Neurological aspects of Gaucher and Fabry disease

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2

‘NON-NEURONOPATHIC’ GAUCHER DISEASE RECONSIDERED. PREVALENCE OF NEUROLOGICAL MANIFESTATIONS IN A DUTCH COHORT OF TYPE I GAUCHER DISEASE PATIENTS AND A SYSTEMATIC REVIEW OF THE LITERATURE

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SUMMARY

Gaucher disease is a lysosomal storage disorder, which is classically divided into three types. Type I Gaucher disease is differentiated from types II and III disease by the absence of nervous system involvement. However, an increasing number of reports has emerged on neurological manifestations in patients with type I Gaucher disease. Whether a strict division in three different phenotypes is still valid has been the subject of debate. The main objective of this study was to provide scientific arguments whether a distinction between type I (non-neuronopathic) and types II and III (neuronopathic) Gaucher disease should be maintained. We investigated retrospectively a large Dutch cohort of type I Gaucher disease patients for the prevalence of neurological manifestations and provide an overview of the literature on this topic. A diagnosis of a neurological disease was made 34 times in 75 patients. Forty-five patients reported at least one neurological symptom during the median follow-up time of 11 years. The literature search revealed 86 studies in which type I Gaucher disease patients or carriers of a glucocerebrosidase mutation were described with a neurological disease or a condition which is known to be associated with neurological disease. In conclusion, the term non-neuronopathic Gaucher disease does not seem to be an appropriate characterization of type I Gaucher disease. However, the neurological signs and symptoms in type I Gaucher disease are of a totally different kind from and, in the majority of cases, of much less severity than the signs and symptoms associated with types II and III disease. Therefore, type I disease should be classified as a separate phenotype.

INTRODUCTION

Gaucher disease is a lysosomal storage disorder characterized by intralysosomal accumulation of glucocerebroside in macrophages throughout the body caused by deficiency of the enzyme glucocerebrosidase. The inheritance pattern is autosomal recessive. The gene encoding glucocerebrosidase (GBA) is located on chromosome 1q21. More than 200 different mutations have been identified in patients with Gaucher disease[1]. Genotype-phenotype correlations have been the subject of many studies, but it is clear that patients sharing the same glucocerebrosidase mutation may exhibit a wide phenotypic variation. Gaucher disease is classically divided into three types, based upon the presence or absence and rate of progression of neurological manifestations. Type I, also known as 'non-neuronopathic', 'adult' and 'chronic' Gaucher disease, is the most prevalent form (94%), with an onset usually in adolescence or early adulthood[2, 3]. In this type, visceral organs are involved to varying degrees. The most common manifestations include splenomegaly, hepatomegaly, anaemia, thrombocytopenia, bone disease and growth retardation. Absence of central nervous system involvement is considered to be mandatory for a diagnosis of type I disease. 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 2 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 types II and III Gaucher disease is made on the basis of age of onset and the rate of progression of neurological manifestations. However, an intermediate phenotype has been described[4]. Also, an increasing number of reports have emerged on neurological manifestations in patients with type I disease. For example, recent reports have shown that there is an association between Gaucher disease and parkinsonism, leading to an increased incidence not only in patients but also in carriers of a glucocerebrosidase mutation[5-30]. Whether a strict division into three different phenotypes is still valid has been the subject of debate. Some authors believe that the three types of Gaucher disease are more correctly characterized as a continuum of phenotypes[1, 31], whereas others believe that the most relevant distinction is that some patients have neurological manifestations and others do not[32, 33].

The main objective of this study was to investigate the prevalence of any neurological manifestation in a large cohort of patients with type I Gaucher disease from the Netherlands and to systematically review the literature for presence and nature of neurological manifestations in type I disease and in carriers of a glucocerebrosidase mutation.

METHODS

Cohort study

The clinical records of all patients referred to the outpatient clinic for inherited metabolic diseases at the Academic Medical Centre between 1991 and 2007 were reviewed. This clinic is the only referral centre in the Netherlands for Gaucher patients. Using a standardized data extraction sheet, neurological signs and symptoms, neurological diagnoses and relevant ancillary investigations with their results were obtained from all patients. Any neurological sign, symptom or diagnosis documented in the patient notes at any time during follow-up was extracted. Special attention was paid to diseases known from the literature to occur in patients with type I Gaucher disease. Neurological manifestations were as much as possible attributed to a neurological diagnosis if available data permitted this. Otherwise, the manifestation was kept descriptive at the symptom and/or sign level.

