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ORIGINAL ARTICLE

Quantitative natural history characterization in a cohort of 142 published cases of patients with galactosialidosis—A cross-sectional study

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Abstract

Galactosialidosis (GS; OMIM #256540) is a rare multisystemic inborn glycoprotein storage disease caused by biallelic mutations in the *cathepsin A* gene resulting in combined deficiency of the lysosomal enzymes β-galactosidase and α-neuraminidase. The precise understanding of the natural course of the disease is limited. Development of enzyme replacement therapy is at the preclinical stage. The purpose of this research project was to quantitatively characterize the natural history of the condition. Quantitative analysis of all published cases in the literature with sufficient data (N = 142 patients) was carried out. Main outcome variables were survival, diagnostic delay, description of symptoms, biomarker-phenotype associations, and radiological findings. STROBE criteria were respected. Median survival age of the cohort was 48 years. Median age of onset was 4.25 years with interquartile range (IQR) 1 to 16 years. Median age at diagnosis was 19 (IQR: 8.92-29) years, with median diagnostic delay of 8 (IQR: 4-12) years. Patients with residual β-galactosidase activity of more than 8.6% (leukocytes) survived significantly longer than patients with lower enzyme activities.

KEYWORDS

drug development, galactosialidosis, orphan disease, radiological findings, survival

1 | INTRODUCTION

Galactosialidosis (GS; OMIM #256540) is an autosomal recessive lysosomal storage disease (LSD) first reported by Goldberg et al.[1] Biochemically, GS is defined by combined enzyme deficiency of β-galactosidase (β-Gal; EC 3.2.1.23) and α-neuraminidase (Neu1; EC 3.2.1.18), both enzymes forming a complex with lysosomal protective protein, also known as *cathepsin A* (*PPCA*).[2–5] PPCA protects the two glycosidases from intralysosomal proteolysis, regulating their stability and activity within lysosomes and, therefore, combined enzymatic deficiency in GS is the consequence of impairment or even loss of this protective function.[6,7] PPCA's protective function toward the two glycosidases is separable from its equally important catalytic activity. The enzyme functions as a carboxypeptidase at acid pH and deamidase/esterase at neutral pH. A combined assay of β-Gal, Neu1, and PPCA in white blood cells or cultured skin fibroblasts confirms the diagnosis.[2,8] The disease is due to a mutation in the *cathepsin A* (*CTSA*) gene localized on 20q13.12. The Human Gene Mutation Database currently lists 36 pathognomonic mutations, mostly missense/nonsense (http://www.hgmd.cf.ac.uk/, as of 24 June 2018). The disease is very rare, the precise frequency not known, Orphanet currently lists 100 cases (https://www.orpha.net, as of 24 June 2018). Deficiency of PPCA results in the combined phenotype of G_{M1} gangliosidosis and sialidosis.[9] Depending on the age of onset and severity of clinical

symptoms, GS patients are categorized into three subgroups: early infantile (EI), late infantile (LI), and juvenile/adult (J/A) type.[8] GS affects following organ systems: central nervous system including vision and hearing, cardiovascular, gastrointestinal, and urinary systems; as well as skin, blood, skeletal system, and connective tissue. Patients with GS are presenting typical symptoms of a LSD, such as developmental delay and regression, coarse facies, corneal clouding, cherry-red spots, hepatosplenomegaly, cardiomegaly, hernias, angiokeratoma, dysostosis multiplex, vertebral changes, a history of hydrops fetalis or ascites, vacuolated lymphocytes in blood smears, and foamy cells in bone marrow.

Knowledge gaps in GS include missing quantitative definition of the natural history. As the disease is rare and potentially underdiagnosed, disease awareness may be rather low. In addition, biomarker-phenotype associations are unknown. We therefore directed our efforts in investigating survival, onset of disease as quantitative hard endpoints, time-to-diagnosis as indirect measure for disease awareness. In addition, we explored the clinical phenotype as well as phenotype-biomarker associations and provide an exhaustive overview of radiological findings in GS patients.

2 | METHODS

Our study was conducted in accordance to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) criteria (http://www.strobe-statement.org).

No human experimentation was part of this study; therefore no informed consent was obtained for this study. This article does not contain any studies with human or animal subjects performed by the any of the authors.

