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Exploring the patient journey to diagnosis of Gaucher disease from the perspective of 212 patients with Gaucher disease and 16 Gaucher expert physicians

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ABSTRACT

Gaucher disease (GD) is a rare hereditary disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase. Diagnosis is challenging owing to a wide variability in clinical manifestations and severity of symptoms. Many patients may experience marked delays in obtaining a definitive diagnosis. The two surveys reported herein aimed to explore the patient journey to diagnosis of GD from the perspectives of Gaucher expert physicians and patients. Findings from the surveys revealed that many patients experienced diagnostic delays and misdiagnoses, with nearly 1 in 6 patients stating that they were not diagnosed with GD for 7 years or more after first consulting a doctor. Physicians and patients both reported multiple referrals to different specialties before a diagnosis of GD was obtained, with primary care, haematology/haematology-oncology and paediatrics the main specialties to which patients first presented. Splenomegaly, thrombocytopenia, anaemia and bone pain were reported as the most common medical problems at first presentation in both surveys. These findings support a clear need for straightforward and easy-to-follow guidance designed to assist non-specialists to identify earlier patients who are at risk of GD.

Abbreviations: GD, Gaucher disease; GED-C, Gaucher Earlier Diagnosis Consensus; ICGG, International Collaborative Gaucher Group; MN, multiples of normal

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1. Introduction

Gaucher disease (GD) is a chronic condition caused by a recessively inherited deficiency of the *GBA1* gene, which encodes the lysosomal enzyme β-glucocerebrosidase (glucosylceramidase; EC 3.2.1.45) [1]. The disease is characterised by the accumulation of storage materials, predominantly glucosylceramide, in the lysosomes of cells of the monocyte–macrophage system, leading to multi-systemic disease manifestations including splenomegaly, hepatomegaly, thrombocytopenia, anaemia and bone disease [1]. It can be categorised into three types based primarily on phenotypic differences; however, a considerable overlap of clinical features between types has led to GD being regarded as a phenotypic continuum [2], with GD types used mainly to aid management decisions. The most common form seen in Europe and North America is type 1 GD, which accounts for ~95% of all cases [3,4] and is conventionally characterised by an absence of early onset primary central nervous system disease. Types 2 and 3 GD are neuronopathic forms of the disease in which the central nervous system is also affected [1]. Type 2 (acute neuronopathic) GD, the rarest form, affecting < 1% of all GD patients, is characterised by rapid deterioration, with death usually occurring before 2 years of age, while patients with type 3 (chronic neuronopathic) GD (~5% of all GD patients) experience a slower disease course [5].

GD is typically diagnosed via enzyme assay to detect β-glucocerebrosidase, but patients may be diagnosed by genotype testing to identify GD-associated *GBA1* mutations [1]. A timely and definitive diagnosis minimises the impact of misdiagnoses and unnecessary and invasive diagnostic procedures, and can aid the optimal management of symptomatic patients [6–9]. Since enzyme replacement therapies and substrate reduction therapies have been introduced, they have shown to be effective at preventing and reducing the systemic manifestations and some complications of type 1 GD, including hepatomegaly, splenomegaly, cytopenia, growth delay and some bone disease [6,10–15]. Conversely, delay in diagnosis and access to appropriate management can potentially increase the risk of irreversible complications, such as avascular necrosis, in certain symptomatic patients. No treatment is specifically approved for the management of the neurological manifestations of GD.

Diagnosis of GD presents a significant challenge to the non-GD specialist owing to the wide variability in age, severity and type of clinical manifestations at time of presentation. This is compounded by a lack of familiarity among physicians with the early clinical features of the disease because of its low prevalence [6,16]. The earliest presenting clinical features of GD are often general and non-specific, such as nosebleeds, fatigue and pain. Further, while the evaluation of biomarkers, e.g. chitotriosidase activity or chemokine (C-C motif) ligand 18 (CCL18), have been shown to have potential in initial screening for GD [17], they are not routinely tested or available in many local laboratories. Disease-specific early presenting features tend to reflect the haematological aspect of the disease; therefore, many patients are initially referred to haematologists. Nevertheless, in a survey of 406 haematologist/oncologists from the US, Argentina, Brazil, Canada, Japan, Spain and Australia, only 20% considered type 1 GD in their differential diagnosis of patients presenting with the classic clinical features of GD: anaemia, thrombocytopenia, hepatosplenomegaly and bone pain; physicians were more likely to consider leukaemia, lymphoma or multiple myeloma instead [6].