Systematic review

We conducted a PubMed search from May 1965 to July 2007 using the search terms 'Gaucher disease' and 'nervous system disease' to identify all reports about type I Gaucher disease and neurological manifestations. English-, Dutch-, German- and French-language articles concerning human subjects were included. The references cited in relevant articles were scanned to identify additional reports of interest. The search revealed 2464 articles. Title and abstract were read to establish eligibility. An article was considered eligible if: (i) including patients with type I Gaucher disease and a description of a neurological disease in at least one of the patients; (ii) including patients with type I Gaucher disease and a condition which is known to be associated with neurological disease; or (iii) including carriers of a glucocerebrosidase mutation and a concomitant neurological disease in at least one of the carriers. Eighty-six studies were suitable and are included in this survey.

COHORT STUDY

Between 1991 and 2007, 75 adult patients visited the outpatient clinic for inherited metabolic diseases. All patients were seen at regular intervals with a median follow-up of 11 years (range 1-16 years). A diagnosis of Gaucher disease was made by enzymatic and gene mutation analysis. The presence of type I phenotype was established based on the absence of characteristic neurological sequelae such as supranuclear gaze palsy, cognitive decline, epilepsy, myoclonus and/or ataxia. Table 1 shows the characteristics of all patients from the Dutch cohort.

In the 75 patients, 27 patients (36%) had 34 neurological diagnoses. None of these problems was the presenting complaint; they were all incidental findings during follow-up. One patient had a possible type III disease on the basis of

Table 1 Characteristics of the Dutch cohort, n = 75

Sex, M/F	38/37
Age (years) [mean (median)]	52 (52) range 20-82
Splenectomised (*n*)	24
Untreated (*n*)	16
Enzyme replacement therapy (*n*)	57
Substrate inhibition therapy (*n*)	2
Follow-up time (years) [mean (median)]	10 (11) range 1-16
Possible type 3 disease (*n*)	1
Parkinsonism (*n*)	1
Spinal cord compression (*n*) due to plasmacytoma (1) and vertebral collapse (1)	2
Dementia (*n*)	3
Confusion during illness (*n*)	2
Epilepsy (*n*)	2
Infection (*n*): encephalitis (1), meningitis (2)	3
Syringomyelia (*n*)	1
Basal skull fracture (*n*)	1
Polyneuropathy (*n*)	4
Mononeuropathy (*n*)	3
Plexopathy (*n*): neuralgic amyothrophy (1), ischemia brachial plexus (1)	2
Radiculopathy due to lumbar disc protrusion (*n*)	3
Radiculopathy due to cervical stenosis (*n*)	1
Radiculopathy due to spondylodiscitis (*n*)	1
Lumbar stenosis, low back pain (*n*)	1
Bell's palsy (*n*)	2
Sixth-nerve palsy (*n*)	1

epilepsy, disturbed horizontal eye movements and slight ataxia. Two patients (3%) had possible epilepsy without any other symptom or sign that could lead to a type III diagnosis. One patient (1%) had parkinsonism, likely caused by Parkinson disease. Three patients (4%) suffered from dementia, of whom one patient had a radiologically confirmed hydrocephalus and one had dementia due to multiple vascular events. Two patients (3%) had an acute confusional state during severe illness; one patient suffered from liver failure and one from sepsis. One patient (1%) had neurological complications resulting from compression of the spinal cord by a plasmacytoma. Another patient (1%) had spinal cord compression due to radiologically confirmed vertebral collapse. Three patients (4%) had an infection of the central nervous system; one patient suffered from encephalitis, and two patients from meningitis. One patient (1%) was diagnosed with a syringomyelia without neurological symptoms or signs. One patient (1%) had a basal skull fracture

during childhood. Four patients (5%) had an electromyographically confirmed PNP. Three patients (4%) had a mononeuropathy proven with electromyography; one with carpal tunnel syndrome, and two with carpal tunnel syndrome and ulnar neuropathy. One of the two patients with carpal tunnel syndrome and ulnar neuropathy had concomitant multiple myeloma and amyloidosis. One patient (1%) was diagnosed with neuralgic amyotrophy of his shoulder. Another patient (1%) had pain and paraesthesias of one arm, probably due to ischaemia of the brachial plexus. Three patients (4%) were diagnosed with radiculopathy due to radiologically confirmed lumbar disc prolapse. One of these three patients had also pain in neck and arm resulting from radiologically proven cervical spondylosis and cervical disc protrusion. Another one of these three patients had also an episode of radiculopathy due to spondylodiscitis. One patient (1%) had low back pain radiating to both legs due to lumbar vertebral collapse leading to a stenotic lumbar canal. Two patients (3%) suffered from Bell's palsy, one of them having hemifacial spasms afterwards. Another patient (1%) had a sixth-nerve palsy.