2.1 | Literature review and definitions of variables

We have comprehensively searched for case reports of patients with GS by using PubMed and Google Scholar searching engines with all alternative names of the disease as stated in its OMIM description. Specifically, these search terms were "galactosialidosis," "Goldberg syndrome," "neuraminidase deficiency with beta-galactosidase deficiency," "lysosomal protective protein deficiency," "cathepsin A deficiency," and "PPCA deficiency." We identified 153 publications and examined them further for relevant clinical, biochemical, and genetic data. Content of N = 46 publications of the abovementioned group was not relevant to the subject of our study. Case reports were published between September 1971 and February 2016. Only 105 studies were relevant and provided sufficient data for analysis (Supporting Information, Figure S1). One study was written in French, 1 in German, 19 in Japanese and the rest was written in English. They report in total of 142 patients affected with GS. Database was closed 28 February 2017.

In this cohort of patients the following variables were analyzed: subtype of disease as stated by the author, age at onset, leading signs and symptoms at onset, sex, members of family affected by GS, last reported age, whether the patient was dead or alive at that point, country of patient's origin, country of affiliation of publication's first author, consanguinity in the family, age at diagnosis of the patient and time between first symptoms and diagnosis, date of publication of the case report, levels of biochemical markers, radiological findings, coarse facies, cherry-red spots, conjunctival telangiectasia, scotoma, corneal clouding, fetal hydrops, edema, ascites, visceromegaly, hepatosplenomegaly, vertebral changes, skeletal dysplasia, dysostosis multiplex, short stature, mitral valvular disease, aortic valvular disease, aortic stenosis, other cardiac manifestations, myoclonus, seizures, ataxia, angiokeratoma, mental retardation, mild cognitive disability, hearing loss, hemangiomas, vacuolated Kupfer cells, vacuolated lymphocytes, telangiectasias, vertebral beaking, hernias, decreased visual acuity, pectus excavatum, pectus carinatum, thrombocytopenia, anemia, kyphosis, muscle hypotonia, pyramidal tract signs, kidney involvement, and cause of death. The rationale and inventory of the above listed clinical variables were derived from published clinical descriptions of the condition.[8,10,11] In case of unspecific age description in studies, a conservative estimation was made (eg, if age of onset stated as "4-5 years," 4.5 years were used for our analysis). If country of patients' origin was not mentioned in the respective case reports, country of the first author's institutional affiliation has not been attributed to the patient, that is, only clearly stated origin was considered. Duplicate case reports were omitted, unless they provided additional data on further development of the same patient. We did not impute missing data.

2.2 | Subtype designation by typical clinical patterns observed in case reports

Cases included in this study have been published over a long period of more than 40 years. Many of these cases were not given the correct diagnosis at the time of publication. Therefore, we had to examine every selected publication very carefully. Cases reported as GS and/or meeting diagnostic criteria of combined deficiency of β-Gal and Neu1 were included in the study. Similarly, disease subtype designation was also often missing, inconsistent, or imprecise. The inconsistency of subtype designation is mainly caused by the continuous spectrum of clinical manifestations, as it is in most LSDs.[8] In order to be able to correctly assign a subtype to as many cases as possible, we analyzed our dataset and

with the knowledge of subtype description by d'Azzo et al[8], we carefully narrowed down the broad and continuous spectrum of disease symptoms into a short, focused list of items characteristic only for given subtype. Our summary of typical clinical patterns is as follows:

For patients with EI type, onset in the first 3 months of age, death by 20 months of age in all cases, fetal hydrops, ascites, kidney failure, and almost exclusively in this type also telangiectasias are characteristic.

In LI patients, myoclonus and ataxia are typically absent. Hepatosplenomegaly is typically present, as well as heart involvement, dysostosis multiplex, and often hearing loss. If a patient develops symptoms between the 4th and 12th month of age, he or she is usually a case of the LI type.

Juvenile/adult patients develop first symptoms after their fourth birthday, are usually Japanese, have no ascites, no kidney involvement, and no visceromegaly. Hepatosplenomegaly is very rare in this group. They present with loss of visual acuity. Angiokeratoma was observed almost exclusively in J/A patients, and myoclonus, ataxia, and seizures were often present.

