terms of univariable R^2 was varying from 0.0% (in severe patients in IMPACT and CRASH) to 3.4% (in severe patients in TARN).

Conclusion

MEI is a prognostic factor in patients with TBI, but the strength of the effect decreases with brain injury severity. The large prognostic effect in TARN compared to IMPACT and CRASH for patients with severe head injury is possibly explained by inclusion of patients who die before or shortly after admission. In the total TBI population the incremental prognostic value of MEI compared to known predictors of mortality is limited.

** IMPACT - International Mission on Prognosis and Clinical Trail design in TBI studies, www.tbi-impact.org*
*** CRASH - Medical Research Council Corticosteroid Randomization after Significant Head Injury trial, www.crash.lshtm.ac.uk*
**** TARN - Trauma Audit & Research Network registry, www.tarn.ac.uk*

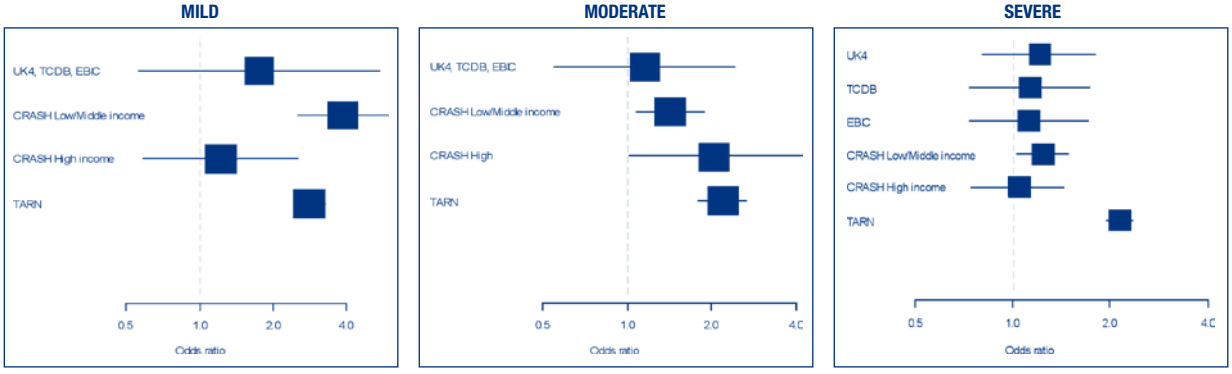

Figure 1 - Forest plots of random effect meta-analyses; showing the strength of the adjusted association between MEI and mortality in mild, moderate and severe TBI patients.

The *JAK2* 46/1 HAPLOTYPE in Budd-Chiari Syndrome and portal veim thrombosis

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The entity splanchnic vein thrombosis (SVT) is used to indicate both the Budd-Chiari syndrome (BCS) and portal vein thrombosis (PVT). Primary BCS is a rare disorder characterized by thrombosis of the hepatic veins and/or the suprahepatic inferior vena cava. Non-malignant, non-cirrhotic PVT is another infrequent thrombotic disorder involving the splanchnic vasculature. In both disorders, pathogenesis is largely dependent on the presence of systemic prothrombotic conditions which promote thrombus formation in the respective hepatic vessels.

In 2005, several groups reported a single, acquired point mutation in the Janus Kinase 2 *(JAK2)* gene, which is present in more than 95% of cases of polycythemia vera and 50% to 60% of essential thrombocythemia and primary myelofibrosis. *JAK2* is a cytoplasmic tyrosine kinase which is responsible for signal transduction by the erythropoietin, thrombopoietin, and granulocyte macrophage colony-stimulating factor receptors in hematopoietic cells, as well as for signal transduction by many cytokine receptors. Recently, the germline *JAK2* 46/1 haplotype has been associated with the development of $JAK2^{V617F}$ positive as well as $JAK2^{V617F}$ negative myeloproliferative neoplasms (MPNs).

In this study we examined the role of 46/1 in the etiology and clinical presentation of patients with SVT, in which MPNs are the most prominent underlying etiological factor. Patients were recruited from the European Network for Vascular Disorders of the Liver (EN-Vie) cohort, consisting of 163 BCS and 138 PVT patients, consecutively enrolled in nine European countries between October 2003 and October 2005. DNA samples were available of 116 BCS patients, 96 PVT patients and 105 healthy controls. Of these, 107 BCS patients (median age 38.1 years, 42% males), 92 PVT patients (median age 49.8 years, 47% males) and 100 healthy controls (median age 36.8 years, 40% males) were successfully genotyped, with the rs12343867 single nucleotide polymorphism.