Forty-five patients (60%) reported at least one symptom during their follow-up period which could be attributable to neurological involvement, but confirmatory testing was not performed because complaints were transitory or diagnostic tests were considered not necessary. Of these patients, 15 (20%) were diagnosed as having migraine. Other symptoms were paraesthesias (31%), low-back pain radiating to one leg (19%), tremor (7%), muscle cramps (5%), neck pain radiating to one arm (4%), difficulty with concentration and memory problems (3%), balance problems (3%), restless legs (1%) and diplopia (1%).

SYSTEMATIC REVIEW

The literature search revealed nervous system involvement in patients with type I Gaucher disease which could be divided into central and peripheral nervous system complications.

In the following section, these two major categories will be discussed. Central nervous system complications will be subdivided into adult-onset Gaucher disease with neurological complications comparable to type III disease, parkinsonism, spinal cord compression and sporadic central nervous system complications. Peripheral nervous system complications will be subdivided into (poly)neuropathy, nerve root compression and sporadic peripheral nervous system complications. Besides the two major categories, several conditions that are known to be associated with Gaucher disease, and are potential risk factors for developing nervous system diseases, will be discussed.

Central nervous system involvement

Probable type III diagnosis

Initially, type III disease was considered to be restricted to children and adolescents. However, over time it has been recognized that neurological involvement in type III Gaucher disease sometimes emerges in adulthood. Before this recognition, several case reports have described patients with type I disease and adult-onset neurological manifestations[34-39], who could better be classified as late-onset type III disease (see Table 2). In our cohort one patient has possible late-onset type III disease.

Parkinsonism

Parkinsonism is a clinical syndrome characterized by bradykinesia, resting tremor, rigidity and postural instability. Parkinson disease is the most common cause of parkinsonism, but this syndrome also occurs in other disorders. In Parkinson disease, abnormal aggregation and misfolding of α-synuclein leads to Lewy body formation in the substantia nigra. Lewy bodies trigger cellular oxidative stress and energy depletion in this area subsequently leading to parkinsonian features.

A link between Gaucher disease and parkinsonism became evident after the description of Gaucher disease patients that exhibit early-onset parkinsonism[21]. In the following years the number of case reports and series has greatly expanded.

Table 2 Late-onset type III disease

Sex	Age at onset (years)	Symptoms and signs	Reference
M	29	Epilepsy preceded by myoclonus, cognitive impairment, ophthalmoparesis in horizontal and vertical gaze, 6th-nerve weakness, generalized muscle atrophy and weakness, ataxia	Miller et al[36]
F	36	Epilepsy, cognitive impairment, abnormal horizontal eye movements, generalized muscle atrophy and weakness, ataxia	Miller et al[36]
M	17	Myoclonic epilepsy, mild intellectual impairment	King[35]
F	41	Psychiatric symptoms, parkinsonism, EEG abnormalities, intellectual deterioration	Neil et al[37, 38]
M	28	Psychiatric symptoms, EEG abnormalities, epilepsy	Neil et al[37, 38]
F	42	Abnormal horizontal saccadic eye movements, parkinsonism with poor response to therapy and rapid progression, pyramidal signs	Tayebi et al[39]
M	49	Parkinsonism with poor response to therapy, ophthalmoparesis in horizontal and vertical gaze, action myoclonus, cognitive impairment, EEG abnormalities	Guimaraes et al[34]
F	25	Epilepsy, abnormal horizontal and vertical eye movements, slight ataxia	Dutch cohort

EEG=electroencephalography

Table 3 summarizes all type I Gaucher disease patients with parkinsonism described in the literature, including the cases extracted from the studies on carriers of a Gaucher disease mutation and supplemented with one case from our cohort[7, 9-11, 13, 15, 16, 18-23, 25-29]. Generally, these subjects demonstrate relatively mild Gaucher symptoms, but have an early onset, aggressive form of parkinsonism, often involving cognitive decline, that is refractory to standard Parkinson therapy. However, some cases have been described with a classic l-dopa-responsive Parkinson disease.

Furthermore, genetic studies revealed an increased frequency (4.3-31.3%) of glucocerebrosidase mutations among probands with parkinsonism[5, 6, 8, 12, 18, 24, 30]. This frequency is surprisingly high, considering that in the high-risk Ashkenazi Jewish population the carrier frequency for Gaucher disease alleles is estimated at 0.0343[40]. Moreover, several studies and observations of relatives of Gaucher probands have revealed multiple cases of parkinsonism among Gaucher disease carriers[8, 13, 14, 17, 23]. This further strengthens the association between these two disorders.

