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Original Research

Patients' perspective on the medical pathway from first symptoms to diagnosis in genetic lipodystrophy

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Abstract

Objective: Underdiagnosis is an important issue in genetic lipodystrophies, which are rare diseases with metabolic, cardiovascular, gynecological, and psychological complications. We aimed to characterize the diagnostic pathway in these diseases from the patients' perspective.

Design: Cross-sectional study conducted through a self-reported patient questionnaire.

Methods: Patients with genetic lipodystrophy were recruited throughout the French national reference network for rare diseases of insulin secretion and insulin sensitivity. Patients completed a self-reported questionnaire on disease symptoms, steps leading to the diagnosis, and healthcare professionals involved. Descriptive analyses were conducted.

Results: Out of 175 eligible patients, 109 patients (84% women) were included; 93 had partial familial lipodystrophy and 16 congenital generalized lipodystrophy. Metabolic comorbidities (diabetes 68%, hypertriglyceridemia 66%, hepatic steatosis 57%), cardiovascular (hypertension 54%), and gynecologic complications (irregular menstruation 60%) were frequently reported. Median age at diagnosis was 30

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years (interquartile range [IQR] 23-47). The overall diagnostic process was perceived as "very difficult" for many patients. It extended over 12 years (IQR 5-25) with more than five different physicians consulted by 36% of respondents, before diagnosis, for lipodystrophy-related symptoms. The endocrinologist made the diagnosis for 77% of the patients. Changes in morphotype were reported as the first symptoms by the majority of respondents.

Conclusions: Diagnostic pathway in patients with genetic lipodystrophy is rendered difficult by the multisystemic features of the disease and the lack of knowledge of non-specialized physicians. Training physicians to systematically include adipose tissue examination in routine clinical evaluation should improve diagnosis and management of lipodystrophy and lipodystrophy-associated comorbidities.

Keywords: diagnostic pathway, lipodystrophy syndrome, rare disease, self-report

Significance

Genetic lipodystrophies are largely underdiagnosed rare diseases with potentially severe cardio-metabolic complications. We evaluated, through a patient self-reported questionnaire, the pathway from the first symptoms to the final diagnosis of the disease, in 109 patients recruited through the dedicated French national reference center for rare diseases (PRISIS). Metabolic, cardiovascular, and/or gynecological complications were reported by 54% to 68% of patients. The median age at diagnosis was 30 years (IQR 23-47), 12 years (IQR 5-25) after the first symptoms (morphotype changes for most patients). The endocrinologist was the healthcare professional most frequently involved in making the correct diagnosis (77%). For non-specialized physicians, increasing awareness on clinical signs of lipodystrophy is central to promote an earlier diagnosis and management of the disease.

Introduction

Lipodystrophy syndromes are rare multisystemic diseases characterized by a marked loss or absence of adipose tissue. Limited fat storage capacity, resulting in ectopic fat accumulation in non-adipose organs such as muscle or liver, predisposes toward developing insulin resistance and risk of metabolic complications such as diabetes mellitus, hypertriglyceridemia, non-alcoholic fatty liver disease (NAFLD), hypertension, atherosclerotic events and polycystic ovarian syndrome in women.[1]

Lipodystrophy syndromes can be primary or acquired in origin, and present in a wide range of clinical forms.[2-5]

Genetic lipodystrophy syndromes are usually classified based on fat loss distribution from partial forms of lipodystrophy (familial partial lipodystrophy [FPLD]) to generalized lipodystrophy (congenital generalized lipodystrophy [CGL]).[6] Subcutaneous fat loss, and/or abnormal fat distribution are key diagnostic features of lipodystrophy disorders. In the most common monogenic form of FPLD, due to *LMNA* pathogenic variants (FPLD2 or Dunnigan syndrome), lipoatrophy of the limbs contrasts with accumulation of facio-cervical adipose tissue (round face, double chin, supraclavicular adiposity, posterior neck "buffalo hump"), giving patients a cushingoid appearance and android morphotype. Small subcutaneous lipomas, or upper body pseudolipomatous masses are also reported. In CGL, atrophy of Bichat's fat pads with cachectic appearance and exacerbation of facial bone structures are frequently described.[6,7]

In CGL, which are mostly autosomal recessive diseases, generalized lipoatrophy, present at birth, can be associated with metabolic complications (insulin resistance, hypertriglyceridemia, hepatic steatosis with hepatomegaly) which usually gets worse during the pubertal or post-pubertal period.[6,7]

In FPLD, which are mostly autosomal dominant diseases, lipodystrophy and metabolic complications usually occur progressively around puberty. For physicians unaware of these rare diseases, confusion with "common" metabolic syndrome is possible.

Whereas previous studies have estimated the prevalence of inherited lipodystrophies from 1.0[1] to 4.7[8] per million in the general population, it was recently re-evaluated at no less than 1 in 20 000 individuals,[9] suggesting that diagnosis of lipodystrophy syndromes may be largely underestimated.

A timely diagnosis of lipodystrophy is essential to prevent or treat metabolic and/or organ complications, that severely impact morbidity and mortality associated with the disease.[10,11] In addition, the quality of life may be severely impaired in patients with lipodystrophy, with mood illness, chronic pain, and severely altered self-perception of body image, also probably underestimated.[11-13] Patients diagnosed with lipodystrophy can benefit, in specific situations, from orphan drug therapies such as metreleptin, which can lead to improvement in metabolic disorders, quality of life and survival.[14-17]

According to a qualitative study based on interviews of patients with lipodystrophy, the diagnosis is usually made several years after disease-onset.[13] Nevertheless, no data are available on the real-life diagnostic pathway (duration, physicians involved) in patients with lipodystrophy.