The aim of this article is to examine the patient journey in relation to the diagnosis of GD from two perspectives: 1) from patients on their journey towards a diagnosis of GD; and 2) from expert physicians involved in the diagnosis and management of patients with GD.

2. Methods

2.1. GD expert physician survey

The objective of the GD expert physician survey was to examine the pre-diagnosis period of patients with GD from the perspective of international medical experts involved in their care. Sixteen international GD experts from 12 countries who had expressed interest in screening for Gaucher disease, through authorship of published literature or involvement in planned or ongoing disease screening studies (irrespective of funding source), were invited to participate in the survey. Experts were from multiple specialties, including: haematology (4), paediatrics (4), genetics (4), metabolism (3), paediatric genetics (1), bone (1), internal medicine (1), radiology (1) and rheumatology (1) (participants could have more than one specialty).

The survey was conducted from 25 February to 22 March 2015, and comprised nine questions: five regarding the characteristics of the patient population, which requested demographic information; three questions regarding patients' presenting symptoms and patient referrals, which provided a list of pre-specified options from which to choose (with the option to specify "other"); and one question on diagnostic delays, which invited a free-text response (Appendix A). The survey was hosted by SurveyMonkey® (California, US) and was accessible via an online link.

In response to survey questions, experts provided summary data for all GD patients under their care, irrespective of their present treatment status or type of treatment received; no individual patient data were provided. Survey responses were consolidated for comparison between centres. Responses to questions regarding demographics, referrals and presenting clinical features were pooled for further analysis of the larger population.

2.2. GD patient survey (US)

The objective of the survey of patients from this US-based patient support programme (OnePath®) was to examine the pre-diagnosis period of patients subsequently diagnosed with type 1 GD and to better understand the earliest presenting features and the patient journey. The patient support system, funded by Shire Human Genetic Therapies Ltd., provides support to patients with rare diseases, their families and healthcare providers in the US, and is approved by the US Food and Drug Administration [18]. All patients enrolled in this support system provided consent to receive GD-specific information. Patients with type 1 GD were invited by e-mail to participate anonymously in an online survey. At the time of invitation, patients were informed that their anonymised responses could be included in publication(s) intended to help identify issues in the diagnosis of GD. Participation was voluntary and did not influence the services that patients received.

The survey was conducted between 3 and 23 March 2015 using the CustomerSat™ internet portal (Confirmit, Oslo, Norway) and comprised 13 questions: 12 relating to the pre-diagnosis period (including one inviting a free-text response) and one relating to current care (Appendix B). The survey questions were initially designed by the Shire medical team, with review and input from external GD experts. Anonymised responses were pooled and tabulated using frequency distribution.

3. Results

3.1. GD expert physician survey

Sixteen medical experts from 14 GD specialist centres across 12 countries participated (Table 1). At the time of the survey, these medical experts were responsible for managing a total of 1595 patients with GD, of whom 94% had type 1 GD. Of 1540 patients for whom data were available, 88% were ≥ 18 years of age at the time the survey took place, and 55% were of Ashkenazi Jewish ancestry, mainly from sites in

Table 1
Countries and cities of participating GD centres in the physician survey.

Country	City	Patients with GD (N = 1595)			
		Total, n	GD type, %		
			1	2	3
Australia	Melbourne	26	100	0	0
Brazil	Porto Alegre	41	90.3	2.4	7.3
France	Marseille	15	100	0	0
	Paris	80	80	5	15
Germany	Mainz	130	78	2	20
Ireland	Dublin	6	83	17	0
Israel	Jerusalem	648	98.6	0	1.4
Italy	Udine	62	90.3	ND	ND
Japan	Kumamoto	5	20	80	0
Russia	Moscow	260	99	0	1
Spain	Barcelona	15	93.3	0	6.7
UK	Cambridge	149	97.3	0	2.7
	London	103	90.3	0	9.7
US	Washington, DC	55	80	5	15

GD, Gaucher disease; ND, no data.