Nonetheless, most carriers and patients with Gaucher disease never develop parkinsonism, suggesting the involvement of other factors, genetic or environmental, in the disease process.

Spinal cord compression

Bone problems are an important feature of type I Gaucher disease, and commonly include pathological fractures of the weight-bearing bones and avascular necrosis of the femoral head. Vertebral involvement is usually a late complication associated with severe generalized visceral and skeletal Gaucher disease. Fifteen cases with spinal cord compression due to radiologically confirmed vertebral collapse and/or extraosseous accumulation of Gaucher cells have been reported[41-51] (see Table 4). In our cohort two such patients were identified.

Sporadic central nervous system involvement

Several case reports have been published describing type I Gaucher patients who experienced other types of central nervous system diseases than those mentioned above. The literature review revealed three patients with type I disease in whom an astrocytoma developed[52, 53]. Additionally, Melamed et al[54] reported a patient suffering from massive systemic fat embolism, involving mainly the brain and lungs. It was presumed that the severe skeletal involvement due to Gaucher disease led to the development of fat embolization. Cormand et al[9, 10], in their overview on clinical features and genotypes in a cohort of Spanish Gaucher patients, mentioned a patient with type I disease (genotype N370S/unknown) and macrocephaly. No further information about this patient was given. Two siblings with type I Gaucher disease and Joubert syndrome have been described[55]. Joubert syndrome is a rare genetic developmental disorder with agenesis or hypoplasia of the cerebellar vermis and brainstem, which can lead to episodic hyperpnoea, abnormal eye movements, hypotonia, ataxia, developmental delay,

Table 3 Type I Gaucher disease and parkinsonism

Sex	Age at onset (years)	Genotype	Response to therapy for parkinsonism	Course	Reference
F	45	?/?	Transient	Progressive	McKeran et al[20]
?	?	N370S/500insT	Poor	?	Cormand et al[9, 10]
F	?	?/?	?	?	Tylki-Szymanska et al[27]
3M, 3F	41-55	?/?	Unresponsive	Progressive	Neudorfer et al[21]
M	39	N370S/IVS2+1	Poor	?	Machaczka et al[19]
3 M/F	?	?/?	?	?	Pérez-Calvo et al[23]
M	62	N370S/V394L	Transient	Progressive	Várkonyi et al[28]
M	44	N370S/L444P	Transient	Progressive	Bembi et al[7]
F	43	G377S/G377S	Transient	Progressive	Bembi et al[7]
F	59	N370S/?	Transient	Progressive	Bembi et al[7]
F	55	N370S/?	Good	Progression after 17 years	Bembi et al[7]
M	63	N370S/V394L	Transient	Progressive	Várkonyi et al[29]
F	47	N370S/N370S	Poor	?	Várkonyi et al[29]
M	4th decade	R463C/R120W	No response	Progressive	Várkonyi et al[29]
M	45	N370S/c.1263-1317del	No response	?	Várkonyi et al[29]
F	43	G377S/G377S	Transient	?	Tayebi et al[26]
M	48	N370S/c.84-85 insG	?	?	Tayebi et al[26]
M	62	N370S/N370S	Some	?	Tayebi et al[26]
M	59	N370S/?	Some	?	Tayebi et al[26]
F	50	N370S/?	Minimal	Died at age 62	Tayebi et al[26]
M#	6th decade	N370S/N370S	Poor	Died at age 75	Tayebi et al[26]
F	45	N370S/N370S	Transient	?	Tayebi et al[26]
M	4th decade	N370S/N370S	Poor	Died at age 54	Tayebi et al[26]
3 M/F	?	?/?	?	?	Pastores et al[22]
F	51	?/?	?	?	Goker-Alpan et al[13]
M	62	N370S/N370S	?	?	Goker-Alpan et al[13]
M	63	?/?	No response	Died at age 69	Goker-Alpan et al[13]
M#	6th decade	N370S/N370S	?	Died at age 75	Lwin et al[18]
M	?	N307S/1263del55	?	?	Hamlat et al[15]
18 M/F*	?	?/?	?	?	Eblan et al[11]
M	43	N370S/L444P	Some	?	Spitz et al[25]
M	42	L444P/R463C	Good	Symptoms and signs resolved	Itokawa et al[16]
F	50	N370S/?	Recently started on therapy	Recently diagnosed	Dutch cohort

#Probably the same patient; *Unclear whether or how many patients have been described previously; ?=Unknown or could not be extracted from the paper.