Given the significant burden of underdiagnosed or undertreated lipodystrophy syndromes, this work was designed to describe, from patients' perspective, the route of diagnosis in genetic lipodystrophy, from symptom onset to the time of diagnosis.

Patients and methods

Study design and population

We conducted a cross-sectional study using a self-completed patient questionnaire. Participants were recruited between September 2021 and March 2022 throughout the French National Reference Network for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS), which aims, among others, to improve the diagnosis of lipodystrophy and the management of affected patients. The center coordinates a network of 21 local centers, named as competence centers, throughout the country. This network is represented in French overseas territories, such as La Reunion island, where the prevalence of genetic lipodystrophy is particularly high due to a *LMNA* founder variant[18-20] and is also open to patients coming from neighboring countries such as Belgium. PRISIS is part of the French national Federation for Rare

Endocrine diseases FIRENDO, and the Endo-ERN rare disease network.

In each center within the PRISIS network, adult patients with genetic lipodystrophy syndromes (CGL or FPLD) were identified from medical registers by their referent physician and invited to participate by an information letter sent by e-mail or postal service. Information about this study was also relayed by the French patient lipodystrophy association (AFLIP) through social networks and media. Patients under the age of 18, with acquired lipodystrophy, or with insufficient fluency of the French language, were not considered eligible. After reception of their informed consent, patients received access codes to complete the online self-reported questionnaire. Patients who felt uncomfortable with the online format were proposed to fill out a paper version of the self-reported questionnaire.

This study was approved by the INSERM's Institutional Review Board (no. 21-787) and consent was obtained from patients according to national ethical and legal requirements. This research follows the principles of the Declaration of Helsinki.

Data collection

The questionnaire was constructed into two parts.

Data on the diagnostic pathway were collected using a patient self-filled questionnaire (available on demand) based on the study used in Cushing syndrome as published by Kreitschmann-Andermahr et al.[21] Patients were asked about their weight, height, and lipodystrophy-related comorbidities with age of onset. The questionnaire included items on number and specialty area of healthcare professionals visited from the onset of lipodystrophy-associated symptoms until the announcement of diagnosis, with age at the time of diagnosis and type of lipodystrophy ("partial" or "generalized" lipodystrophy). Patients were asked about their self-perception of the onset of lipodystrophy using an open-ended question (ie, "What was, for you, the first sign or symptom of lipodystrophy?"). Answers were categorized and counted as follows: *changes in morphotype* including lipohypertrophy, lipoatrophy, lipomas, thinness; *muscular symptoms* including prominent muscles, muscular hypertrophy, or functional muscular symptoms; *metabolic complications* including diabetes, dyslipidemia, and hepatic steatosis; *gynecologic symptoms* including hirsutism and amenorrhea; *cardio-respiratory complications* including cardiopathy, hypertension and sleep apnea syndrome; *general symptoms* including asthenia and lack of satiety. They also indicated whether they were "index" cases or "secondary" cases (defined in the questionnaire as "the first, second, or more case diagnosed in their family").

Sociodemographic data included gender, age, birthplace (Metropolitan France, Overseas territory, Other), city of residency (current residency and during adolescence), personal and maternal educational level and current occupational status. Coordinates of the city of residence (latitude/longitude) were used to plot the location of patients on a map. The type of area of residency (rural, small urban, large urban)[22] was assessed using classification provided by INSEE (French National Bureau of Statistics), as well as the educational level and occupational category (recorded into three categories: low, intermediate, and high-level).

The questionnaire was reviewed by the patient lipodystrophy association AFLIP.

Statistical analyses

Statistical analyses were conducted using R software (Version 4.2.0) and SAS software (Version 9.4). Mapping was designed using QGIS software (Version 3.30.0).

Diagnostic delay was calculated as the time lag between the age at the first symptom and age at final diagnosis of lipodystrophy, as self-reported by patients. Descriptive statistics of interval-scaled data were expressed as median and interquartile ranges (IQR). Nonparametric tests were conducted. Chi-squared tests of independence were used for qualitative variables or, if expected frequencies were below 5%, Fisher's exact test was used.

Group comparison for type of lipodystrophy (CGL and FPLD), gender, birthplace, area of current and previous residency, educational and occupational category (patients and mother) were performed for all variables. Comparisons between two groups were conducted by unpaired Mann–Whitney U-test, and between more than two groups by the Kruskal–Wallis test. For all analyses, two-sided P values $\leq .05$ indicated statistical significance.

Results

Study population

From the participating centers, 155 patients were identified and 20 were recruited through the media communication campaign. Out of the 175 eligible patients, 122 consented to fill out the questionnaire but among them, 13 failed to return it (Figure 1). A total of 109 patients were included in the population of analysis. Sociodemographic data are summarized in Table 1 and corresponding genetic data in the Table S1. Among the whole group, 93 patients were diagnosed with FPLD (86% of women) and 16 with CGL (75% of women). Lipodystrophy was more frequently diagnosed in women (84%) than in men (16%), without significant difference between FPLD and CGL. The majority of respondents were born in metropolitan France (62%), 27% in French overseas territories and 11% were born outside of France. This repartition tended to differ between patients with FPLD as compared with patients with CGL (Table 1, $P = .07$). Overall, 28 patients with FPLD (30% of all patients with FPLD) were born in French overseas territory as compared to only one patient with CGL. Repartition of current residency city of respondents is illustrated in Figure 2, along with the localization of the PRISIS expert centers in France. Respondents with CGL lived more frequently in large urban areas (Table 1, $P = .003$).

