Neurological aspects of Gaucher and Fabry disease
Biegstraaten, M.

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SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES
SUMMARY

The first section of this thesis focuses on the neurological complications in type I Gaucher disease.

Although several case reports on coincidental neurological complications in type I Gaucher disease patients had been published the non-neuronopathic character of the disease has not been debated until recently and the terms type I Gaucher disease and non-neuronopathic Gaucher disease were used as synonyms. Since the description of 6 type I Gaucher disease patients with concomitant early-onset parkinsonism in 1996, many reports and studies on the concurrence of type I Gaucher disease and parkinsonism have been published. Attention was drawn to the possible association between type I Gaucher disease and neurological diseases and the division into neuronopathic and non-neuronopathic phenotypes became subject of debate. To elaborate on this issue, a literature search was performed, the results of which are described in chapter 2. The search revealed 86 reports on neurological diseases in patients with type I Gaucher disease. Moreover, the Dutch type I Gaucher disease cohort was retrospectively studied for the presence of neurological diseases which revealed 34 neurological diagnoses in 75 patients with type I Gaucher disease during a median follow-up time of 11 years. These findings resulted in the proposal to reject the term non-neuronopathic Gaucher disease. However, we argue to uphold the division in three phenotypes, as the neurological symptoms and signs encountered in type I Gaucher disease are of a totally different order and magnitude as compared to the symptoms and signs associated with type II and type III Gaucher disease.

In chapter 3 the results of a large multicentre study on the prevalence and incidence of polyneuropathy in type I Gaucher disease are presented. A few single polyneuropathy cases had been reported, but it remained unclear whether polyneuropathy should be considered part of the clinical spectrum of type I Gaucher disease. Our study showed a diagnosis of polyneuropathy in 11 out of the 103 patients studied (prevalence: 10.7%). The two-year study period revealed another six cases of polyneuropathy (incidence: 2.9 per 100 person-years). After a systematic review of the literature, the prevalence and incidence of polyneuropathy in the general population are estimated between 0.09 and 1.3% and 0.0046 and 0.015 per 100 person-years, respectively. Thus, polyneuropathy is more common in type I Gaucher disease patients than in the general population.

In the same cohort, the cognitive profile of type I Gaucher disease patients was studied. These results are described in chapter 4. Considering the entire cohort, type I Gaucher disease patients showed slightly impaired speed measures compared with age- and gender-matched control values. Subgroup analyses revealed that severely affected patients scored worse than mildly affected patients on several cognitive function measures. Likewise, age was associated with cognitive impairment: older patients scored worse on the composite scores Quality of Working Memory and Variability of Attention. These findings suggest
that the central nervous system may become involved during life. However, clinical relevance of this finding is uncertain since type I Gaucher disease patients usually do not report difficulties in conducting daily activities or cognitive problems.

In chapter 5 a monozygous twin pair with type I Gaucher disease with highly discordant phenotypes is described. One had severe visceral involvement, epilepsy and a cerebellar syndrome. Her twin did not manifest any symptoms or signs of Gaucher disease. Interestingly, they had a presumably mild Gaucher mutation, although this genotype has also been described in relation to a mild type III phenotype with myoclonic epilepsy. The occurrence of highly discordant phenotypes in monozygotic twins and the concurrence of a mild Gaucher mutation and a severe phenotype, are both discussed. It is speculated that modifiers and/or environmental factors play an important role in the initiation and progression of Gaucher disease.

In section II, studies on small fibre neuropathy in Fabry disease are described. In chapter 6 and chapter 7 the results of a study on function and structure of small nerve fibres are presented. The small fibre neuropathy in Fabry disease is a length-dependent and Aδ-fibre preferential neuropathy. The length-dependent character was shown by the complete nerve fibre function loss at the lower limbs in almost all male patients, whereas nerve fibre function at the upper limbs was worse at older age and with more severe disease. Female patients exhibited incomplete small nerve fibre function loss at the lower limbs which was worse at older age and when disease was more severe, while small nerve fibres at the upper limb were relatively spared. In line with this observation, a decrease of intraepidermal nerve fibres was associated with more severe nerve fibre function impairment at the lower limbs in females. Males showed a more pronounced reduction of intraepidermal nerve fibre density; a further decrease was associated with more severe loss of nerve fibre function at the upper limbs.

Interestingly, the severity of small nerve fibre damage was not associated with pain intensity. On the contrary, young patients with relatively mild nerve fibre damage had high pain scores, whereas a subset of older patients with more severe nerve fibre damage reported no pain. This could be due to the mechanism of peripheral sensitisation - i.e. limited nerve fibre damage leads to abnormal excitability and pain - in young patients. Conversely, with increasing age and thus with increasing disease burden small nerve fibre damage can become so widespread and severe that pain may abate.

The preference for Aδ-fibres was already known from previous studies in Fabry disease, and is unique when compared with other small fibre neuropathies. In diabetes, amyloidosis and other diseases known to cause small fibre neuropathy, C-fibres and Aδ-fibres are equally affected. Therefore, the small fibre neuropathy in Fabry disease is most likely caused by the disease itself and not by comorbidities and/or co-medications.