Table 4 Type I Gaucher disease and spinal cord or nerve root compression

Sex	Age at onset (years)	Spinal cord and/or nerve root involvement	Findings	Reference
F	41	Spinal cord compression	Collapse of T12	Raynor[51]
M	58	Spinal cord compression	Collapse of T12 and L3	Markin and Skultety[49]
M	58	Spinal cord compression	Collapse of T6	Goldblatt et al[42]
M	62	Spinal cord compression	Collapse of T11	Hermann et al[44]
?	36	Myelopathy	Thoracic vertebral collapse	Grewal et al[43]
M	64	Spinal cord and nerve root compression, cauda equina syndrome	Collapse of T5, 6 and 12, L2, 4 and 5	Grewal et al[43]
?	60	Myelopathy	Thoracic vertebral collapse	Grewal et al[43]
F	70	Spinal cord compression	Collapse of T7	Neau et al[50]
M	9	Spinal cord and root compression	Collapse of T5, 7 and 12 and L1-5 resulting in a kyphoscoliotic spine	Katz et al[46]
M	16	Spinal cord compression	Collapse of T12	Katz et al[46]
F	31	Spinal cord compression	Collapse of T12	Katz et al[47]
M	40-50	Spinal cord compression	Collapse of T12	Kaloterakis et al[45]
M	18	Spinal cord compression	Collapse and wedging T8-12	Kocher and Hall[48]
M	53	Spinal cord compression	Plasmacytoma and collapse of T10	Dutch cohort
F	72	Spinal cord compression	Collapse of T12	Dutch cohort
F	?	Paraplegia	Extraosseous accumulation of Gaucher cells in the thoracolumbar region	Goldblatt et al[41]
M	73	Sensory deficit corresponding to the T2-3 level	Extraosseous accumulation of Gaucher cells	Hermann et al[44]
?	?	Electrophysiological signs of long sensory spinal tract involvement	-	Mercimek-Mahmutoglu et al[62]
?	33	Conus medullaris syndrome	Haematomyelia	Grewal et al[43]
M	65	Cauda equina syndrome	Intradural sacral cyst due to subdural haemorrhage	Hamlat et al[15]
F	41	Bilateral nerve root compression	Not confirmed by imaging	Bischoff et al[63]
F	68	Low back pain and a bilateral positive Lasègue sign	Osteoporosis of spine and lumbar discopathy	Benjamin et al[67]
F	67	Pain in right leg	Multiple myeloma L5	Miller et al[68]
F	31	Low-back pain radiating to the right lower extremity	Collapse of T12	Hermann et al[44]

Table 4 Continued

Sex	Age at onset (years)	Spinal cord and/or nerve root involvement	Findings	Reference
F	57	Low-back pain radiating to the right leg	Collapse of L2	Butora et al[58]
?	25	Lumbosacral radiculopathy	Lower thoracic vertebral osteomyelitis	Grewal et al[43]
F	12	Nerve root compression	Collapse of T7-L5 resulting in a kyphoscoliotic spine	Katz et al[46]
M	43	Radiculopathy L4-S1	Spinal stenosis L3-4	Spitz et al[25]
F	66	Radiculopathy L5	Lumbar disc herniation L4-5	Dutch cohort
	66	Radiculopathy	Spondylodiscitis	
F	50	Lumbosacral radicular syndrome	Lumbar disc herniation L5-S1	Dutch cohort
	55	Neck pain radiating to right arm	Cervical stenosis and cervical disc bulging	
M	64	Lumbosacral radicular syndrome	Lumbar disc herniation	Dutch cohort
F	59	Low-back pain radiating to both legs	Vertebral collapse L3 and L4 and lumbar stenosis	Dutch cohort

?=Unknown or could not be extracted from the paper

and mental retardation. However, the diagnosis of Joubert syndrome in these cases has been questioned, although no alternative diagnosis was given[56]. In a study with the aim of establishing co-morbidity in type I Gaucher disease patients and carriers, two patients with type I disease and a neurological disorder were reported: one case of stroke and one case of dementia[23]. Two other patients have been described in the literature with Gaucher disease and a cerebrovascular accident; one patient with a not further specified cerebrovascular accident[57] and another patient with intracerebral haemorrhage[58]. Soffer et al[59] reported a patient experiencing disorientation, mild hemiparesis, focal seizures and multifocal myoclonus during an episode of severe illness. In our cohort, 12 patients had sporadic central nervous system involvement.