Patients' lipodystrophy-related comorbidities

At the time of study, respondents with CGL were younger than patients with FPLD (median age [IQR] 29.2 [25.2-44.5] vs 46.4 [32.2-56.1] years, respectively; $P = .02$) (Table 2). Patients with FPLD had a higher BMI (24.7 kg/m^2 [22.8-27.7]) than patients with CGL (22.7 kg/m^2 [18.9-25.3], $P = .02$). They were aware of their final diagnosis at a younger age than patients with FPLD (respectively: 10 [1-25] vs 33 [24-47] years old, $P < .0001$).

Patients with FPLD or CGL did not declare significantly different frequencies of past and current lipodystrophy-related comorbidities. Metabolic complications were frequent: 68% of all respondents declared having diabetes, 66% hypertriglyceridemia, and 57% hepatic steatosis. Regarding cardiovascular comorbidities, 54% subjects reported hypertension, 12%

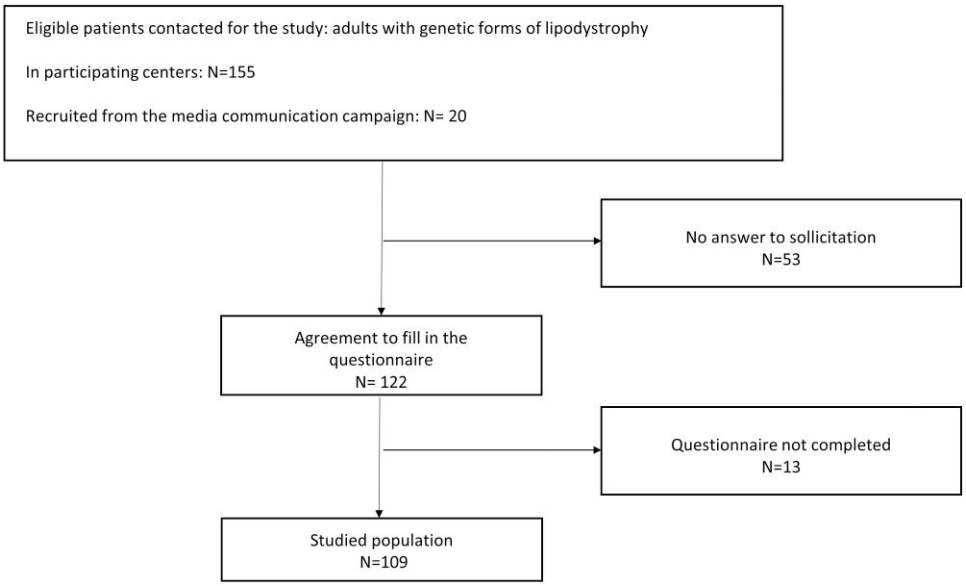

Figure 1. Flow chart of the study.

Table 1. Sociodemographic data of the overall population of patients with genetic lipodystrophy.

	Total, $N = 109$		Familial partial lipodystrophy (FPLD), $N = 93$		Congenital generalized lipodystrophy (CGL), $N = 16$		P (FPLD vs CGL)
	n	%	*n*	%	*n*	%	
Gender $N = 109$							.36
Women	92	*84*	80	*86*	12	*75*	
Men	17	*16*	13	*14*	4	*25*	
Age (years) $N = 106$							.04
18-44	*55*	*52*	43	*48*	12	*75*	
45-64	36	*34*	35	*39*	1	*6*	
65-74	11	*10*	9	*10*	2	*13*	
≥75	4	*4*	3	*3*	1	*6*	
Birthplace $N = 108$							.07
Metropolitan France	67	*62*	*55*	*60*	12	*75*	
Oversea territories	29	*27*	28	*30*	1	*6*	
Other	12	*11*	9	*10*	3	*19*	
Location of current residency $N = 100$							.003
Rural	14	*14*	11	*13*	3	*19*	
Small urban area	*56*	*56*	53	*63*	3	*19*	
Large urban area	30	*30*	20	*24*	10	*62*	
Location of residency in adolescence $N = 95$							.06
Rural	15	16	13	16	2	15	
Intermediate density urban	48	50	45	55	3	23	
Big density urban	32	34	24	29	8	62	
Educational level $N = 106$							.45
Low	40	38	36	40	4	27	
Intermediate	37	35	32	35	5	33	
High	29	27	23	25	6	40	
Occupational category $N = 98$							.14
Low	23	24	17	20	6	43	
Intermediate	56	57	51	61	5	36	
High	19	40	16	19	3	21	

Results are expressed as percentage (%, italic values) for qualitative variables. Results are from all patients unless specified (N). P values are obtained from Wilcoxon tests for quantitative variables and from chi-squared tests for qualitative variables.
CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy.

cardiac rhythm disturbances, and 9% ischemic cardiac disease. Interestingly, in 4 out of 10 patients with ischemic cardiac disease and 6 out of 13 patients with cardiac rhythm disturbances, diagnosis of the lipodystrophy syndrome was made, respectively, 14 and 4 years (median values) after the cardiac event. In women responders, 60% declared irregular