Aside from pain and temperature, small nerve fibres carry autonomic functions. As a consequence, patients with small fibre neuropathy often suffer
from autonomic neuropathy. Abnormalities of tears and saliva formation, cardiac rhythm disturbances, defective sweating and gastrointestinal complaints in Fabry disease are therefore generally accepted to be caused by autonomic neuropathy. However, Fabry patients do not report symptoms and signs such as orthostatic intolerance and male sexual dysfunction that are invariably found in other autonomic neuropathies. Moreover, previous studies revealed that end-organ failure rather than autonomic neuropathy underlies the sweating problems and vascular hyperreactivity in Fabry disease. Therefore, the presence of autonomic neuropathy was doubted. We investigated the presence of autonomic neuropathy in a large cohort of Fabry patients. Results are described in chapter 8. Only a few Fabry patients reported orthostatic intolerance or male sexual dysfunction. Moreover, the cardiovascular autonomic function tests showed normal cardiovascular autonomic control in almost all Fabry patients. These findings make it unlikely that Fabry patients suffer from autonomic neuropathy despite the presence of small fibre neuropathy in this patient group. This seemingly contradiction may be explained by the difference between nerve fibre types involved in the autonomic control of organs and the nerve fibre type affected by Fabry disease; preganglionic autonomic fibres consist of small myelinated B-fibres and postganglionic autonomic fibres are small unmyelinated C-fibres, whereas Fabry disease causes relatively selective damage to A-δ-fibres. Possibly, the selective damage to ‘non-autonomic’ A-δ-fibres in Fabry disease leads to the preservation of some of the autonomic functions in Fabry disease. Symptoms and signs that have been attributed to autonomic neuropathy are more likely caused by end-organ failure.

In chapter 9 a male Fabry patient with poikilothermia is described. Laboratory investigations, neuro-imaging and autonomic function tests were all normal. Assessment of intraepidermal nerve fibre density and quantitative sensory testing revealed small nerve fibre damage with a highly impaired cold sensation. The poikilothermia may be either caused by a vascular lesion in the hypothalamus not visible on MRI, or related to the small fibre neuropathy which could have led to a disturbed body temperature perception and consequently to an impaired thermoregulation.

GENERAL DISCUSSION

Gaucher disease

Does the non-neuronopathic phenotype exist?

Gaucher disease is classically divided into three types, based upon the presence or absence and rate of progression of neurological manifestations. Type II is known as ‘acute neuronopathic’ or ‘infantile’ Gaucher disease, with infantile onset of severe central nervous system involvement leading to death usually by the age of two years. Type III is known as ‘chronic neuronopathic’ or ‘juvenile’ Gaucher disease,
with an onset of central nervous system involvement in childhood, adolescence or early adulthood and a more indolent course. The distinction between type II and III Gaucher disease is made on the basis of age of onset and the rate of progression of neurological manifestations. Type I Gaucher disease, also known as ‘non-neuronopathic’ Gaucher disease, is the most prevalent form (94%), with an onset usually in adolescence or early adulthood. In this type, visceral organs are involved to varying degrees. Absence of nervous system involvement is traditionally considered mandatory for a diagnosis of type I Gaucher disease. However, after the description of a small cohort of type I Gaucher disease patients with concomitant early-onset parkinsonism in 1996, studies were reported in which absence of neurological manifestations as phenotypic hallmark of type I disease was questioned. As outlined in the first section of this thesis, we also found considerable evidence for neurological complications in type I Gaucher disease. The systematic review of the literature as well as the results of the retrospective Dutch cohort study pointed to a broad range of neurological manifestations in this type of Gaucher disease. Many of the - in the literature described - neurological complications in type I Gaucher disease patients are sequelae of vertebral involvement. Vertebral involvement is in turn a complication associated with severe generalized visceral and skeletal Gaucher disease. Spinal cord compression as well as nerve root compression due to vertebral collapse and/or extraosseous accumulation of Gaucher cells have been reported. Furthermore, peripheral neuropathy was reported in patients with type I Gaucher disease, but whether this was related to the disease, medication or pure coincidence was unclear. Also, the co-occurrence of type I Gaucher disease and Parkinson disease has received increasing attention over the last decade. These patients may demonstrate an early onset, aggressive form of parkinsonism that is refractory to standard Parkinson therapy, but cases with a classic l-dopa-responsive Parkinson disease have also been described.

It should be noted that the literature search as described in chapter 2 revealed mostly case reports and case series. Systematic studies on neurological manifestations in type I Gaucher disease are very scarce. Following the observations of two cases of painful peripheral neuropathy and one case of dementia during a clinical trial with the substrate reduction therapy miglustat the European Medicines Agency required a systematic study as part of a post-marketing study for miglustat. To find out whether the polyneuropathy and cognitive decline were miglustat-related, coincidence or part of type I Gaucher disease, the prevalence of these neurological manifestations were prospectively studied in a large cohort of type I Gaucher disease patients. The peripheral neurological evaluations in this cohort identified sensory motor axonal polyneuropathy in 10.7% of the patients studied. Furthermore, an incidence of 2.9 per 100 person-years was found. Since we did not include a control group, the prevalence and incidence of polyneuropathy in the general population were estimated by reviewing the
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literature; according to this review, the prevalence of polyneuropathy in the general population was estimated between 0.09 and 1.3% (see chapter 3, Table 4) and the incidence was estimated between 0.0046 and 0.015 per 100 person-years. Thus, polyneuropathy is more often encountered in patients with type I Gaucher disease than in the general population.