Peripheral nervous system involvement

(Poly)neuropathy

Poly- and mononeuropathies in type I Gaucher disease have been described incidentally (see Table 5) and comprise mononeuropathies caused by spontaneous or postoperative bleeding[56], a plexopathy due to a fracture of the pelvis[58], mono- and polyneuropathies as a consequence of an associated disease[60, 61] or idiopathic mono- and polyneuropathies[22, 57, 62, 63]. Despite the small number of reports, polyneuropathy is probably more common in type I disease than has

been generally recognized. Various studies have been initiated after reports on the occurrence of peripheral neuropathy in type I Gaucher disease patients during a trial with miglustat. The relationship with the drug is unclear so far, and a prospective cohort study is currently being performed to establish the incidence and prevalence of peripheral nerve disease in patients with type I Gaucher disease who have not been treated with miglustat. Preliminary results of this large multicentre study suggest that polyneuropathy does indeed occur more often in type I disease than would be expected given the estimated prevalence of polyneuropathy in the general population (Hollak et al, unpublished 2006). This is in line with two previously published surveys. One survey of 55 patients with type I Gaucher disease, not using miglustat, revealed that 73% experienced at least one neurological symptom (sciatica, paraesthesias, muscle weakness, muscle cramps and tremor)[22]. Another survey of 107 patients and 104 controls confirmed these findings; patients reported a significantly larger number of symptoms versus controls (4.4 vs 2.4)[64]. In the Dutch cohort we identified four patients with a polyneuropathy and three with a mononeuropathy. The pathogenesis of peripheral nerve involvement is unclear. Bischoff et al[63] described a patient with polyneuropathy in association with type I Gaucher disease. A sural nerve biopsy of this patient revealed accumulation of a lipid-containing substance in Schwann cells and, to a lesser extent, in axons. The authors hypothesized that the peripheral nervous system was involved in the storage process of glucocerebrosides. However, as already stated by Winkelman et al[65], the published findings were not diagnostic for any specific disease and the authors failed to rule out common causes of polyneuropathy.

Frankel et al[66] recently studied 65 treated and untreated Gaucher patients using the Current Perception Threshold (CPT) test, which evaluates Aβ-, Aδ- and C-fibres. Abnormal results were seen in 26/65 patients (40%). Most patients had abnormal results at the median nerve and the most common affected nerve fibres were C-fibres. These findings suggest that small fibre neuropathy is more common in patients with Gaucher disease.

Nerve root compression

Five cases have been reported with nerve root compression due to radiologically confirmed vertebral collapse with or without extraosseous accumulation of Gaucher cells, osteoporosis or spinal stenosis[25, 43, 44, 46, 58, 67] (see Table 4). Other causes of nerve root involvement are rare; only two case reports have been published on patients presenting with a conus medullaris and cauda equina syndrome caused by an intra- or subdural haematoma[15, 43], and two isolated cases with nerve root compression due to multiple myeloma and osteomyelitis[43, 68].

Sporadic peripheral nervous system complications

In rare instances, the concurrence of type I Gaucher disease and peripheral nervous system complications has been reported. Bleeding tendency, which is

Table 5 Gaucher disease type I and neuropathy

Sex	Age at onset (years)	Peripheral nerve disease	Additional information	Reference
F	41	Polyneuropathy	Sural biopsy showed accumulation of glycolipids in Schwann cells and axons	Bischoff et al[63]
M	71	Possibly polyneuropathy	Paraesthesia and weakness of extremities	Chang-Lo et al[57]
F	44	Polyneuropathy	In association with antisulfatide antibodies	McAlarney et al[61]
?	?	Axonal polyneuropathy	Confirmed by nerve conduction studies	Mercimek-Mahmutoglu et al[62]
M	43	Polyneuropathy	Diagnosed during participation in a trial, vitamin B_{12} deficiency	Dutch cohort
M	44	Polyneuropathy	Diagnosed during participation in a trial	Dutch cohort
M	63	Polyneuropathy	Diagnosed during participation in a trial	Dutch cohort
M	70	Polyneuropathy	History of treatment with thalidomide	Dutch cohort
26 M/F	?	Predominantly small fibre neuropathy	-	Frankel et al[66]
4 M/F	?	Carpal tunnel syndrome	-	Pastores et al[22]
M	26	Carpal tunnel syndrome	-	Dutch cohort
F	62	Ulnar neuropathy and carpal tunnel syndrome	-	Dutch cohort
M	53	Ulnar neuropathy and carpal tunnel syndrome	In association with multiple myeloma and amyloidosis	Dutch cohort
F	70	Left ulnaropathy	In association with cryoglobulinaemia	Benjamin et al[60]
F	56	Lumbosacral plexopathy	Due to a fracture of the pelvis	Butora et al[58]
?	36	Femoral neuropathy	Postoperative bleed	Grewal et al[43]
?	23	Femoral neuropathy	Spontaneous retroperitoneal bleed	Grewal et al[43]
?	27	Sciatica	Spontaneous pelvic hematoma	Grewal et al[43]
M	61	Neuralgic amyotrophy of one shoulder	-	Dutch cohort
F	47	Ischaemia of the brachial plexus	Following embolization of an AV-shunt	Dutch cohort