Thanks to this list we managed to classify all but 5 cases out of our total of 142. A juxtaposition of the subtype designations as stated in the studied case reports and our secondary subtype designation is available in Table S1.

2.3 | Statistics

Variables were illustrated using counts and percentages of the total study population. Enzyme activities as stated in the studies were measured in different laboratories with different reference intervals. Therefore, to provide these data in a comparable form, we calculated the mean of reference intervals given in each study and expressed the activities of investigated enzymes as percentage of the mean normal. Survival was estimated using the Kaplan-Meier method. Survival was defined as the time difference between birth and age at death. Diagnostic delay is the difference between age of onset of symptoms and age at diagnosis. Unbiased recursive partitioning was used to determine impact of phenotype biomarkers β-Gal, Neu1, and PPCA.[12] All analyses were performed using R environment for statistical computing and graphics (https://www.r-project.org). The world map was plotted using the R extension ggmap.[13] P values reported were two-sided. $P \leq 0.05$ was considered statistically significant.

3 | RESULTS

We identified N = 142 patients from N = 123 families. Detailed demographics of the study population are summarized in Table S2. Predominant patients' ethnicity (Table S3) in our cohort was Japanese (N = 57/142, ie, 40%), followed by Portuguese (N = 6/142, ie, 4%). The geographical distribution is shown in Figure S2A. Visualization of origin of published case reports, that is, probable countries of diagnosis, is available in Figure S2B.

3.1 | Survival

The median survival of the overall group of patients with GS was 48 years (Figure 1). Survival outcome varied according to disease subtype (Figure 2). Cause of death was reported in 16 out of 142 patients. Most frequent reasons for death were cardiac failure, renal failure, and acute bronchopneumonia. Complete overview of all causes can be found in Table S4. Date of publication had no significant influence on survival.

3.2 | Onset of disease, age at diagnosis, and time-to-diagnosis

Mean age of onset of the overall group (N = 114) was 8.8 years, that is, 105.66 months (SD 125.58; median 51; interquartile range [IQR] 1-168; range 0-564). Mean age of onset of the EI group (N = 30) was 4 days, that is, 0.13 months (SD 0.43; median 0; IQR 0-0; range 0-2). Mean age of onset of the LI group (N = 27) was 2 years, that is, 24.3 months (SD 17.19; median 24; IQR 7.5-36; range 0-55). Mean age of onset of the J/A group (N = 57) was 16.6 years, that is, 199.74 months (SD 116.26; median 168; IQR 120-264; range 3-564).

Mean age at diagnosis of the overall group (N = 34) was 20.2 years, that is, 242.16 months (SD 171.54; median 228; IQR 125.25-330; range 0-636). Mean age at diagnosis of the

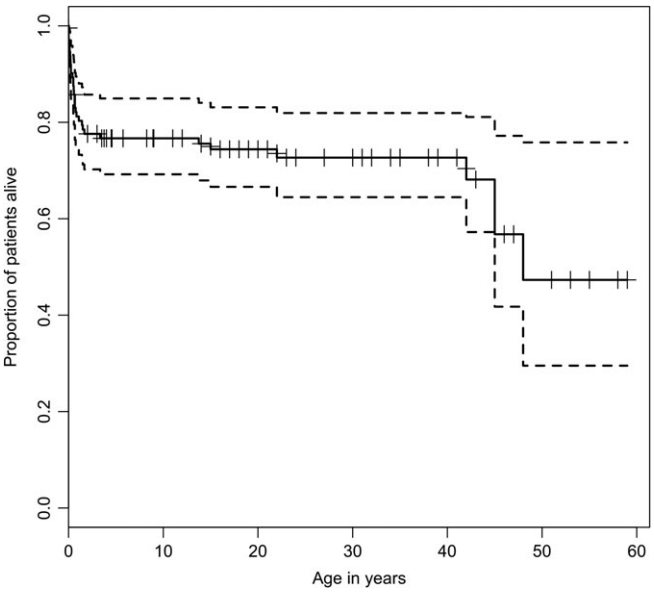

FIGURE 1 Estimated overall survival distribution in patients with galactosialidosis (GS) with 95% confidence intervals (N = 113)