Israel (Jerusalem, 93%), the US (Washington, DC, 60%), France (Paris, 55%) and the UK (London, 45%).

The results confirmed findings from the literature that many different medical specialties are involved in the pre-diagnosis period of their patients with GD. Haematology/haematology-oncology, paediatrics and primary care were the most cited specialties to which patients first presented with GD-related clinical features (Fig. 1A). The same specialties also were cited as being involved in a large proportion of patient referrals to their expert centres, with approximately 31% of 798 patients (12 responses) referred from haematologists/haematologist-oncologists, 21% from paediatricians and 9% from primary care physicians.

Splenomegaly was reported as one of the main presenting features by 11 centres, occurring in 59% of 668 patients, while thrombocytopenia was reported as a main feature by 10 centres but occurred in greater numbers of patients overall (66% of patients). Anaemia was a main feature in 39% of patients from 10 centres, hepatomegaly in 57% of patients from nine centres and bone or joint pain in 49% of patients from nine centres (Fig. 1B).

Experts were asked about the causes of diagnostic delays frequently experienced by patients. The main causes of diagnostic delays in patients referred to their centres were cited as lack of awareness of GD/misdiagnosis (7 [54%] of experts), followed by phenotypic heterogeneity/non-specific symptoms (3 [23%]), mild symptomology (2 [15%]) and outsourced testing (1 [8%]) (Fig. 1C). No specific data were collected on the time to diagnosis.

3.2. GD patient survey (US)

Survey responses were provided by 212 of 583 (36%) invited patients (or patients' parents), all of whom were located in the US, with a median (range) age of 50 (5–92) years. Of these, 109 (19%) patients provided free-text responses on their journey to diagnosis.

Abdominal distension was the most common health problem to be cited as the first clinical feature of type 1 GD that patients recalled experiencing (20%), followed by moderate/severe bleeding (14%) and bone or joint pain (13%) (Fig. 2). Of the 158 patients who indicated the specialty from which they first sought help for their symptoms, the majority cited paediatricians (42 [27%] patients), haematologists/haematologist-oncologists (41 [26%] patients) or primary care physicians (38 [24%] patients) (Fig. 3A). Thirty-five of the 38 patients who initially presented to primary care were referred to another specialty, 24 (63%) of whom were referred to haematologists/haematologist-oncologists (Fig. 3B). Seventy of 116 (60%) respondents reported that they were eventually diagnosed by physicians within this specialty (Fig. 3C). The majority of patients reported that they were diagnosed with GD either as children (0–9 years, 78 of 212 [37%] responses) or young adults (19–39 years, 61 of 212 [28%]) (Fig. 4). Most patients (112/154 [73%]) were diagnosed within 1 year of first seeing a doctor, but for others (22/154 [14%]), diagnosis took 7 years or more.

In the free-text responses provided by 109 patients, eight patients commented that their diagnosis was largely serendipitous, e.g. from a routine heath check or on the basis of clinical suspicion from their physician, while 11 patients reported that diagnosis was the result of the previous diagnosis of an older sibling or, in one case, due to both parents being known carriers. Eight patients commented on the impact of undiagnosed disease on their lives during the period leading up to diagnosis, including reduced quality of life owing to bone pain and chronic fatigue, emotional distress due to initial suspicions of cancer, and depression and suicidal thoughts as a result of having no explanation for their symptoms. Twenty-five (23%) described experiences of physicians lacking awareness of GD, with one patient commenting that general practitioners in particular should be more educated about rare diseases. Fourteen (13%) patients mentioned receiving previous misdiagnoses, six of whom reported a previous misdiagnosis or strong suspicion of cancer (leukaemia, multiple myeloma or liver cancer). Other misdiagnoses noted were Legg-Calvé-Perthes disease, Boeck's sarcoid or sarcoidosis, von Willebrand disease, folic acid and B12 deficiency, allergies and growing pains. One patient reported "several other illnesses" while another did not specify the misdiagnosed condition.