The 46/1 haplotype was overrepresented in $JAK2^{V617F}$ positive SVT patients compared with controls (P<0.01) (Table). Prevalence of 46/1 in $JAK2^{V617F}$ negative SVT patients did not differ from the controls. However, $JAK2^{V617F}$ negative SVT patients with a proven MPN also exhibited an increased frequency of 46/1 (P=0.06). $JAK2^{V617F}$-negative SVT patients homozygous for 46/1 had a 4 to 5-fold increased risk of an underlying MPN compared with heterozygous or noncarriers. Also, $JAK2^{V617F}$ negative patients homozygous for 46/1 had higher hemoglobin levels (P<0.01), hematocrit (P<0.01), red blood cell count (P=0.02) compared to individuals with homozygous non-carriers. These associations remained significant when we excluded the 12 $JAK2^{V617F}$ negative patients in whom MPNs were objectively confirmed.

We conclude that the 46/1 haplotype is associated with the development of $JAK2^{V617F}$ positive SVT. Our study suggests that 46/1 may be used as a diagnostic tool in the risk assessment of MPNs in SVT patients in addition to the $JAK2^{V617F}$ mutation. Furthermore, our findings of an increased erythropoiesis support the theory that 46/1 indeed may be functionally different form other *JAK2* alleles.

This study was carried out on behalf of the European Network for Vascular Disorders of the Liver (EN-Vie).

Abstract

Table. Association between the JAK2 46/1 haplotype and patients with Budd-Chiari syndrome and portal vein thrombosis.

		rs 12343867 genotype						C allele
	N (%)	CC	(%)	CT	(%)	TT	(%)	frequency
Controls	100	7	(7)	40	(40)	53	(53)	0.27
Splanchnic vein thrombosis								
Overall	199	23	(12)	83	(42)	93	(47)	0.32
JAK2V617F positive	54 (27)	9	(17)	28	(52)	17	(31)	0.43
JAK2V617F negative, MPNs present	12 (6)	4	(33)	3	(25)	5	(42)	0.46
JAK2V617F negative, MPNs absent	133(67)	10	(8)	52	(39)	71	(5)	0.2
Budd-Chiari syndrome								
Overall	107	16	(15)	46	(43)	45	(42)	0.36
JAK2V617F positive	34 (32)	7	(21)	16	(47)	11	(32)	0.44
JAK2V617F negative	73 (68)	9	(12)	30	(41)	34	(47)	0.33
Portal vein thrombosis								
Overall	92	7	(8)	37	(40)	48	(52)	0.28
JAK2V617F positive	20 (22)	2	(10)	12	(60)	6	(30)	0.40
JAK2V617F negative	72 (78)	5	(7)	25	(35)	42	(58)	0.24

		Odds ratio (95% CI)**				Odds ratio (95% CI)***			
	P*	CT vs. TT		CC vs. TT		CT vs. TT		CC vs. TT	
Controls									
Splanchnic vein thrombosis									
Overall	0.18	1.2	(0.7-2.0)	2.0	(0.8-4.9)	1.4	(0.8-2.6)	2.1	(0.7-5.9)
JAK2V617F positive	<0.01	2.1	(1.01-4.5)	4.1	(1.3-13.2)	2.7	(1.2-6.2)	4.7	(1.3-16.7)
JAK2V617F negative, MPNs present	0.06	0.6	(0.1-2.9)	5.3	(1.1-26.2)	0.8	(0.2-4.0)	5.1	(0.9-28.5)
JAK2V617F negative, MPNs absent	0.98	1.0	(0.6-1.7)	1.1	(0.4-3.2)	1.2	(0.6-2.2)	1.1	(0.3-3.6)
Budd-Chiari syndrome									
Overall	0.04	1.4	(0.8-2.4)	2.7	(1.01-7.1)	1.6	(0.8-3.1)	2.7	(0.9-8.2)
JAK2V617F positive	0.01	1.9	(0.8-4.5)	4.8	(1.4-16.6)	2.0	(0.7-5.4)	5.3	(1.4-20.6)
JAK2V617F negative	0.24	1.2	(0.6-2.2)	1.9	(0.7-5.8)	1.4	(0.7-2.9)	1.8	(0.5-6.2)
Portal vein thrombosis									
Overall	0.88	1.0	(0.5-1.8)	1.3	(0.4-4.4)	1.1	(0.5-2.3)	1.4	(0.4-5.3)
JAK2V617F positive	0.10	2.6	(0.9-7.6)	3.1	(0.5-20.2)	4.0	(1.2-13.7)	3.8	(0.5-27.6)
JAK2V617F negative	0.57	0.7	(0.3-1.4)	0.9	(0.2-3.6)	0.7	(0.3-1.6)	0.9	(0.2-4.2)

MPNs, myeloproliferative neoplasms

*P, P- value for C-allele frequency comparisons.