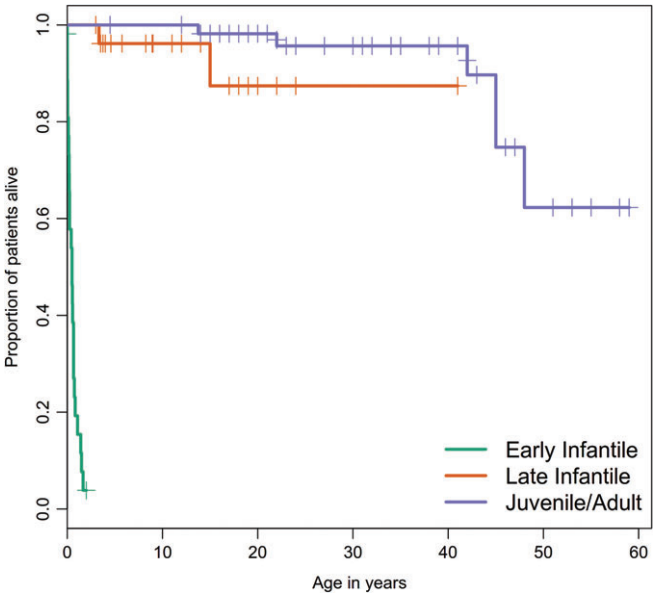

FIGURE 2 Estimated survival distribution in galactosialidosis (GS) patients (N = 111) by subtype after our subtype designation. Median survival for early infantile (EI) was 6 months. EI patients N = 27, late infantile (LI) patients N = 27, juvenile/adult (J/A) patients N = 57

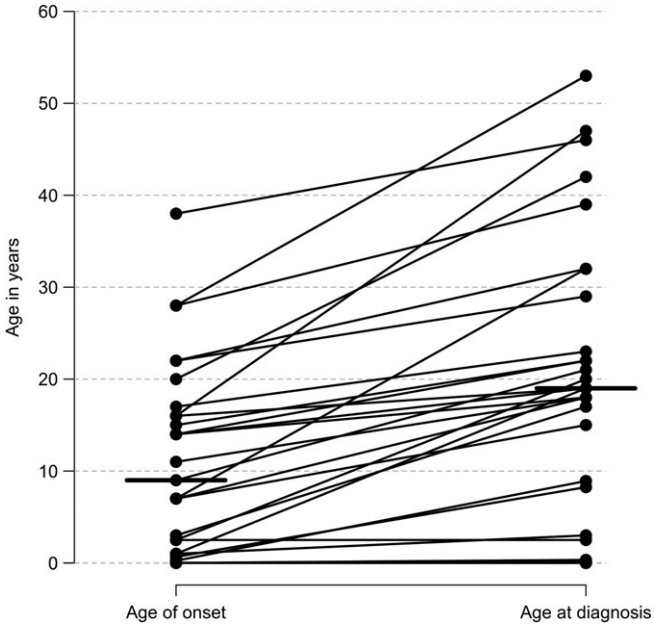

FIGURE 3 Age at onset (in years) and age at diagnosis representation. Data were available for N = 29 patients. Horizontal lines indicate the medians. The slopes of connecting lines represent the delays between onset of the disease and times of diagnosis

EI group (N = 4) was 1.38 months (SD 1.89; median 0.75; IQR 0-2.12; range 0-4). Mean age at diagnosis of the LI group (N = 7) was 10 years, that is, 119.57 months (SD 102.56; median 99; IQR 33-216; range 0-240). Mean age at diagnosis of the J/A group (N = 22) was 27.1 years, that is, 325.59 months (SD 141.01; median 270; IQR 228-384; range 107-636).

Mean diagnostic delay of the overall group (N = 29) was 9.6 years, that is, 115.12 months (SD 98.85; median 96; IQR 48-144; range 0-372). Mean diagnostic delay of the EI group (N = 4) was 1.38 months (SD 1.89; median 0.75; IQR 0-2.12; range 0-4). Mean diagnostic delay of the LI group (N = 6) was 9.8 years, that is, 118.17 months (SD 93.87; median 129.5; IQR 40.75-199.5; range 0-216). Mean diagnostic delay of the J/A group (N = 19) was 11.5 years, that is, 138.11 months (SD 96.52; median 96; IQR 84-138; range 36-372).