4. Discussion

The diagnosis of GD can be particularly challenging to the non-GD specialist, owing to the variability in the type and severity of presenting clinical features and patient age at presentation, combined with a lack of familiarity because of its low prevalence [6,16]. As a result, GD may not always be considered by non-specialists in their differential diagnosis. Here we review results from surveys of patients and GD expert physicians in an attempt to understand better the Gaucher patient journey in the period prior to obtaining a correct diagnosis.

Findings from both the patient and physician surveys reveal that many patients presenting with clinical features of GD experience diagnostic delays and misdiagnoses, while several patients reported multiple referrals to different specialties before obtaining a diagnosis of GD. This is in agreement with a global survey of patients and haematologist-oncologists, in which patients consulted up to eight physicians (mean of three) before receiving a diagnosis [6]. Nearly 1 in 6 patients participating in the US patient survey stated that they did not receive a diagnosis of GD for 7 years or more after first consulting a doctor, in line with previous reports in which the time from first onset of clinical features to diagnosis ranged from 0.5 to 26 years [6,12,19].

The demographic characteristics of US patients participating in the patient survey were similar to those previously reported from the International Collaborative Gaucher Group (ICGG) registry. In the US patient survey, 45% were diagnosed by the age of 18 years, compared with 56% patients (with disease onset or diagnosis by the age of 20 years) in the ICGG registry [20]. The main presenting clinical features in patients from the ICGG registry were splenomegaly (55% with spleen volume 5–15 multiples of normal [MN]), hepatomegaly (53% with liver volume 1.25–2.5 MN), moderate thrombocytopenia (50–70% with platelet count $\leq 60–120 \times 10^9$/L) and anaemia (20–30% patients), consistent with findings from both the physician and patient surveys. Bone pain was experienced by 38% patients and bone crisis by 12% patients in the ICGG registry at the time of diagnosis [20], compared with 13% of patients in the patient survey recalling bone symptoms at time of presentation.

Although the consistency of these survey findings with previously published registry data are reassuring, data from surveys are inherently limited because of the voluntary nature of participation, leading to possible bias in the selection of participants as well as the potential for missing, incomplete or inaccurate responses. This is particularly pertinent for those questions relying on patient memory. The US patient