The patients who were diagnosed with polyneuropathy in the clinical trial with miglustat had a painful polyneuropathy, while the patients in our study exhibited a mild polyneuropathy without pain\textsuperscript{33, 34}. Patients with type I Gaucher disease who receive miglustat were excluded from the study on the prevalence of neurological manifestations. We hypothesised that miglustat had an additional, pain inducing effect in patients with pre-existing polyneuropathy, similar to findings in patients who are treated with cytotoxic drugs such as thalidomide or bortezomib in whom pre-existing neuropathy is a strong risk factor for a severe painful polyneuropathy\textsuperscript{50}. However, recently presented results of a study on neurological manifestations in miglustat-treated type I Gaucher disease patients showed that miglustat-treated patients with concomitant polyneuropathy did not develop a painful neuropathy during a two-year follow-up period which makes it unlikely that miglustat has such an effect.

In addition to an increased prevalence and incidence of polyneuropathy in type I Gaucher disease patients, our study revealed mild impairments for Power of Attention and Speed of Memory in type I Gaucher disease patients, reflecting a poorer ability to focus attention and a slowed retrieval of information held in memory in comparison to age-matched healthy controls. Memory complaints were not assessed. Since cognitive complaints are considered mandatory for a diagnosis of mild cognitive impairment or dementia\textsuperscript{51}, patients could not be diagnosed as such. However, clinical practice has shown that type I Gaucher disease patients usually do not report difficulties in conducting daily activities or cognitive problems suggesting that the deficits in these patients were subtle and of doubtful clinical relevance.

Altogether, the peripheral as well as the central nervous system can be affected in type I Gaucher disease. The term non-neuronopathic Gaucher disease should therefore no longer be maintained.

Is there still a distinction between type I and types II/III? Or is it a spectrum? The notion of frequent neurological involvement has been used by some as an argument for the existence of a wide Gaucher disease spectrum rather than separate types of Gaucher disease\textsuperscript{2, 52}. However, the neurological manifestations in type I patients differ from those found in type II/III patients. Peripheral neuropathy, for instance, has been found to be part of the clinical spectrum of type I Gaucher disease, but has not been described in the neuronopathic types of Gaucher disease.

Neurological manifestations in type II Gaucher disease include saccade initiation abnormalities, strabismus and dysphagia. Neurologic progression
is marked by severe hypertonia, rigidity, opisthotonus and seizures. Type III Gaucher disease has a more heterogeneous presentation than type II disease. The clinical course may range from nervous system involvement that is limited to saccade initiation failure to progressive dementia, ataxia and myoclonus\textsuperscript{53}. Also rigidity may be part of the neurological picture which is a sign of extrapyramidal involvement. Interestingly, type I Gaucher patients as well as carriers of glucocerebrosidase mutations have also displayed an increased risk to develop extrapyramidal manifestations in the form of Parkinson disease and Lewy body dementia\textsuperscript{54}. Furthermore, the frequency of glucocerebrosidase mutations in cohorts of patients with parkinsonism (Parkinson disease as well as other Lewy body disorders) is increased around fivefold as compared to age-matched controls\textsuperscript{54}. Neuropathology in a series of Gaucher brains revealed some clues to the pathophysiological link between Gaucher disease and Parkinson disease. Gaucher patients showed selective vulnerability of the hippocampal CA2-4 regions, cerebral cortical layers 3 and 5 and calcarine cortex layer 4b with normal adjacent regions\textsuperscript{55}. Pathologic changes in the three brain regions were present in all three types of Gaucher disease, although there were qualitative and quantitative differences between the three types; neurodegeneration predominated in type II and III disease, whereas astrogliosis was the only manifestation in type I patients\textsuperscript{55}. The pattern of involvement corresponds with the pattern of neuropathological abnormalities seen in Lewy body dementia which is one of the few disorders that selectively target the hippocampal CA2-3 regions. Among the brains that were neuropathologically investigated, four patients had concomitant type I Gaucher disease and parkinsonism with dementia. One of these patients exhibited brain abnormalities similar to patients with Parkinson disease, i.e. neuronal loss of substantia nigra neurons accompanied by brainstem-type Lewy bodies, the second patient showed changes that were consistent with Lewy body dementia, i.e. diffuse brainstem- and cortical-type Lewy bodies and dystrophic neuritis in the CA2-3 region. The other two patients had hippocampal CA2-4 synuclein-positive inclusions similar to the Lewy bodies seen in Parkinson diseases and Lewy body dementia. Apparently, there are brain regions that are specifically vulnerable to damage in all three types of Gaucher disease. In type II/III disease this vulnerability leads to neuronal cell death and a severe neurological phenotype, whereas in type I disease it results in an increased risk of developing Lewy bodies with subsequent Parkinson disease or Lewy body dementia.