Detailed graphical presentation of the data can be found in Figure 3. No correlation between diagnostic delay and country of case report publication was found (data not shown).

3.3 | Cardinal disease features at disease onset

Most frequent signs and symptoms at disease onset for the overall group of patients in our dataset were visual impairment (N = 15), fetal hydrops (N = 11), decrease of visual acuity (N = 8), ascites (N = 8), seizures (N = 8), gait disturbance (N = 7), and edema (N = 6). When divided by subtypes, most common symptoms at onset were as follows. In EI patients it was fetal hydrops (N = 11), ascites (N = 7), and edema (N = 5). In patients suffering from LI form of the disease, seizures (N = 5), visual impairment (N = 4), and hepatosplenomegaly (N = 4) were the most often presented initial symptoms. Finally, patients with J/A form of GS presented with visual impairment (N = 11), decrease of visual acuity (N = 8), and gait disturbance (N = 6). A more detailed overview can be found in Table S5.

3.4 | Multisystemic exploration of the clinical phenotype

A detailed synopsis of described signs and symptoms of patients with GS is provided in Table 1. In our dataset, most observed symptoms overall were coarse facies (N = 98), cherry-red spots (N = 71), corneal clouding (N = 50), and vertebral changes (N = 49). Hepatosplenomegaly (N = 26), fetal hydrops (N = 16), edema (N = 16), and ascites (N = 14) were the most frequent symptoms of EI patients in our analysis apart from the abovementioned symptoms. In LI patients, hepatosplenomegaly (N = 17), heart involvement (N = 16), and skeletal involvement were most often described in our dataset. According to our analysis, N = 53 J/A patients developed myoclonus, N = 39 ataxia, N = 38 angiokeratoma, N = 37 decrease of visual acuity, and N = 35 vertebral changes.

TABLE 1 Reported symptoms in GS patients by subtype and overall assorted by organ systems

Organ systems and symptoms	Early infantile (N = 32)	Late infantile (N = 31)	Juvenile/adult (N = 74)	Overall (N = 142)
General				
Coarse facies	21	20	53	98
Hernias	9	5	7	22
Edema	16	2	0	18
Fetal hydrops	16	0	0	16
Ascites	14	2	0	16
Gastrointestinal				
Hepatosplenomegaly	26	17	4	48
Visceromegaly	5	6	0	11
Vacuolated Kupffer cells	5	1	0	6
Integumentary				
Angiokeratoma	0	3	38	41
Telangiectasias	7	0	1	8
Hemangioma	0	0	1	1
Visual				
Cherry-red spots	5	13	53	71
Corneal clouding	7	6	35	50
Decreased visual acuity	0	10	37	47
Scotoma	0	0	4	4
Conjunctival telangiectasias	3	0	1	4
Musculoskeletal				
Vertebral changes	2	12	35	49
Short stature	4	7	14	28
Kyphosis	2	8	12	22
Muscle hypotonia	5	7	9	21
Vertebral beaking	2	4	10	16
Dysostosis multiplex	3	11	1	15
Skeletal dysplasia	0	4	4	11
Pectus carinatum	0	7	1	8
Pectus excavatum	0	2	1	3
Cardiovascular				
Aortic valvular disease	0	10	0	10
Mitral valvular disease	0	9	1	10
Aortic stenosis	0	4	0	4
Other heart involvement	12	8	16	37
Nervous				
Myoclonus	0	4	53	57
Ataxia	0	1	39	40
Seizures	1	5	18	24
Mental retardation	0	4	14	18
Pyramidal tract signs	0	2	7	9
Mild cognitive disability	0	1	0	1

TABLE 1 (Continued)

Organ systems and symptoms	Early infantile (N = 32)	Late infantile (N = 31)	Juvenile/adult (N = 74)	Overall (N = 142)
Auditory				
Hearing loss	0	9	9	21
Urinary				
Kidney involvement	3	3	2	8
Blood				
Vacuolated lymphocytes	12	14	40	67
Anemia	8	2	3	14
Thrombocytopenia	8	0	0	9