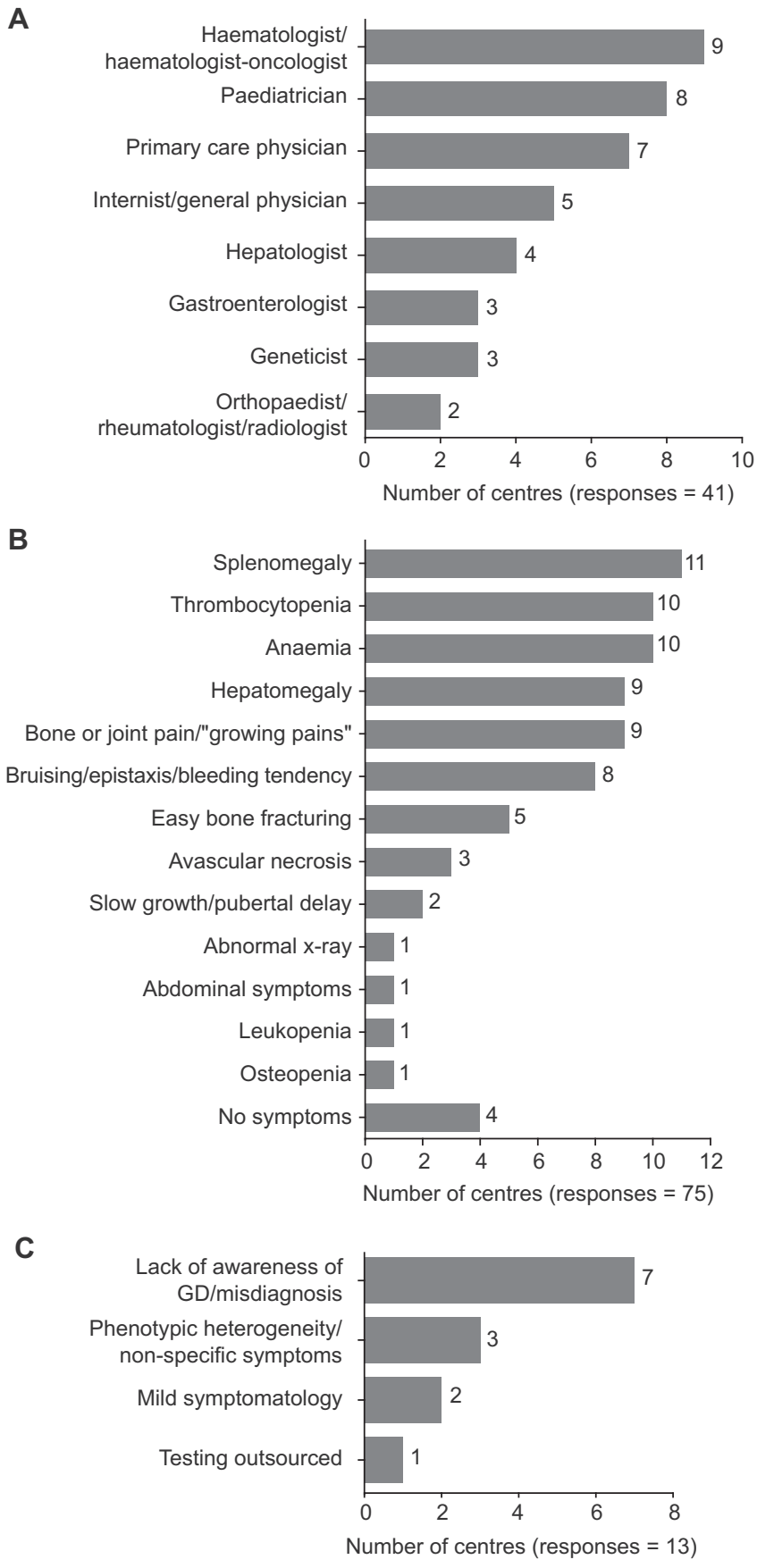

Fig. 1. Results of the physician survey. Respondents could select > 1 answer. A) Specialties to which patients of Gaucher disease experts first presented with Gaucher disease-related symptoms (41 responses from 10 centres, 663 patients). B) Main presenting features at diagnosis of patients presenting to Gaucher disease experts (75 responses from 11 centres, 668 patients). C) Main causes of diagnostic delay in patients presenting to Gaucher disease experts (13 responses from 11 centres, 736 patients). GD, Gaucher disease.