It is uncertain whether the neuropathological findings in type I Gaucher disease are of clinical relevance, aside from implicating a possible increased risk for developing parkinsonism. The cognitive profile of type I Gaucher disease patients shows some similarities with the profile of type III patients: a study in type III Gaucher disease children has shown that the cognitive deficits in these patients typically affect general nonverbal skills with a relative preservation of verbal skills. About 60% had below-average intellectual skills, and the weaknesses were
specifically observed in the areas of processing speed, visual-spatial relationships, and perceptual organization skills. Thus, type I as well as type III patients exhibit decreased speed measures. However, type III patients have a broader spectrum of cognitive function deficits with weaknesses not only in the area of processing speed, but also in visual-spatial relationships and perceptual organization skills. Moreover, type III patients encounter problems in conducting their daily activities, while patients with type I Gaucher disease do not. These observations suggest that the deficits in type I patients are subtle and of doubtful clinical relevance, in contrast to type III patients. However, it cannot be excluded that patients with type I Gaucher disease have a higher chance of developing dementia after a certain age. Having a mildly impaired cognitive profile at young age could make the patient more prone than healthy people to develop dementia later in life. Our patients were all below the age of 75, making it impossible to analyse this hypothesis. Future observational studies in large cohorts of patients are clearly needed.

Altogether, unlike the neuronopathic types of Gaucher disease, peripheral nervous system involvement seems to be part of type I Gaucher disease. On the other hand the central nervous system involvement in types II and III is extensive and results in progressive neurological disease whereas type I patients generally do not exhibit overt central nervous system disease. These findings justify maintaining the distinction in the three types. In view of the neurological features in all types, we propose to change the classification of Gaucher disease phenotypes as follows: primarily visceral (type I), primarily neuronopathic (type II) and mixed (type III).

This classification into different phenotypes has important practical consequences, especially in view of counselling. Patients at high risk for or with established neuronopathic Gaucher disease are often confronted with severe disability and invalidity. Professional counselling may improve quality of life for patients and their families. In addition, counselling for decision making for ‘end-of-life issues’ as well as bereavement counselling is often helpful for parents and siblings of infants with type II disease.

Besides, classification of Gaucher disease may guide the therapeutic approach. Given the rapid disease progression observed in individuals with type II Gaucher disease, these patients are not considered as appropriate candidates for enzyme replacement or substrate reduction therapy. On the other hand, type I and III Gaucher disease patients may benefit greatly from treatment. Symptomatic type I patients are usually treated with enzyme replacement therapy in dosages ranging from 15 to 60 U/kg every other week. Substrate reduction therapy is only indicated for patients with mild to moderate type I Gaucher disease for whom enzyme replacement therapy is unsuitable. Until recently patients with type III Gaucher disease were treated with high doses of enzyme replacement therapy (120 or even 240 U/kg every other week), but treatment recommendations have
been revised following new available data showing that there was no evidence that high-dose enzyme replacement therapy prevented or slowed down neurological progression. It is therefore agreed that treatment should aim at ameliorating the visceral aspects of Gaucher disease. Nowadays it is recommended to treat type III children with enzyme replacement therapy in a dose of at least 60 U/kg every other week, and to treat type III adults with 30-60 U/kg\textsuperscript{57}. Substrate reduction therapy used in combination with enzyme replacement therapy for type III patients does not appear to have significant benefits on the neurological manifestations of the disease\textsuperscript{59}, although data are scarce and longer follow-up is needed in cases that are treated as such\textsuperscript{60}.

Although classification into different phenotypes has important consequences, sometimes physicians are confronted with a patient that does not seem to fit in one specific category. The patient that is described in chapter 5 serves as an example, as she has severe visceral involvement together with epilepsy and a mild cerebellar syndrome\textsuperscript{61}. In cases like this, neurological examination can be best performed by a neurologist with experience in type III Gaucher disease\textsuperscript{57}. Examination should include eye movement analysis; elicitation of repeated maximal amplitude horizontal saccades can be performed at the bedside and compared with a healthy subject. It is recommended to add an objective measurement, e.g. electro-oculography, as clinical examination alone often misses slowed saccades or gaze palsy\textsuperscript{62}. Additionally, brain imaging by magnetic resonance imaging (MRI), electroencephalography (EEG) and neuropsychological testing should be part of the clinical assessment.

Since difficulties with saccade initiation and slowed horizontal saccades as well as abnormalities on brain MRI are absent in our patient, her Gaucher disease is best classified as type I.

**Pathophysiology**

Up to now, the underlying pathophysiological mechanisms of the peripheral and central nervous system involvement in type I Gaucher disease remain speculative.