Abbreviation: GS, galactosialidosis.
Overall and total sum of subtypes may differ as 5 cases could not be assigned to one of the subtypes

3.5 | Residual enzyme activity and clinical phenotype

We explored the effect of residual enzyme activity on disease outcome determined as survival. Patients with residual enzyme activities of β-Gal below or equal to 8.64% of average normal in leukocytes had a statistically significantly shorter survival than patients with residual enzyme activity of β-Gal in leucocytes above this threshold ($P = 0.011$, unbiased recursive partitioning, Figure S3). For residual enzyme activities of β-Gal in fibroblasts, Neu1 in leukocytes or fibroblasts, and PPCA in fibroblasts, no threshold predicting shorter survival could be calculated.

As a part of our statistical analysis, we studied relations between residual enzyme activities of GS biomarkers and age of onset. For β-Gal, Neu1, PPCA in fibroblasts and for Neu1 and β-Gal in leukocytes no correlation was discovered.

For residual enzyme activities of β-Gal, Neu1, PPCA in leukocytes and fibroblasts measured in individual disease subtypes see Appendix S1.

3.6 | Radiological findings

We analyzed the reported radiological findings in the study population, which were assessed by X-ray, magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound in patients suffering from GS. Consistent with the multisystemic nature of the disease, these were not focused on one organ system or body part. Imaging data were available for 46 out of 142 patients, X-ray examination was performed in N = 29 patients, MRI in N = 9 patients, CT in N = 12 patients, and ultrasound examination in N = 15 patients. With regards to X-ray examinations, anterior-beaking of vertebrae (N = 10), vertebra plana (N = 6), scoliosis (N = 4), and dysostosis multiplex (N = 4) were the most frequent findings (Table S6). In cranial MRI, 44% of examined patients had white-matter disease (Table S7). One-third of patients examined with CT showed dense thalami and cerebral atrophy (Table S8). Furthermore, wide sulci and wide interhemispheric fissures were described in this group of examinees. Patients examined with ultrasound presented most often with fetal hydrops (N = 4), thickened cardiac septa (N = 3), enlarged kidneys (N = 2), thickened mitral and aortic valve (N = 2), ventricular enlargement (N = 2), ascites (N = 2), and dilatation of the left atrium (N = 2) (Table S9).

4 | DISCUSSION

Data from 142 patients with GS from all over the world were quantitatively analyzed. We defined survival, time to diagnosis, age of onset, age of diagnosis, initial symptoms, explored the clinical phenotype, and summarized the spectrum of radiological findings. In addition, we found a biomarker-phenotype association, that is, residual enzyme activities of β-Gal below or equal to 8.64% of normal in leucocytes led to shorter survival than patients with residual enzyme activity of β-Gal in leucocytes above this threshold. The geographical distribution of reported patients shows a major concentration of patients with late presentation in Japan, however, it also suggests, that GS is not specific to one ethnic group, nor is it dependent on economic development of a respective region.

Diagnostic delay and underdiagnosing of the disease are a substantial issue of GS patients and patients with other rare diseases as well.[14–16] A median diagnostic delay of 8 years highlights this problem. The diagnostic delay increases from EI to J/A patients, that is, with age of patients. This phenomenon might be caused by the fact, that the older the patients are, the milder or less life-threatening are the symptoms of the disease and as a result, the diagnostic pressure may decrease. Although the prevalence of this disease is, for example, in Japan relatively high when compared to other countries, we have found no correlation between diagnostic delay and

country of the case report's first author affiliation in any country. This illustrates the low awareness of this rare disease. Management of clinical symptoms does not seem to be improving over time as no influence on survival was found in relation to the date of publication of respective case reports (data not shown). Raising disease awareness as well as screening of high-risk populations may be of substantial help to reduce time to diagnosis, in addition, time-to-diagnosis may decrease once a specific therapy becomes available.[15,16]

GS is a progressive and multisystemic LSD. The phenotypical spectrum is broad and outlines the typical features of LSDs with its specifics depending on subtype. Multiple organ systems are involved, that is, nervous system (seizures, myoclonus, ataxia, muscle hypotonia, mental retardation), eyes (cherry-red spots, clouded cornea, loss of visual acuity), internal organs (visceromegaly), physical appearance (coarse facies), and musculoskeletal system (dysostosis multiplex, skeletal dysplasia, vertebral beaking, pectus carinatum).