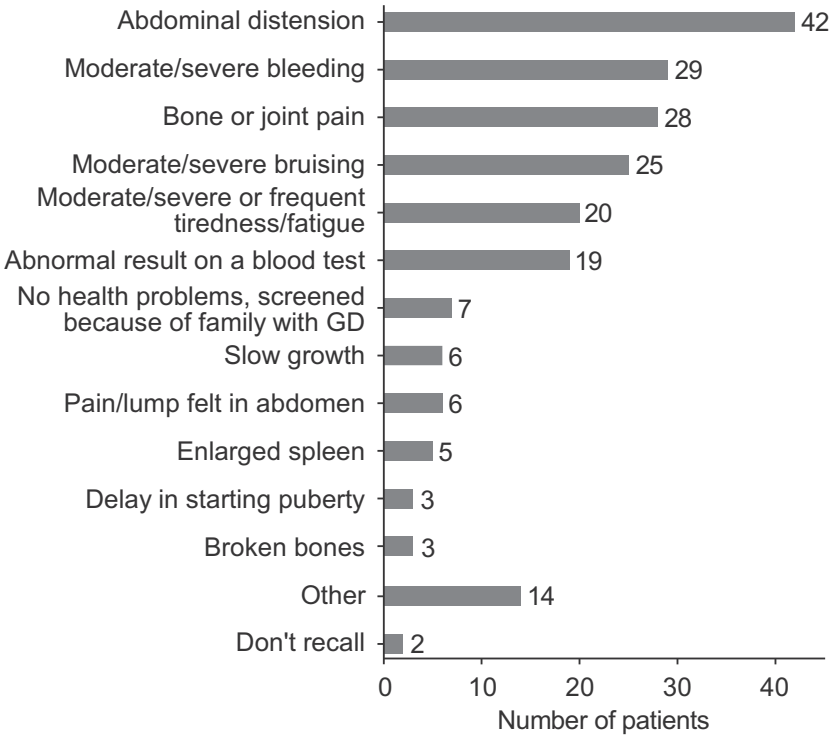

Fig. 2. Earliest health problem experienced by patients taking part in the US patient survey (N = 209). GD, Gaucher disease.

survey recruited patients from the OnePath patient support system, which is funded by Shire and designed to support patients receiving Shire's approved rare disease products. Therefore, data cannot be extrapolated to the general disease population.

Nonetheless, these findings support a clear need for straightforward and easy-to-follow guidance designed to assist non-specialists in diagnosing symptomatic patients earlier in the course of their disease. A proportion of patients diagnosed with GD remain asymptomatic [21]. However, for symptomatic patients a timely and definitive diagnosis of GD can enable access to appropriate management, thereby potentially reducing the risk of unnecessary invasive diagnostic investigations, misdiagnosis and the development of irreversible complications. Obtaining a diagnosis in asymptomatic or pre-symptomatic patients through screening is questionable owing to the unlikelihood that an early diagnosis will impact their management or disease course. Although the inclusion of GD in newborn screening panels has been considered in several countries [22–25], the high cost and potential psychological/emotional impact on patients diagnosed with adult-onset or mild disease [26] means that newborn screening for GD remains unlikely to be widely adopted.

A number of consensus diagnostic algorithms have been developed to aid non-specialists in the diagnosis of GD in symptomatic patients. In 2011, Mistry et al. proposed a straightforward diagnostic algorithm for patients presenting with splenomegaly and/or thrombocytopenia, with variations for patients with or without Ashkenazi Jewish heritage [7]. In 2014, Di Rocco et al. proposed an algorithm targeted at haematologists for the diagnosis of GD in paediatric patients, based on published studies and data from the ICGG registry [27]. More recently, in 2016, Elmonem et al. reported on the application of a diagnostic algorithm to children who were suspected of having a lysosomal storage disorder [19]. However, while these algorithms offer invaluable guidance to non-specialists for the differential diagnosis of patients already suspected of having a lysosomal storage disorder, there is no guidance for he identification of these at-risk individuals.

Motta et al. [16] investigated the impact of applying a previously published diagnostic algorithm [7] in combination with the dried blood-spot enzyme test [28] to identify type 1 GD among adults presenting with unexplained splenomegaly and/or thrombocytopenia, the most common presentation of the disease [6,27], in Italian haematology units. Considering only these two parameters, 34 of 196 (17%) patients included in screening had a positive dried blood-spot result and 7 (4%) were confirmed to have type 1 GD, indicating that this approach can result in the successful identification of patients with GD by non-specialists.

In an attempt to expand on these findings, the first phase of the Gaucher Earlier Diagnosis Consensus (GED-C) initiative [29–31] aimed to identify the presenting signs and patient co-variables that are most indicative of types 1 and 3 GD during the early stages of disease. GED-C is an ongoing international project that applies Delphi methodology, a widely accepted technique for gathering and processing data from expert groups [32], to achieve consensus on aspects relating to the diagnosis and management of GD [29–31]. Similar methodology has been used previously to develop a disease severity scoring system for type 1 GD with the aim of standardising disease monitoring [33]. The GED-C panel consists of 22 GD experts recognised globally as leading GD experts, and a non-clinical chair with expertise in the Delphi technique. Using this technique, the panel reached consensus on the identification of clinical signs and co-variables indicative of types 1 and 3 GD during the early stages of disease, and their classification as major or minor using 5-point Likert scales of importance (Table 2). The signs and co-variables identified by this study are consistent

Table 2
Consensus on major signs and co-variables in types 1 and 3 GD (GED-C initiative) [29–31].