Regarding the central nervous system involvement, neuropathology has shown astrogliosis of several brain regions in type I Gaucher disease patients\textsuperscript{55}. The most consistent and characteristic regions of pathology were the hippocampal CA2-4 regions. These parts of the hippocampus are known to have a massive association network: CA2-4 pyramidal cell neurons receive input from several parts of the brains, and contact for their part thousands of neurons in the ipsilateral hippocampus. Also, there is a pronounced positive feedback system in the CA2-4 regions that produces a hyperexcitable state and predisposes the CA2-4 regions to large synchronous discharges initiated in these regions. In healthy individuals the hyperexcitable state is moderated by strong inhibitory influences, but subtle alterations of the CA2-4 neurons can result in pathologic hyperexcitability states\textsuperscript{55}. Elevated glucosylceramide levels in these neurons may be such an alteration. In healthy people glucocerebrosidase expression is high in the affected CA2-4
regions which may be necessary to maintain low glucosylceramide levels in CA2-4 regions. In Gaucher patients, glucocerebrosidase activity is decreased, leading to increased glucosylceramide levels: a study in human brain tissue obtained post-mortem from Gaucher patients revealed glucosylceramide levels that varied between 0.7 and 2.9 nmol/mg in control brains, and between 6.1 and 13.9 in type I Gaucher disease patients. Elevated glucosylceramide levels have been shown to induce an elevated intracellular calcium release in these neurons, with a significant correlation between levels of glucosylceramide and the amount of calcium release. A disturbed calcium balance in the vulnerable CA2-4 neurons may explain the involvement of these hippocampal sub regions in patients with type I Gaucher disease.

The correlation between age and both cognitive function impairments and polyneuropathy in type I Gaucher disease patients suggests that the central and peripheral nervous system are affected simultaneously in the disease. Possibly, a similar process underlies the central and peripheral nervous system damage. Just like in the central nervous system, an imbalance in calcium homeostasis due to slightly increased glucosylceramide levels may play a role in the pathophysiology of peripheral nerve disease - increased intracellular calcium has been implicated in the pathophysiology of diabetic neuropathy and neuropathic pain as well.

The relationship between glucocerebrosidase mutations and Lewy body disorders (including Parkinson disease and Lewy body dementia) still has to be elucidated. Lewy body disorders are neurodegenerative disorders that are characterised by the presence of insoluble intracellular aggregates of α-synuclein (Lewy bodies). Gaucher patients as well as carriers of a glucocerebrosidae mutation have displayed an increased risk of developing synucleinopathies which is possibly due to a gain-of-function mechanism whereby mutated enzyme enhances the quantity of aggregates. Recently, seven brain samples from Gaucher disease patients and carriers were investigated. Glucocerebrosidase has been shown to be present in 75% of Lewy bodies in these patients compared to 4% in samples from subjects without mutations, which indicates that mutant glucocerebrosidase directly or indirectly induces α-synuclein aggregation through a gain-of-function mechanism. Mutant glucocerebrosidase could for example lead to lysosomal dysfunction or may interfere with receptor binding of α-synuclein at the lysosomal membrane, thereby contributing to impaired α-synuclein clearance and thus to the formation of α-synuclein inclusions. Aside from gain-of-function mechanisms, loss of function has been postulated to play a role. Studies in mice suggested a correlation between glucosylceramide and α-synuclein aggregation. Also, disturbed binding of α-synuclein to brain-derived glycosphingolipids - normally preventing the formation of fibrillar protein structures - due to accumulated glucosylceramide has been proposed as an underlying mechanism.
**Fabry disease**

*Small fibre neuropathy in Fabry disease*

Previous studies have explicitly shown that small nerve fibres are affected in Fabry disease\(^7\text{-}^{13},\,71\text{-}^{75}\). Neuropathological studies revealed loss of cell bodies in the dorsal root ganglia together with a pronounced reduction of small, thinly myelinated (A\(\delta\)) and unmyelinated (C) nerve fibres in sural nerve biopsy specimens\(^71,\,72\). Reduced intraepidermal nerve fibre densities were found in 19 out of 20 male patients\(^73\) and in 3 out of 11 female patients\(^7\). In addition, up to now more than hundred male and female Fabry patients have been studied with quantitative sensory testing. These studies have repeatedly shown small fibre hypofunction with a predilection for cold sensation in Fabry patients\(^7\text{-}^{13}\). Sixty-three to 100% of male patients\(^8,\,9,\,12,\,13\) and 16 to 33% of female patients\(^7,\,10\) were shown to have an impaired temperature perception.

We investigated small nerve fibre function and structure in 48 male and female Fabry patients. Our studies confirm previous findings in that we found solid evidence for the presence of small fibre neuropathy. A comparable percentage (100%) of male patients was shown to have an abnormal intraepidermal nerve fibre density, but a higher percentage (57%) of females exhibited abnormal skin biopsy results. However, nerve fibre densities in female patients were comparable to results from another study\(^10\). Just like earlier studies, we found a decreased thermal sensation in most Fabry patients\(^76\). Considering the cold detection threshold, the warm detection threshold and the thermal sensory limen at the upper and lower limb, almost all males (13 out of 15) showed at least one pathologically decreased thermal threshold (Z-score < 1.96) (see Table 1). In females, these numbers were somewhat different (see Table 2): almost half of the females (16 out of 33) studied with quantitative sensory testing had at least one abnormal thermal threshold at the upper or lower limb.

A quarter of the females studied exhibited abnormal thermal sensation while their nerve fibre density was normal. Of the females who underwent a skin biopsy as well as quantitative sensory testing measurements, three quarters had either an abnormal intraepidermal nerve fibre density, or a decreased thermal detection thresholds, or both.