?=Unknown or could not be extracted from the paper

a common feature of type I Gaucher disease, has incidentally led to pain and/or inability to walk due to an iliopsoas muscle haematoma[69-71]. Muscle involvement as a result of infection has been published twice. A patient with Gaucher disease presenting with back pain radiating anteriorly to the left thigh and down to the knee, and at physical examination mild weakness of the iliopsoas muscle, was found to have a paravertebral pneumococcal abscess with displacement of the iliopsoas muscle[72]. Berger et al[73] demonstrated a patient with an isolated Candida infection of the pterygoid muscles. One patient reported by Melamed et al[54] had a history of an episode of right peripheral facial palsy. Eight patients in our cohort had sporadic PNS involvement.

Co-morbidity known to be associated with nervous system diseases

Gaucher disease is associated with an increased incidence of immunoglobulin abnormalities[67, 68, 74-90]. The pathogenesis is unclear, but increased pro-inflammatory cytokines that are known to play a role in the growth and survival of B-cells may be a causative factor[91]. Polyclonal gammopathy is very common, and even monoclonal gammopathies have been described in up to 20% of adult Gaucher type I patients. Accordingly, the incidence of multiple myeloma is greatly increased[77]. Monoclonal gammopathy of undetermined significance (MGUS), especially of the IgM type, is a known cause of polyneuropathy[92]. However, no reports have been published on patients with Gaucher disease, MGUS and concomitant polyneuropathy. Similarly, radiculopathy and spinal cord compression are common neurological complications of multiple myeloma, resulting from compression of a nerve root or the spinal cord by a paravertebral plasmacytoma or by a collapsed vertebral body[92]. We found only one report in the literature of a patient with Gaucher disease, multiple myeloma and radiculopathy[68] and identified one patient in our cohort.

The increased incidence of immunoglobulin abnormalities may explain the cases with both Gaucher disease and primary amyloidosis[45, 93-96]. Primary (AL) amyloidosis is characterized by extracellular deposition of insoluble fibrils composed of low-molecular-weight subunits of monoclonal immunoglobulin light chains. Peripheral neuropathy, especially small fibre neuropathy and compression of the median nerve within the carpal tunnel, is a frequent complication of primary amyloidosis. Both can be the presenting feature of the disease. Symptoms of bowel or bladder dysfunction and findings of orthostatic hypotension may be due to autonomic nervous system damage[97, 98]. The above-mentioned cases with Gaucher disease and amyloidosis did not show concomitant peripheral nervous system disease.

Vitamin deficiencies have sporadically been reported in association with Gaucher disease. A patient has been described with Gaucher disease and coincidental vitamin B_{12} deficiency anaemia[99]. She was a vegetarian, making dietary deficiency a likely explanation. It has been questioned whether vitamin B_{12} deficiency is more prevalent among patients with Gaucher disease. Gielchinsky

et al[100] found that, among a cohort of 89 untreated type I patients, 40% had low serum levels of vitamin B_{12}, but they did not find a significantly different prevalence in neighbourhood control subjects (31%) and in healthy blood donors of different ethnicities (12-38%). Delpre et al[101] suggested that repeated blood donations might result in vitamin B_{12} deficiency, making blood donors unsuitable as control group. Vitamin B_{12} deficiency is a known cause of a subacute combined degeneration of the spinal cord and concomitant polyneuropathy[102]. However, no case reports have been published describing the concurrence of Gaucher disease, vitamin B_{12} deficiency and nervous system disease.

Decreased plasma vitamin E levels were thought to be associated with Gaucher disease. Rachmilewitz et al[103] found low levels in 17 out of 20 patients with Gaucher disease. These patients did not show clinical symptoms or signs that could result from vitamin E deficiency[104].

Another concomitant condition was mentioned in the epidemiological survey of 55 patients with type I Gaucher disease; 5 (9%) had diabetes mellitus[22], a disease that is highly associated with central and peripheral nervous system diseases. No other reports on patients with Gaucher disease and diabetes mellitus have been published.