** Adjusted for age and gender.

** Adjusted for Factor V Leiden mutation, prothrombin G2021A variant, age and gender.

Whole orbital tissue culture identifies imatinib mesylate and adalimumab as potential therapeutics for Graves' Ophthalmopathy

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Background and Aims
Biologicals and small inhibitory molecules are used to treat inflammatory diseases, but their efficacy varies upon clinical application. Furthermore, for many diseases, such as Graves' ophthalmopathy (GO), inclusion of enough patients to test novel therapies in a randomised way is unfeasable. Therefore, we tested the potential efficacy of imatinib mesylate (a tyrosine kinase inhibitor that blocks PDGF-receptor, c-Abl and c-Kit activity) and adalimumab (an anti-TNF-α antibody) for the treatment of GO using a whole orbital tissue culture system.

Methods
Orbital fat tissue from GO patients (n = 10) was cultured with or without imatinib mesylate or adalimumab. PDGF-B and TNF-α mRNA expression levels were determined in the primary orbital tissue and IL-6 and hyaluronan (as parameters for orbital inflammation and extra-cellular matrix production) were measured in tissue culture supernatants.

Results
Imatinib mesylate significantly ($p=0.005$) reduced IL-6 and hyaluronan production (Fig. 1A). The inhibition of hyaluronan production correlated positively and significantly ($p<0.05$) with the PDGF-B mRNA level in the primary tissue (Fig. 1B). Adalimumab only significantly ($p=0.005$) reduced IL-6 production (Fig. 1C). The amount of IL-6 inhibition correlated positively with the TNF-α mRNA level in the primary tissue, but this was not significant (Fig. 1D).

Conclusions
Imatinib mesylate can be expected to reduce inflammation and extra-cellular matrix production in GO, while adalimumab can mainly be expected to reduce inflammation. This *in vitro* tissue culture model may, in future, prove valuable to test novel therapeutics for their presumed effect in GO as well as in other inflammatory diseases which have difficulties including enough patients for randomized controlled trials. Furthermore, such a whole tissue culture system may become valuable guiding future patient-tailored treatment strategies.

Based on:
Van Steensel L, van Hagen PM, Paridaens D, Kuijpers RW, Van den Bosch WA, Drexhage HA, Hooijkaas H, Dik WA. *Whole orbital tissue culture identifies imatinib mesylate and adalimumab as potential therapeutics for Graves' ophthalmopathy.* *Br J Ophthalmol. 2011;95:735-8.*