Altogether, almost all male and about half of female Fabry patients suffer from small fibre neuropathy. Although our observations in females differ somewhat from previous findings, we feel that our results give a more reliable estimate due to the larger number of females studied. Since some male and many female patients are non- or oligosymptomatic, these estimates suggest that small nerve fibres are affected early during the course of the disease (i.e. before overt multisystem disease) which is not surprising considering the fact that neuropathic pain is one of the first symptoms in most Fabry patients\(^77\). This observation may be helpful in the ongoing discussion about the timing of treatment with enzyme replacement therapy in Fabry patients. It is assumed that enzyme replacement therapy is best...
started before irreversible organ damage is present. If nerve fibre function and/or structure are monitored in Fabry children, therapy may be commenced at the time small nerve fibre damage is revealed.

**Diagnosis of small fibre neuropathy in atypical patients**

Interestingly, the two male patients with normal thermal detection thresholds are so called ‘atypical’ patients; they carry a mutation that is usually not associated with classical Fabry symptoms such as neuropathic pain, angiokeratoma and hypo- or anhidrosis. Moreover, they are biochemically different from ‘classical’ Fabry patients in that they do not show elevated lyso-Gb3 levels. It has been even questioned whether these patients should be considered as Fabry patients at all. While a diagnosis of small fibre neuropathy is usually straightforward in ‘classical’ Fabry patients, it may be difficult to diagnose small fibre neuropathy due to Fabry disease in ‘atypical’ cases. This is of particular importance since small fibre neuropathy may be the reason to start enzyme replacement therapy - a therapy that has great implications for the patient involved as it exposes a patient to lifelong bi-monthly intravenous therapy which disrupts his/her quality of life and involves considerable health care expenses. Therefore, there is a need for robust criteria to diagnose small fibre neuropathy due to Fabry disease in individual patients. Considering this, we should keep in mind that neuropathies may develop in a considerable number of people as a consequence of many

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IENFD= intraepidermal nerve fibre density, CDT= cold detection threshold, WDT= warm detection threshold, TSL= thermal sensory limen
Table 2 Intraepidermal nerve fibre density and quantitative sensory testing results in female Fabry patients (n = 33)

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<th>Age</th>
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<th>WDT hand</th>
<th>TSL hand</th>
<th>CDT foot</th>
<th>WDT foot</th>
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</table>

IENFD = intraepidermal nerve fibre density, CDT = cold detection threshold, WDT = warm detection threshold, TSL = thermal sensory limen
different disorders, of which (pre) diabetes is the most common cause. We should therefore look for Fabry disease-specific small fibre neuropathy features. According to our experience as well as to the literature, Fabry patients usually report burning or shooting pains or painful pins and needles in hands and/or feet, starting at young age and with typical heat-provoked pain crises. We would propose to consider a diagnosis of small fibre neuropathy due to Fabry disease only in patients with (a history of) neuropathic pain in hands and/or feet, with either an onset of pain in childhood or adolescence (i.e. < 18 years of age), or a course of pain that is characterised by ongoing pain with exacerbations that are provoked by fever, exercise or heat, or both (see Fig. 1). Patients, who additionally exhibit a decreased cold sensation at the upper or lower limb or an abnormal intraepidermal nerve fibre density, probably suffer from small fibre neuropathy due to Fabry disease. Patient with typical pain complaints, a decreased cold sensation and an abnormal intraepidermal nerve fibre density have confirmed small fibre neuropathy due to Fabry disease.

**The course of small fibre neuropathy and pain in Fabry disease**

The course of small nerve fibre involvement and pain has been studied only scarcely. Moreover, the few studies that have been done showed conflicting results. One study showed more severe small nerve fibre impairment with older age, while no correlation between thermal thresholds and pain severity was found, another study found a positive correlation between age and pain severity but no associations between intraepidermal nerve fibre density, thermal sensation...
and pain severity\textsuperscript{10}, a third did not reveal an association between small nerve fibre function and age or disease severity\textsuperscript{9}, the fourth study did not demonstrate correlations between age, pain severity and nerve fibre function, although they did find an association between intraepidermal nerve fibre density and pain intensity\textsuperscript{7}, and the last study could not demonstrate a correlation between intraepidermal nerve fibre density and disease severity\textsuperscript{73}. Due to these divergent observations, the course of small fibre neuropathy in Fabry disease has been unclear so far.

These conflicting results are probably due to the small number of patients included in each of those studies. By studying 48 Fabry patients, we wanted to establish the course of small nerve fibre damage in Fabry disease. Our investigation revealed a clear association between age and disease severity on the one hand and small nerve fibre function and structure on the other hand: older and more severely affected patients exhibit more severely impaired thermal sensation and a lower intraepidermal nerve fibre density\textsuperscript{76}. Moreover, more severe loss of intraepidermal nerve fibres turned out to be clearly associated with more severe loss of nerve fibre function.

Our findings point to a length-dependent neuropathy that starts at young age and leads to an abnormal intraepidermal nerve fibre density and complete loss of small nerve fibre function at the lower limbs in male patients in the first two decades. Nerve fibre function at the upper limbs decreases in the years thereafter. In females this process starts later in life, and most females will never develop complete loss of nerve fibre function at the lower limbs.