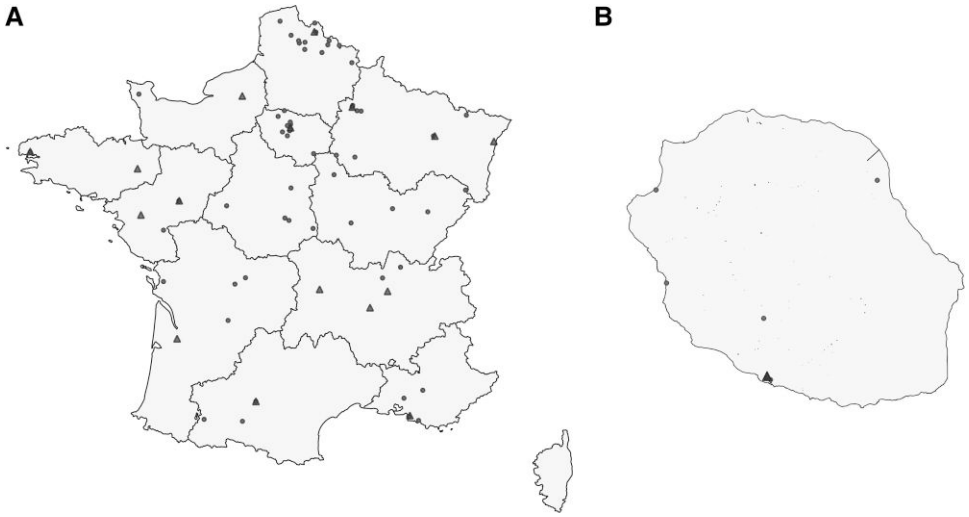

Figure 2. Location of the current city of residency of participants (black circles) and of the medical centers of the French National Reference Network PRISIS (*Rare Diseases of Insulin Secretion and Insulin Sensitivity*) (black triangles) in Metropolitan France (A) and the Reunion Island (B), $n = 102$. The same black dot can represent several respondents living in the same city.

Table 2. Self-reported comorbidities in patients with genetic lipodystrophy.

	Total ($n = 109$)	Familial partial lipodystrophy (FPLD, $n = 93$)	Congenital generalized lipodystrophy (CGL, $n = 16$)	*P* (FPLD vs CGL groups)
Clinical factors				
Current age (years) $N = 106$	43.1 (30.1-55.5)	46.4 (32.2-56.1)	29.2 (25.2-44.5)	.02
Current body mass index (kg/m^2) $N = 102$	24.2 (22.6-27.5)	24.7 (22.8-27.7)	22.7 (18.9-25.3)	.02
Age at diagnosis of lipodystrophy (years) $N = 94$	30 (23-47)	33 (24-47)	10 (1-25)	<.0001
Comorbidities				
Metabolic comorbidities				
Hypertriglyceridemia	71/108 (66)	62/92 (67)	9/16 (56)	.63
Age at diagnosis of hyperTG (years) $N = 59$	25 (18-35)	25 (19-37)	17 (6-34)	.14
Diabetes	74/108 (68)	63/92 (69)	11/16 (69)	1.0
Age at diagnosis of diabetes (years) $N = 71$	28 (19-45)	30 (21-45)	16 (10-27)	$<10^{-3}$
Hepatic steatosis, *n/n* (%)	60/106 (57)	49/90 (54)	11/16 (69)	.25
Age at diagnosis of hepatic steatosis (years) $N = 54$	30 (19-45)	33 (21-45)	14 (0-30)	.01
Antecedent of acute pancreatitis	9/107 (8)	7/91 (8)	2/16 (13)	.43
Age at diagnosis of acute pancreatitis (years) $N = 9$	32 (19-39)	32 (19-43)	24 (12-35)	.56
Cardiovascular comorbidities				
High blood pressure	57/107 (54)	47/91 (51)	10/16 (63)	.49
Age at diagnosis of HBP (years) $N = 52$	28 (19-39)	30 (22-40)	16 (11-28)	.01
Antecedent of myocardial infarction	10/109 (9)	9/93 (10)	1/16 (6)	1
Age (years) $N = 8$	45 (40-57)	43 (40-59)	50	.51
Antecedent of cardiac rhythm disturbances	13/106 (12)	12/90 (13)	1/16 (6)	.77
Age (years) $N = 13$	35 (26-53)	36 (28-56)	1	.11
Gynecological comorbidities				
Irregular menstruation in women	55/92 (60)	46/80 (57)	9/12 (75)	.19
Age (years) $N = 50$	16 (13-18)	16 (13-18)	16 (14-21)	.84
Hirsutism in women	48/91 (53)	42/79 (53)	6/12 (50)	1.0
Age (years) $N = 42$	18 (13-25)	18 (14-25)	20 (12-21)	.67
Fertility disorders in women	21/89 (24)	19/77 (24)	2/12 (17)	.26
Age (years) $N = 19$	22 (20-25)	22 (20-25)	21 (16-25)	.59

Data are based on patients' answers to the questionnaire, reflecting knowledge and self-perception of the different sign or symptom, or diagnosis. Results are expressed as median (25% percentile-75% percentile) for quantitative variables and as number (*n*/number of available answers) and percentage (%) for qualitative variables. Results are from all patients unless specified (*N*). *P* values are obtained from Wilcoxon tests for quantitative variables and from chi-squared tests for qualitative variables.
CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; TG, triglycerides; HBP, high blood pressure.

menstruation, 53% hirsutism, and 24% fertility disorders. In comparison to patients with FPLD, patients with CGL were younger at diagnosis of diabetes, hepatic steatosis, and hypertension. We found no significant differences in prevalence and age at diagnosis of any studied lipodystrophy-related comorbidities between men and women, for FPLD and CGL.

Diagnostic pathway

Before lipodystrophy syndrome diagnosis, 15% of patients had consulted only one type of doctor for lipodystrophy-related symptoms. Conversely, 36% of patients consulted more than five types of doctors. The number of physicians visited before diagnosis did not differ according to the patients' type of lipodystrophy, gender, or educational and occupational category. The proportion of patients having consulted more than five physicians for lipodystrophy-related signs before the diagnosis was significantly higher in metropolitan France than in the overseas territories (45% vs 12%, $P = .03$).