DISCUSSION

Although type I Gaucher disease is known as non-neuronopathic Gaucher disease, this cohort study and review of the literature revealed that central and peripheral nervous system involvement is not uncommon. In our cohort 36% of patients had at least one confirmed neurological disease. It is hard to estimate whether the prevalence and incidence of the different neurological diseases are different in Gaucher type I patients compared with the general population. Reliable prevalence and incidence data of diseases are hard to find and often not applicable to the population under study. Data may vary between countries owing to different registration systems or 'real' differences in prevalence and incidence. Furthermore, the study group consists of only 75 patients with sometimes only one or two affected patients, making 95% confidence intervals wide. Keeping these pitfalls in mind, estimates of the prevalence of some of the neurological diseases in the general population are as follows: epilepsy 0.9%[105]; Parkinson disease 0.2% at age 55-64 years to 4.8% at age 85 years and over[106]; dementia 0.4% at age 55-59 years to 43% at age 95 years and over[107]; polyneuropathy 0.1-3.6%[108, 109]; carpal tunnel syndrome 2.7%[110]; and lumbar disc herniation 0.2-0.4% (Continuous Morbidity Registration Nijmegen). In the general population, the lifetime prevalence of migraine in women is 33% and in men 13.3%[111]. Between 25% and 60% of hospitalized persons experience an acute confusional state (delirium)[112], the annual incidence rate of Bells' palsy is between 13 and 34 cases per 100 000 population[113]. The prevalence of most of these neurological diseases seems

to be higher in Gaucher type I patients compared with the general population, but owing to the above mentioned pitfalls it would be reckless to draw any firm conclusions about the relative risks for the specific problems in patients with type I Gaucher disease.

The notion of frequent CNS and PNS 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. However, although neurological involvement is quite often encountered in type I disease, a clear distinction between type I and the other two types still can be made on clinical as well as neuropathological grounds. The presence of supranuclear gaze palsy, cognitive decline, epilepsy, myoclonus and/or ataxia should, in our opinion, lead to a diagnosis of type II or type III Gaucher disease. We think that a diagnosis of late-onset type III disease should be made even when these symptoms occur in the second, third or even fourth decade (see Table 2). The distinction between types I and III is also supported by the type of pathological changes in the brain. Changes involving specific regions of the brains were common in all three Gaucher disease types; patients classified as having type I disease have only astrogliosis, whereas neuronal loss predominated in both type II and type III disease patients[114]. Moreover, the distinction between type I and the two other types is of importance since it predicts prognosis and enables genetic counselling. One may speculate on the existence of a continuum of type II and III disease as the difference between types II and III mainly depends on the age of onset and rate of progression, and the pathological findings in the brains of type II and III patients indicate quantitative rather than qualitative differences.

It could be debated whether parkinsonism, the most prevalent central nervous system manifestation in type I Gaucher disease subjects, should lead to a reclassification into type III disease. There are several reasons why this should be rejected: (i) the lack of other neurological manifestations typical of type III disease; (ii) brain pathology revealed astrogliosis without neuronal loss[114], and (iii) the fact that elevations in brain glucosylsphingosine, a neurotoxic glycolipid, have not been found in patients with type I disease and parkinsonism[26], whereas an elevated level was found in all type II and III patients[115].

A difficulty in classification may also exist when a patient with type I Gaucher disease and parkinsonism develops abnormal horizontal saccadic eye movements[29, 39]. Oculomotor signs, especially difficulty or inability to generate saccades, are characteristic of type III Gaucher disease. Their presence is considered to be diagnostic of neuronopathic disease, and they may precede the emergence of overt neurological signs by many years. However, abnormalities in saccadic eye movements are also associated with parkinsonism, although they usually develop when the disease progresses. Unfortunately, it is often unclear whether the oculomotor signs preceded or developed in the course of parkinsonism. These patients should, in our opinion, be classified as type I disease in the presence of

other symptoms that point in the direction of a diagnosis of parkinsonism and without other symptoms or signs indicating type III disease.

In conclusion, the division into the three types should be maintained. The term non-neuronopathic Gaucher disease, however, does not seem to be an appropriate description for type I Gaucher disease, given the many neurological symptoms and diseases in the Dutch cohort and the many reports on central and peripheral neurological involvement in literature. As the neurological changes in type I Gaucher disease are of a totally different kind and, in the majority of cases, of much less severity in comparison with the changes associated with type II and III disease, the presence of neurological changes in type I disease should not lead to the concept of a continuum of symptoms and signs in the three types of Gaucher disease.

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