	Type 1 GD	Type 3 GD
Major signs	Splenomegaly, thrombocytopenia, anaemia, hepatomegaly, bone issues (pain, crises, avascular necrosis and fractures), hyperferritinaemia and gammopathy	Splenomegaly, thrombocytopenia, anaemia, hepatomegaly, oculomotor disturbances, myoclonic epilepsy, bone pain, motor disturbances and kyphosis
Major co-variables	Family history of GD, Ashkenazi Jewish ancestry	Family history of GD

GD, Gaucher disease; GED-C, Gaucher Earlier Diagnosis Consensus.

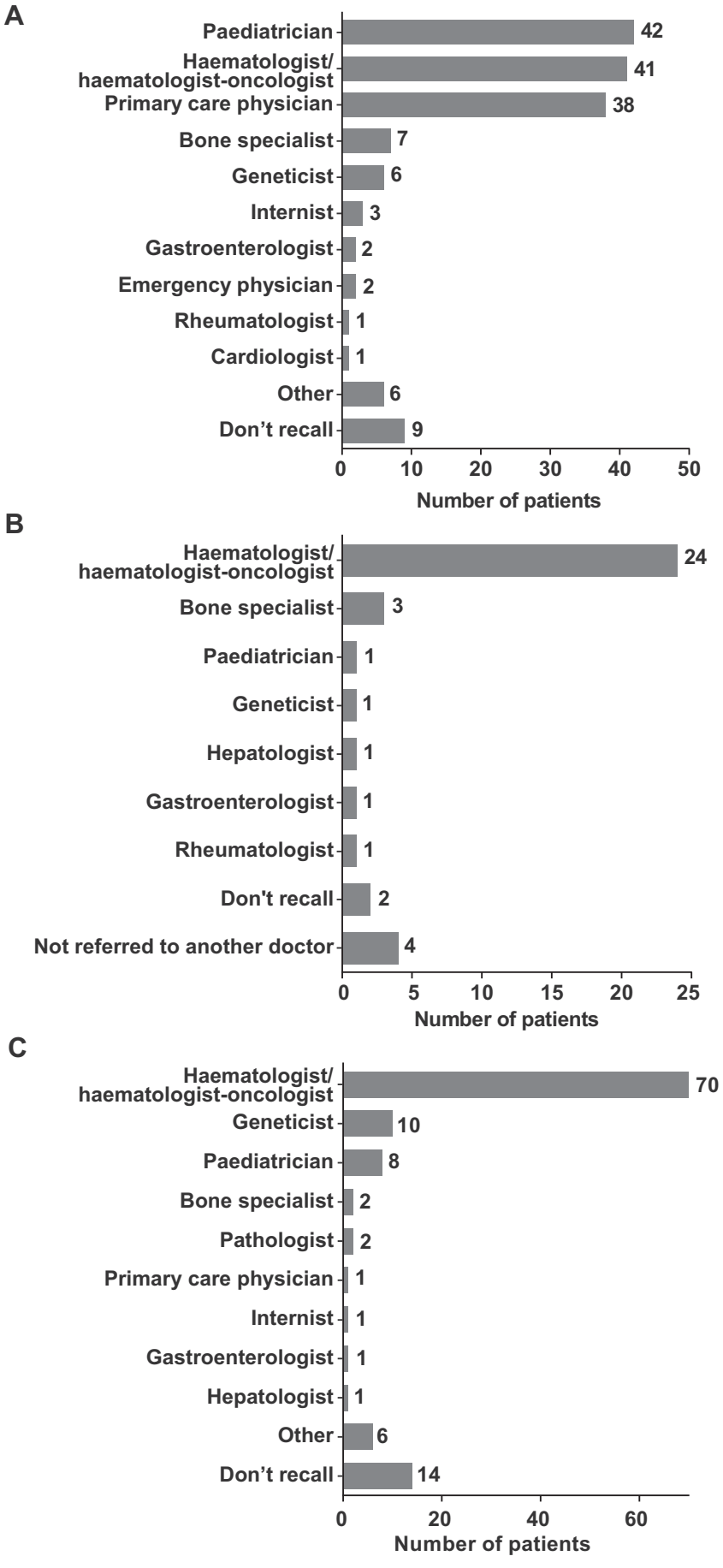

Fig. 3. Specialties involved in the diagnosis of patients with Gaucher disease taking part in the US patient survey. (A) Specialty first seen regarding health problems (N = 158). (B) Specialty to which patients who first saw a primary care physician were first referred (N = 38). (C) Specialty that made the final diagnosis of Gaucher disease (N = 116).