Abstract

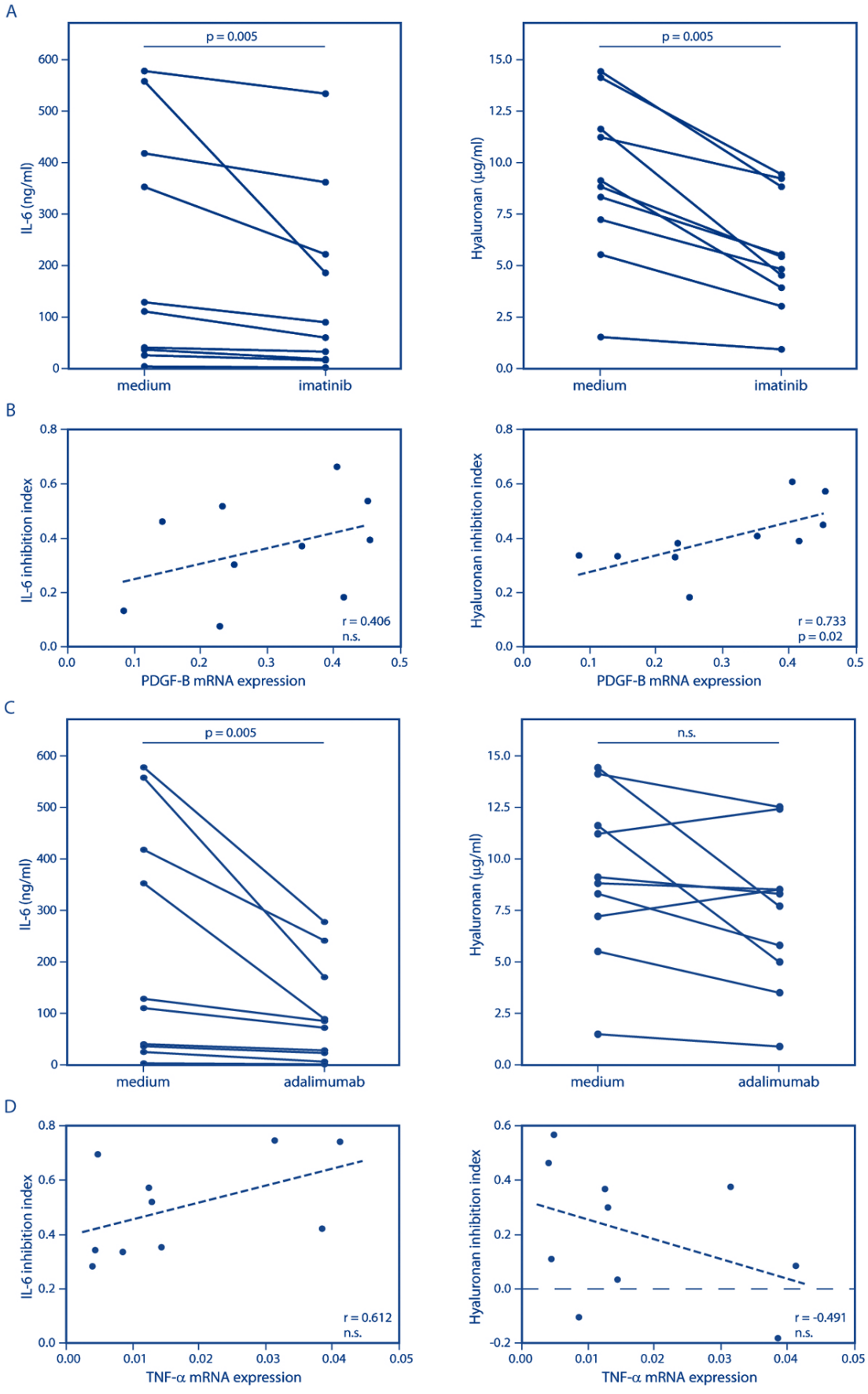

Figure 1 - The effect of imatinib mesylate (2.5 µg/ml) and adalimumab (10 µg/ml) on cultured GO orbital tissues (n=10). (A) IL-6 and hyaluronan production is significantly reduced by imatinib mesylate. (B) A positive correlation exists between the IL-6 and hyaluronan inhibition indexes and PDGF-B mRNA expression in the primary tissue, but is only significant for the hyaluronan inhibition index. (C) IL-6 production is significantly reduced in tissues by adalimumab, while hyaluronan production is reduced in 8 of 10 orbital tissues. (B) A positive correlation exists between the IL-6 inhibition index and TNF-α mRNA expression in the primary tissue and a negative correlation exists between the hyaluronan inhibition index and TNF-α mRNA expression in the primary tissue, but neither are significant. Each dot represents a single orbital tissue. The effect of imatinib mesylate and adalimumab on IL-6 and hyaluronan production was analyzed using the paired Wilcoxon rank sum test. Correlations were analyzed using Spearman's correlation test. p-values < 0.05 were considered significant.

Brain Tumors

The current research projects in the laboratory of the department of neurosurgery are focused on the preclinical evaluation of novel therapies for malignant brain tumors. Patients with a glioblastoma multiforme, the most common malignant brain tumor, have a mean survival of 14 months. This is despite current therapy, consisting of surgery and chemo-radiotherapy. This dismal prognosis indicates that there is a desperate need for novel therapies.
One research line is focused on the use of (combination of) specific inhibitors as a novel therapy. These compounds are tested in several in vitro assays on clinically obtained specimens. Results are correlated to the molecular profile of the original tumor and this will ultimately allow identification of responders and non-responders to specific agents.
The other research line is focused on the use of oncolytic adenoviruses, which can specifically replicate in and kill tumor cells. This virus has been tested extensively and demonstrated impressive therapeutic potential in preclinical models for malignant glioma. We work on novel systems for improving delivery of the virus and on gaining insight into the immunological response to the virus. Recently, a phase I/II trial was initiated testing the oncolytic adeno-virus Delta24-RGD. Clinical specimens of treated patients are collected and will be assessed for immunological response to treatment. For this, there is a close collaboration with the clinical department.

At the moment our research group consists of two group leaders, 1 post-doc, 2 PhD students, 2 research-technicians and several students. If you are interested in participating in one of the above described research projects for an internship (min 5 months) in translational research and want to learn and work with a divers range of laboratory techniques, please contact prof. dr. S Leenstra or dr. M. Lamfers.

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dr. M. Lamfers, m.lamfers@erasmusmc.nl, 010-7043825

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