Before final diagnosis, 91% of patients had visited their family physician for lipodystrophy-related symptoms, 72% an endocrinologist, 60% a cardiologist, 59% a dermatologist, and 54% a dietician. A gynecologist was consulted before diagnosis for symptoms associated with lipodystrophy by 69% of the women (Figure 3A).

An endocrinologist announced the diagnosis of genetic lipodystrophy in 77% of subjects (60% of patients with CGL and 81% of patients with FPLD, NS between the two groups). For the remaining subjects, geneticists, and pediatricians were the physicians more frequently involved in the announcement of the final diagnosis (Figure 3B). Pediatricians more frequently ascertained diagnosis of lipodystrophy syndrome in CGL patients than in patients with FPLD (64% vs 12%, $P < .001$), without significant differences for other physicians. The involvement of medical specialists in the announcement of diagnosis was not different in men and women (except for gynecologists), or when comparing the birthplace, location of residency in adolescence, or educational and occupational category of the patients or their mother.

The access to a specialist aware of lipodystrophy was perceived as "very difficult" for one quarter of respondents. This opinion did not differ according to the type of lipodystrophy, gender, educational, and occupational category of the patients or their mother. Nevertheless, the referral to a specialist was reported easier for patients living in French overseas territories in comparison to patients living in metropolitan territory ($P = .03$).

In all responders, the most frequently reported first symptom was a change in morphotype (39% with FPLD, 53% of patients with CGL), followed by a muscular symptom (18% in CGL and FPLD) and a metabolic complication (17% in FPLD and 18% in CGL) (Figure 4A and B). Gynecological symptoms were considered as the first sign of FPLD in 14% of affected women. Non-specific symptoms such as "asthenia" were reported by few patients ($n = 4$). In patients with partial forms of lipodystrophy, the most frequent combination of symptoms was facio-cervical lipohypertrophy associated with muscular hypertrophy. In patients with generalized lipodystrophy, lipoatrophy associated with prominent abdomen was the most frequent combination of first symptoms.

Considering all respondents, median delay for diagnosis was 12 years (IQR: 5-25) ($n = 88$) (Figure 5). The median diagnostic delay was not different according to sex, type of lipodystrophy, birthplace, or location of residency. It was not different whether the patient was an "index" ($n = 30$) or a "secondary" case ($n = 44$). This time lag was higher if the maternal educational level was low vs high (respectively 14 [6-26] vs 3 years [1-6], $P < .001$). Young responders with FPLD (aged less than the median age of 46 years old at the time of the study) reported a shorter diagnostic delay than their older counterparts (10 [4.0-13.5] vs 20.5 years [5.0-31.25], $P = .003$). Overall, diagnosis of lipodystrophy was considered as "delayed" by 71% of affected subjects (59/83). Patients with a high occupational category self-reported more frequently a delayed diagnosis than patients with a low occupational category (respectively, 82% vs 47%, $P = .01$).

Discussion

With more than 100 respondents, this is the largest cross-sectional study, developed from a patient perspective, to give an overview on perceived diagnostic pathway in patients with genetic lipodystrophy. This study was conducted throughout a national dedicated rare disease network which is similar to other European rare diseases networks, which broadens the scope of this work.

Lipodystrophic syndromes are multisystemic diseases, as confirmed by the wide variety of comorbidities reported by respondents and the different physicians involved in the diagnostic pathway.

Self-reported data regarding lipodystrophy-related comorbidities such as diabetes and hypertriglyceridemia are consistent with previously published medical data.[10,19,23-26] Disease onset and metabolic complications appear earlier in patients with CGL in comparison to those with FPLD, as already observed.[2,27] However, for both FPLD and CGL, hepatic steatosis is reported with a higher prevalence in literature than that reported by the patients in the current study.[10,26] Hepatic steatosis is mostly asymptomatic and does not require a specifically targeted therapy, which could explain its underestimation by patients. Regarding cardio-vascular outcomes, patient-reported prevalence of coronary artery disease, and myocardial infarction were in line with those assessed by healthcare professionals.[10,24] It is important to note that in nearly half of patients who experienced a life-threatening cardiac event, diagnosis of genetic lipodystrophy syndrome was made several years after. Few studies have specifically addressed the gynecological consequences of lipodystrophy in affected women.[25,28-30] Estimated prevalences of irregular menses, hirsutism, and decreased fertility are as high as 54%, 43%, and 28%, respectively, in a limited cohort of patients with FPLD,[30] in keeping with self-reported data in women with FPLD from our study (57%, 53%, and 24% respectively). Polycystic ovaries syndrome affected 82% of women with CGL in the Turkish cohort.[10] This is consistent with the self-reported estimated prevalence of irregular menses in women with CGL in our study (75%). The role of the gynecologist could thus be very valuable in pointing to the diagnosis of lipodystrophy syndromes in women.