Just like the observations in other studies, there was no linear relationship between structural and functional nerve fibre impairment and pain intensity. Young patients reported more severe pain and young females exhibited slightly positive heat pain threshold Z-scores which could have pointed to increased sensitivity (peripheral sensitisation) in young patients. Besides, one-third of females aged 50 years and older reported no pain on the visual analogue scale for mean pain in the last 4 weeks. The lack of a linear relationship between quantitative sensory testing results, intraepidermal nerve fibre density and pain severity is therefore probably explained by peripheral sensitisation in the youngest patients, and disappearance of pain in a subset of the oldest patients (see chapter 6, Fig. 2a and Fig. 2b). However, conclusive proof of a causal relationship between small fibre damage and pain could not be established. Possibly, the absence of a linear correlation between small fibre damage and pain severity is caused by another underlying pain mechanism: for example, nociceptive pain may play a role in Fabry disease. However, taking the pain description and length-dependent character into account it is far more likely that the pain in Fabry disease is caused by small fibre damage rather than nociceptive pain.

**Autonomic neuropathy**

Aside from temperature and pain, small nerve fibres carry autonomic functions. As a consequence, small fibre damage often results in autonomic dysfunction. In
Fabry disease an- or hypohydrosis, decreased tears and saliva formation, abnormal cerebrovascular reactivity, cardiac rhythm disturbances as well as gastrointestinal complaints have been ascribed to autonomic neuropathy. However, doubts have arisen about the existence of autonomic neuropathy in Fabry disease: orthostatic intolerance and male sexual dysfunction that are invariably found in autonomic neuropathies are infrequently reported by Fabry patients. Moreover, the defective sweating which has long been thought to originate from autonomic neuropathy is no longer considered to be caused by autonomic neuropathy as skin biopsy studies did not reveal a decrease in nerve fibre density of sweat gland innervation, but revealed storage of lipids in sweat glands. Also, the non-length dependent distribution of the an- or hypohydrosis and the rapid effect of single enzyme infusions, suggested a sweat gland dysfunction rather than an autonomic neuropathy.

Indeed, the assumption that Fabry patients suffer from autonomic neuropathy is probably not true. The low prevalence of orthostatic intolerance and male sexual dysfunction, the normal cardiovascular autonomic control, and the low resting heart rate of our study patients make it unlikely that Fabry patients suffer from autonomic neuropathy.

In our study, autonomic function tests were restricted to those evaluating cardiovascular autonomic function which was criticised by others. However, abnormalities in the autonomic control of other organ systems such as peripheral vascular reactivity probably reflect end-organ pathology and not real autonomic neuropathy, in line with defective sweating. A study on vascular hyperreactivity in Fabry disease supports this hypothesis; absence of a difference in plasma epinephrine or norepinephrine levels between patients and controls suggested that the altered vessel response in Fabry disease may be attributed to vasogenic and not to neurogenic factors. Studies on heart rate variability (HRV) in pediatric Fabry patients revealed significantly different results between Fabry boys and Fabry girls and between Fabry boys and controls, with significant improvement of heart rate variability in Fabry boys upon enzyme replacement therapy. However, it is likely that cardiac pathology (left ventricular hypertrophy and/or conduction system pathology) has influenced the abnormalities observed in these patients.

Since the peripheral autonomic nervous system comprises of preganglionic small myelinated B-fibres and postganglionic small unmyelinated C-fibres, the relatively selective damage to ‘non-autonomic’ small myelinated Aδ-fibres in Fabry disease possibly underlies the preservation of autonomic function in Fabry disease. Although this is no more than a hypothesis, we found some support for this thought by similar findings, i.e. no evidence for autonomic failure, in hereditary sensory and autonomic neuropathy type 5 that is also known to cause selective loss of Aδ-fibres.
The observation that Fabry patients do probably not suffer from autonomic neuropathy makes it unlikely that the poikilothermia in the Fabry patients that is described in chapter 9 is caused by autonomic failure\(^9\). This case has posed a diagnostic challenge to the physicians involved. Poikilothermia in humans has been reported only scarcely, and those patients that have been described in literature invariably had hypothalamic pathology as underlying cause. Our patient does neither have a history of hypothalamic contusion or infarction, nor hypothalamic lesions on cerebral MRI. It could still be possible that a hypothalamic infarction, not visible on MRI, causes his fluctuating body temperature. Alternatively, the poikilothermia could be related to his small fibre neuropathy. Since quantitative sensory testing showed severely impaired cold sensation in this patients, and the hypothalamus receives its cold information by input from cold receptors in the skin\(^9\), low body temperature is possibly not perceived properly by the hypothalamus. Subsequent impaired feedback might lead to lower body temperatures, especially during the cold winter time. Unfortunately, we are not able to support this hypothesis by thermal stress testing since these tests are considered unethical due to the well-known heat-provoked painful acroparesthesias in Fabry disease. Besides, the fact that most Fabry patients have a normal body temperature regulation despite impaired temperature sensation makes this hypothesis questionable.