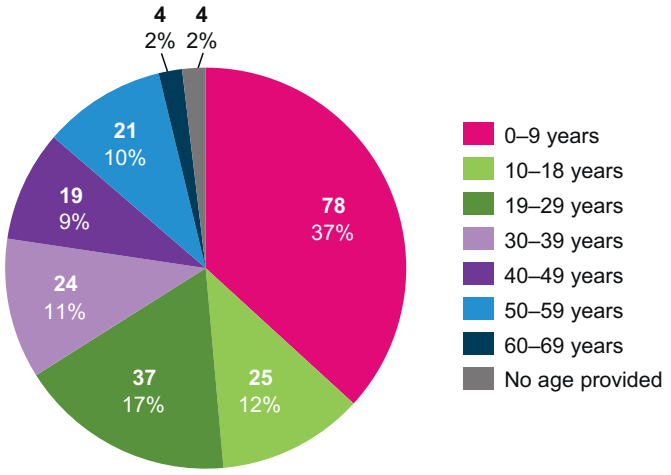

Fig. 4. Age at which patients taking part in the US patient survey were diagnosed with Gaucher disease (N = 212).

with results from the patient and physician surveys reported in the present article, and will inform the second phase of the GED-C, the development of an online assessment algorithm to help non-specialists identify patients at risk of GD.

In conclusion, this publication presents findings from GD expert physicians and GD patients that highlight an ongoing need for improvement in disease awareness among non-specialists. Data from both surveys are consistent in demonstrating the occurrence of diagnostic delays owing to misdiagnoses and the involvement of multiple specialties in making a diagnosis. A lack of awareness of the early signs and symptoms of GD among non-specialist physicians may contribute to misdiagnoses, delayed diagnoses and unnecessary diagnostic procedures, as well as potentially resulting in the development of irreversible complications. These findings highlight a continuing need for practical and robust guidance on the differential diagnosis of GD to support non-specialists in reaching a timely and definitive diagnosis. Work by groups such as GED-C may help address this unmet need.

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Competing interests

A.M. has a direct financial interest in a company whose area of interest is covered by the article; is a member of the advisory board or similar committee for Genzyme and Shire; has received consulting fees or other remuneration including fees as a speaker from Shire; is currently and has recently participated in clinical trials sponsored by Amicus, Genzyme and Shire; and has received research support from Amicus, Genzyme and Shire.

N.B. has received consulting fees or other remuneration including fees as a speaker from Sanofi/Genzyme and Shire and has received grants from Sanofi/Genzyme and Shire given to Beaujon University Hospital.

B.B. has received consulting fees or other remuneration including fees as a speaker from Actelion, Genzyme and Shire; is currently and has recently participated in clinical trials sponsored by Actelion, Genzyme and Shire; and has received research support from Actelion, Genzyme and Shire.

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D.E. is an employee of Shire.

O.G.A. has a direct financial interest in a company whose area of interest is covered by the article; is a member of the advisory board or similar committee for Genzyme, Protalix and Shire; is assisting in the design of and/or participating in clinical studies using products manufactured by Genzyme, Protalix and Shire; has received consulting fees or other remuneration including fees as a speaker from Actelion, Genzyme, Pfizer and Shire; is currently and has recently participated in clinical trials sponsored by Alexion, Amicus, Genzyme, Protalix and Shire; and has received research support from Genzyme, Pfizer and Shire.

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I.S. has a direct financial interest in a company whose area of interest is covered by the article; is a member of the advisory board or similar committee for Shire; has received consulting fees or other remuneration including fees as a speaker from Shire; and has received research support from Shire.

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Appendix A. Supplementary data

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