Unsurprisingly, women were more represented than men in our study. Misdiagnosis is frequent in men since android morphotype and muscular appearance can be more easily considered as normal. However, although prevalence and severity of the lipodystrophy-associated complications is reported to be lower in men than in women in most

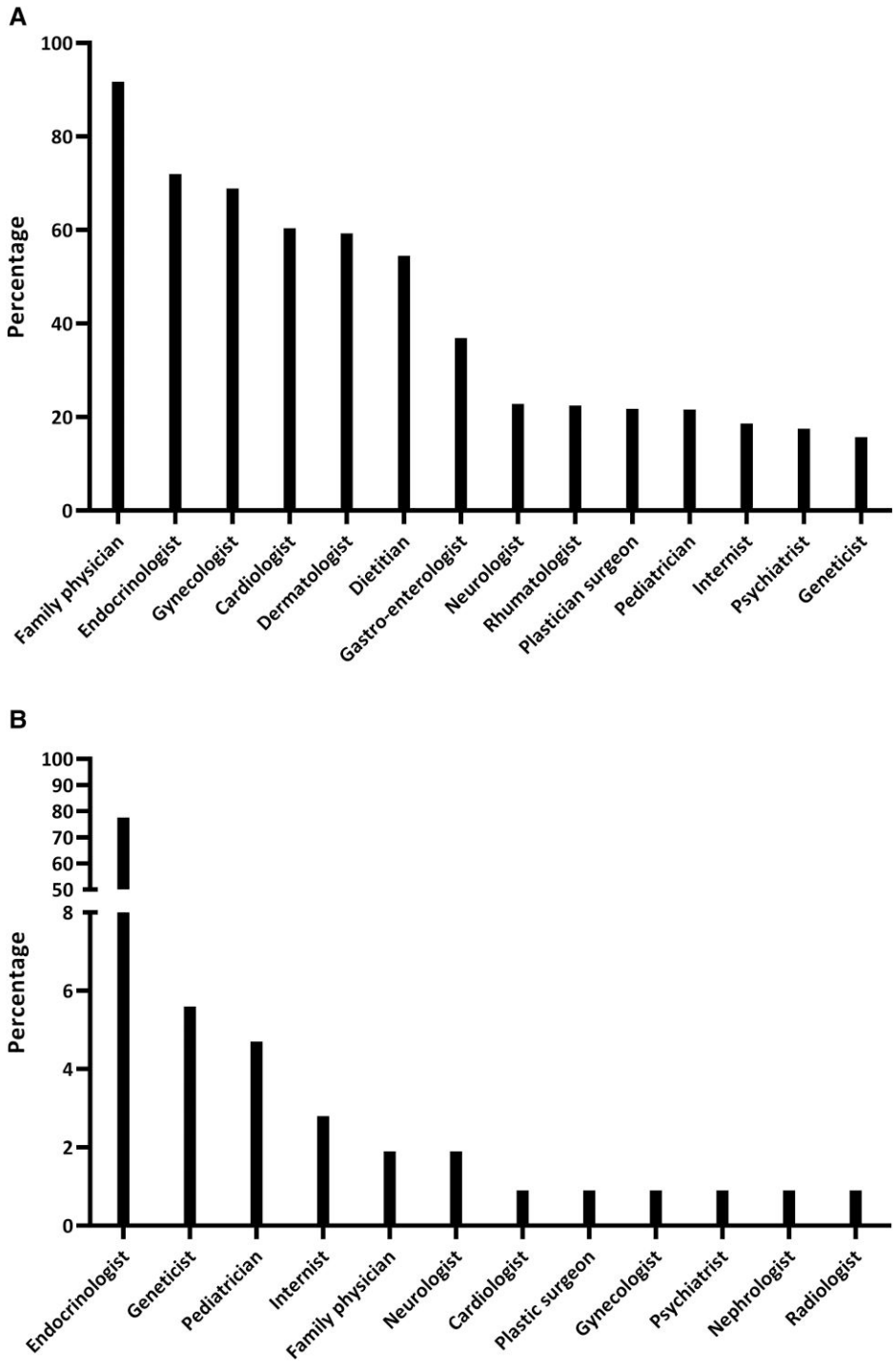

Figure 3. (A) Distribution (%) of the different health care professionals consulted for signs and symptoms related to lipodystrophy, before the diagnosis, in the overall population. (B) Distribution (%) of the different health care professionals that announced the final diagnosis of genetic lipodystrophy to the patient, in the overall population (endocrinologists account for 77% of diagnosis).

studies,[23,31,32] it was not observed here. This lack of statistical significance may be due to the low number of men included in this work.

Respondents came from diverse areas of France, but a large number also came from French overseas territories. Indeed, on Reunion Island, a specific *LMNA* pathogenic variant responsible for FPLD was identified, with a high prevalence due to a founder effect.[18,19,33] In metropolitan France, even if respondents originated from the whole territory, their number was higher in the Paris region and in the North of France where two medical centers are involved in diagnosis and care of lipodystrophy for many years.

The diagnostic pathway of lipodystrophy is frequently perceived as an obstacle course by affected patients. A recent study estimated the time lag between the first hospital admission for lipodystrophy-related symptoms and the definite diagnosis of CGL at 50 ± 97 months in Turkey.[10] A strict comparison of the time lag found in both studies is difficult considering that this study does not start from the first perceived symptoms and does not cover the whole diagnostic