First signs of patients with EI type occur already in the neonatal age, latest at 3 months of age. Between the leading symptoms of this type we can observe fetal hydrops, edema, ascites, heart involvement, and hepatosplenomegaly. Telangiectasias can be found almost exclusively in the EI type.

In LI type, patients manifest first symptoms in the first year of life. Characteristic symptoms of this subtype are hepatosplenomegaly, dysostosis multiplex, heart involvement, hearing loss, and decreased visual acuity. In contrary to the J/A type, they present with myoclonus and ataxia extremely rarely.

The majority of GS patients are classified as the J/A subtype. Most patients suffering from this form are of Japanese origin and the mean age of presentation is in adolescence. They present with myoclonus, ataxia, seizures, mental retardation, vertebral changes, and loss of visual acuity. Hepatosplenomegaly is typically not observed in these patients.[8] Angiokeratoma is also almost exclusive for the J/A GS patients.

Angiokeratoma can be found in other LSDs, such as Fabry disease, sialidosis, fucosidosis, Kanzaki disease, adult-onset GM1-gangliosidosis, aspartylglycosaminuria, and β-mannosidosis. Of interest, in Fabry disease which is a X-linked condition, the presence of angiokeratoma in male pediatric patients was associated with a higher risk of end organ damage.[18]

There are currently no interventional clinical trials available for patients with GS according to Clinicaltrials.gov (www.clinicaltrials.gov, as of 24 June 2018), only four observational studies are listed.

A study of possible enzyme replacement therapy using recombinant human PPCA (rhPPCA) was lately published by Koppaka et al.[17] The authors demonstrated, that rhPPCA is taken up by deficient human fibroblasts mannose-6-phosphate receptor pathway and Neu1 and β-Gal activities have improved subsequently in a mice model with biweekly intravenously administered rhPPCA after 8 weeks.

4.1 | Limitations and ideas for future research

Given the methods used for this study, some crucial limitations of this study must be outlined. Case reports were collected from a very diverse set of journals and are therefore focused on different specific aspects of the disease (ie, ophthalmology articles on cherry-red spots, radiological articles on vertebral changes, biochemical articles on biomarkers etc.), which renders the description of softer endpoints less precise due to ascertainment bias. As a result, this study primarily focused on hard endpoints such as survival, age of onset, and time to diagnosis as a measure of delay and disease awareness. Age of onset may be, however, considered a soft endpoint, particularly in late onset subtypes, as this involves recall after several years or decades and these data may show large variability. Small sample size is another limitation given by the relatively low prevalence of this condition. We are aware, that the analyzed laboratory data may be biased, as they were not collectively re-examined in a standardized manner. Biomarker phenotype correlations should be therefore treated as guiding lights yet to be confirmed in prospective clinical studies.

However, the approach used in this project also has multiple advantages and delivers valuable information. The most significant advantage of the present method is relatively swift availability of information in form of hard endpoints (ie, survival), as opposed to multicenter prospective clinical natural history studies, which may take many years or even decades to precisely describe hard endpoints in similar metabolic diseases presenting often with slow progression. Multicentric prospective studies also require a substantial financial support and cooperation of respective specialized national centers for rare diseases. On the other hand, prospective trials are surely more precise in describing softer clinical (ie, better description of heart involvement or reasons for decreased visual acuity) as well as biochemical endpoints thanks to a standardized protocol. Nonetheless, this method has been successfully applied in the quantitative natural history documentation of other rare inborn metabolic disorders such as molybdenum cofactor deficiency, MPS VII, or Farber disease.[14–16] For this reason, we would like to encourage our international colleagues to publish their cases of patients with rare diseases. Analyzing these data with quantitative retrospective natural history modeling will set important bases for future orphan drug development.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

T.S.: data acquisition and interpretation, drafting and revision of the manuscript. S.F.G.: statistical analysis, drafting and revision of the manuscript. S.K. and G.F.H.: revision of the manuscript. M.R.: study design, data interpretation, drafting and revision of the manuscript. All authors contributed to the critical revision of the manuscript for intellectual content and gave final approval for the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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