Pathophysiology

Despite more extensive knowledge about the course and consequences of small fibre neuropathy in Fabry disease, the underlying pathophysiological mechanism remains speculative. It is uncertain whether the neuropathy arises from storage of lipids in ganglia leading to a so-called dying-back neuropathy, or from direct damage to small nerve fibre axons. The preference for A\(\delta\)-fibres suggests that the ganglia or axons of small myelinated nerve fibres are more vulnerable to lipid accumulation than small unmyelinated fibres are. We found an association between lyso-Gb3 exposure and small nerve fibre function in male hemizygotes; possibly, this sphingoid base exerts a direct pathological effect on the ganglia or axons of small myelinated nerve fibres. The possibility that chronic exposure to lyso-Gb3 is neurotoxic is of interest in connection to hereditary sensory neuropathy type 1A. Hereditary sensory neuropathy type 1A is an autosomal dominantly inherited length-dependent neuropathy caused by mutations in the SPTLC1 subunit of serine palmitoyltransferase. Palmitoyltransferase catalyzes the initial step in the de novo synthesis of sphingolipids. Mutations in the SPTLC1 gene cause a shift in the substrate specificity of palmitoyltransferase resulting in the formation of two toxic side metabolites, the sphingolipid bases 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine, which both lack a hydroxyl group at C1\(^9\). This prevents the further conversion of these metabolites to sphingomyelin and glycosphingolipids but also impedes their degradation. Consequently, 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine accumulate. In vitro, these
metabolites are neurotoxic and interfere with the formation of neuritis, possibly by disturbing neuronal skeleton formation. Interestingly, 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine highly resemble lyso-Gb3, thereby supporting the hypothesis that elevated lyso-Gb3 levels underlie the neuropathy in Fabry disease. Hereditary sensory neuropathy type 1 and the neuropathy in Fabry disease show similarities: patients with hereditary sensory neuropathy type 1 usually present with severe shooting and lancinating pain and painless skin injuries. Ulcers are a common complication as the neuropathy progresses. Motor involvement tends to occur with time and is usually a distal wasting and weakness. Autonomic features are usually absent. Neurological examination detects distal sensory loss which often selectively affects pain and temperature sensation. Vibration and joint position sense are also affected but much less and later than pain and temperature sensation. Sural biopsies in hereditary sensory neuropathy type 1 patients have revealed loss of large and small myelinated nerve fibres with preservation of small unmyelinated nerve fibres whereas large myelinated nerve fibres are spared in Fabry disease. This difference explains the more extensive sensory loss and motor involvement in patients with hereditary sensory neuropathy type 1.

FUTURE PERSPECTIVES

Type I Gaucher disease

Type I Gaucher disease and Lewy body disorders sometimes concur. Neuropathological studies have demonstrated pathology involving the hippocampal CA2-4 regions, the same regions that are affected in patients with Lewy body dementia. Moreover, the cognitive profile of type I Gaucher disease and Lewy body dementia patients have some features in common. Unravelling the relationship between type I Gaucher disease, Parkinson disease and Lewy body dementia would help in the understanding of these disorders.

Also, the occurrence of cognitive dysfunction and dementia in type I Gaucher disease should be studied more extensively. It would be interesting to compare the prevalence and incidence of dementia in older type I Gaucher disease patients (>80 years old) with those in the general population. Do type I patients have an increased risk of developing a subcortical dementia syndrome knowing that they exhibit mildly decreased cognitive speed measures at younger age? This question can be answered if cognitive function is assessed regularly in a large cohort of Gaucher patients. Ideally, cognitive data - for instance minimal mental state examination (MMSE) scores - are prospectively entered in a Gaucher disease registry, thereby generating reliable estimates of prevalence and incidence of dementia in type I Gaucher disease, regardless of disease severity, concomitant medical conditions and medical treatments.
**Fabry disease**

Discussions are ongoing about the timing of treatment with enzyme replacement therapy in Fabry patients. Previous studies showed improvement of nerve fibre function with enzyme replacement therapy\(^\text{83}\), whereas the intraepidermal nerve fibre density did not change after 12 months of treatment\(^\text{74}\). Apparently, structural damage is irreversible, while function of the remaining fibres may improve on enzyme replacement therapy. Enzyme replacement therapy is therefore possibly best started before nerve fibres are structurally damaged. We found subtle evidence for peripheral sensitisation in Fabry girls, in that they had slightly increased heat pain thresholds. The heat pain threshold may serve as a marker of functional but not structural damage to small nerve fibres, i.e. reversible disease. The role of the heat pain threshold as a measure of reversible disease in young boys and girls with ‘classical’ Fabry disease must be studied more extensively.

Furthermore, in-depth studies on the possible neurotoxic character of lyso-Gb3 should be performed. Firstly, the relation between small fibre neuropathy and brain white matter lesions and hearing loss must be investigated. Secondly, it would be worthwhile to investigate whether lyso-Gb3 exposure correlates with any of these parameters. The available mouse model of Fabry disease may also be exploited to determine the neurotoxicity of lyso-Gb3.

**REFERENCE LIST**

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

10

(10-galactosidase A deficiency)-
-investigation of symptomatic and


59. Schiffmann R, Fitzgibbon EJ, Harris C et al. Randomized, controlled trial of