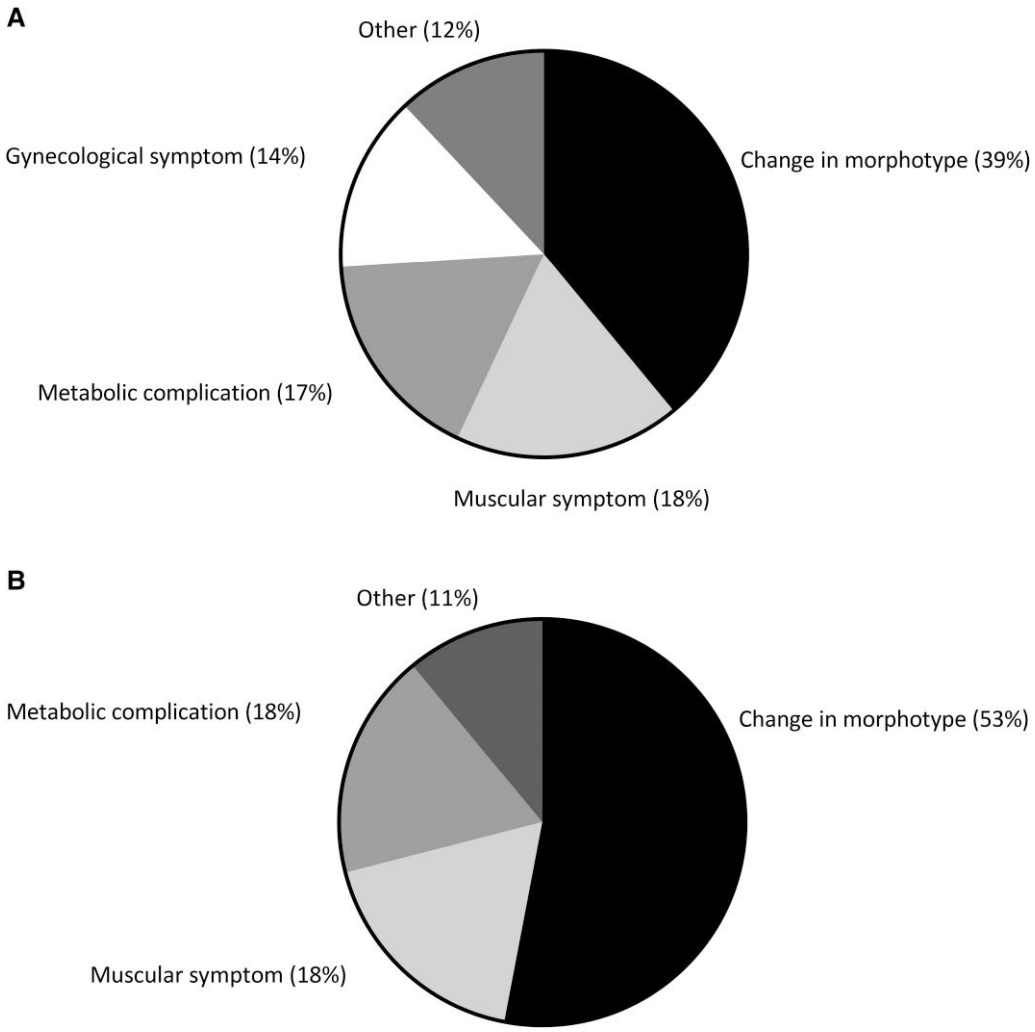

Figure 4. (A) Distribution (%) of first reported symptom in patients with FPLD ($n = 75$). (B) Distribution (%) of first reported symptom in patients with CGL ($n = 12$). FPLD, familial partial lipodystrophy; CGL, congenital generalized lipodystrophy.

pathway as our study does. In a qualitative study addressing the impact of lipodystrophy on body image, participants express a frustrating lack of understanding from health professionals, which was thought to contribute to delay in diagnosis and access to appropriate treatment.[13] In our study, the median time lag between the first symptom of lipodystrophy and the final diagnosis is estimated at about 12 years. Strikingly, diagnostic delay was not significantly different between FPLD and CGL, whereas the latter are generally diagnosed in childhood, which would imply a shorter delay in diagnosis. This may be due to the limited effective of patients with CGL, in comparison to FPLD. Moreover, CGL patients included in this work are only adults, which can overestimate the diagnostic delay. Though, for 50% of respondents with CGL, diagnosis was established after 20 years old. We examined several social determinants known to be related to health-related outcomes such as the degree of urbanization and maternal educational level. Only the latter was associated to diagnostic delay, with very large differences of time lags according to low or high maternal educational level. This confirms that the diagnostic pathway is strikingly impacted by the social health inequalities.[34] The multisystemic character of the disease also contributes to the diagnosis difficulties, as confirmed by the number of different medical specialists consulted for disease-associated symptoms. Even if the endocrinologist was most frequently involved in the diagnosis, the family physician, as well as the cardiologist, gynecologist, and dermatologist were consulted by more than half of the respondents before diagnosis. General practitioners, consulted by 91% of respondents for lipodystrophy-related symptoms, play a pivotal role as first point of contact during the diagnostic process. In our study, 36% of patients had to seek medical attention from more than five different physicians before the diagnosis was made. Similar observations have been reported in other rare and multisystemic endocrine diseases: the mean diagnosis delay was evaluated at 14.2 years (SD 11.3) in 469 patients with acromegaly,[35] and a study reported that patients consulted 4.6 ± 3.8 physicians before diagnosis of Cushing syndrome, during an overall diagnosis process of 3.8 ± 4.8 years (median 2 years).[21] Interestingly, on Reunion Island, the number of physicians consulted for lipodystrophy-associated symptoms before diagnosis was significantly lower than in Metropolitan France. This may result from better knowledge of the disease due to its high prevalence in this area, and from systematic familial screening, easier in a small area, that led to diagnosis in 53.8% of patients in the Reunionese cohort published in 2021.[19] In FPLD, the diagnostic delay was shorter in younger patients, in line with an improvement in the diagnostic

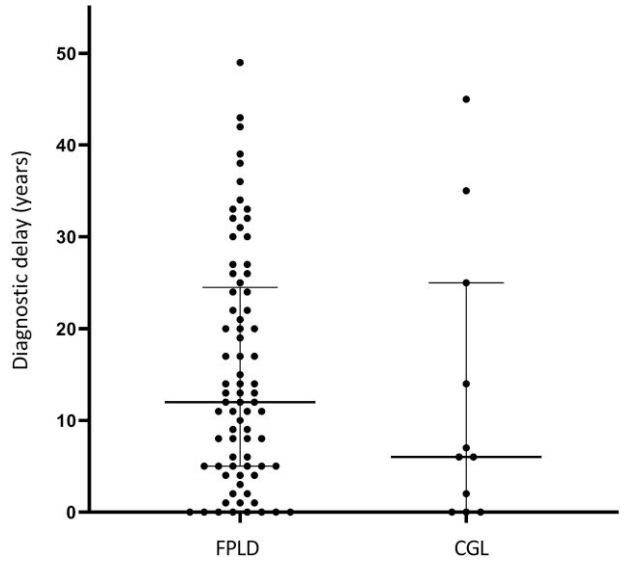

Figure 5. Time lag between first lipodystrophy-related sign and diagnosis in patients with FPLD ($n = 77$) and CGL ($n = 11$). Individual values are depicted as dots. Horizontal lines show median values and interquartile ranges. FPLD, familial partial lipodystrophy; CGL, congenital generalized lipodystrophy.

process and better knowledge of the disease, since the identification of *LMNA* as the first gene involved in partial lipodystrophy in 2000.[36]

More than one-third of patients report a "change in morphotype" including lipohypertrophy and/or lipoatrophy as first symptom. Interestingly, in patients with FPLD, association of facio-cervical lipohypertrophy with muscular hypertrophy, as first symptoms, was the most frequently reported combination. For patients with CGL, the combination of lipoatrophy with prominent abdomen was the most frequently reported, probably referring, at least in part, to an increased volume of the liver due to hepatic steatosis. Examination of adipose tissue and morphotype in routine clinical evaluations is a major leverage point to improve diagnosis of lipodystrophy. Although body composition methods such as dual-energy X-ray absorptiometry can be useful, clinical examination, including measurement of waist and hip circumferences, biacromial diameter and skinfolds, refines the clinical diagnosis to lipodystrophy.[2,37,38] In addition, since changes in physical appearance may appear insidious, requesting photographs from patients at various ages can be very helpful. This is particularly true for FPLD, since changes in physical appearance occur progressively around puberty.[39]

Our study presents the first data on diagnostic pathway in genetic lipodystrophy from patients' perspective. Its robustness lies in the widespread participation and large number of patients included especially given the rareness of the disease. A limitation for the interpretation of results is a degree of uncertainty in the patients' ability to remember the exact time points of symptom onset and the subsequent diagnostic course, which is due to the self-reported character of the data. It will be interesting to compare these data to those extracted from the French national rare disease database, filled by specialized physicians for each patient with a rare disease, which are being implemented for lipodystrophic diseases. In addition, only adult patients were included, which may reduce the recruitment of patients with generalized lipodystrophy in our sample, and limit subgroup analyses. Data on pediatric patients' diagnostic process will be important to collect.

To conclude, our self-reported study highlights the long diagnostic pathway in genetic lipodystrophy syndromes, in accordance with the multisystemic character and rare occurrence of lipodystrophy syndromes. The negative consequences of such a delay to diagnosis on the patient's health, disease outcome, and care expenses are evident. For non-specialized physicians, including family physicians, increasing awareness on clinical diagnosis of lipodystrophy is central, to allow early recognition of symptoms and early diagnosis. Open-access reference documents,[20] online free-access applications to refine diagnosis,[40] media and social networks are important tools to favor the dissemination of knowledge. This can reduce diagnostic delay and improve the quality of clinical care, particularly considering the high prevalence of cardio-metabolic complications. Development of rare disease networks is a key point to improve care pathway in affected patients.

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Supplementary material

Supplementary material is available at *European Journal of Endoicrinology* online.

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Authors' contributions

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[lead], Software [lead]), Inès Belalem (Conceptualization [equal], Formal analysis [equal], Software [equal]), Brigitte Delemer (Conceptualization [equal], Investigation [equal], Resources [equal]), Sonja Janmaat (Conceptualization [equal], Investigation [equal], Resources [equal]), Isabelle Jéru (Data curation [equal], Investigation [equal], Resources [equal]), Lauriane Le Collen (Conceptualization [equal], Investigation [equal], Resources [equal]), Dominique Maiter (Conceptualization [equal], Investigation [equal], Resources [equal]), Estelle Nobécourt (Conceptualization [equal], Data curation [equal], Investigation [equal], Resources [equal]), Marie Vantyghem (Conceptualization [equal], Data curation [equal], Investigation [equal], Resources [equal]), Sophie Beliard (Investigation [equal], Resources [equal]), Claire Briet (Investigation [equal], Resources [equal]), Bruno Donadille (Investigation [equal], Resources [equal]), Noémie Dubois (Investigation [equal], Resources [equal]), Olivier Gilly (Investigation [equal], Resources [equal]), Stéphanie Jellimann (Investigation [equal], Resources [equal]), Julie Maître (Investigation [equal], Resources [equal]), Yves Reznik (Investigation [equal], Resources [equal]), Frédérique Rimareix (Investigation [equal], Resources [equal]), Bruno Vergès (Investigation [equal], Resources [equal]), Corinne Vigouroux (Conceptualization [lead], Formal analysis [equal], Funding acquisition [lead], Investigation [lead], Methodology [lead], Resources [lead], Supervision [lead], Validation [lead], Writing—original draft [supporting], Writing—review & editing [supporting]), and Agnès Dumas (Conceptualization [lead], Formal analysis [lead], Funding acquisition [lead], Investigation [lead], Methodology [lead], Resources [equal], Supervision [lead], Validation [lead], Writing—original draft [supporting], Writing—review & editing [supporting])

Data availability

The datasets presented in this article are not readily available because of the sensitive nature of the data and possible high risks associated with patient confidentiality. Requests to access the datasets should be directed to camille.vatier@aphp.fr.

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