Deciphering the premature mortality in PIGA-CDG

An untold story

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Abstract

Objective

Congenital disorder of glycosylation (CDG) due to a defective phosphatidylinositol glycan anchor biosynthesis class A protein (PIGA) is a severe X-linked developmental and epileptic encephalopathy. Seizures are often treatment refractory, and patients have intellectual disability and global developmental delay. Previous reports have suggested that patients with PIGA-CDG have a high risk of premature mortality. This study aimed to evaluate the observed high mortality and the causes of death in PIGA-CDG patients.

Methods

We reviewed the literature and collected additional unpublished patients through an international network.

Results

In total, we reviewed the data of 88 patients of whom 30 patients born alive were deceased, and the overall mortality before the age of 20 years was 30% (26/88). Age at death ranged from 15 days to 48 years of life. The median age at death was two years and more than half of the patients deceased in early childhood. The PIGA-specific mortality rate/1000 person-years was 44.9/1000 person-years (95% CI 28.7–70.0). There were no cases of definite or probable Sudden Unexpected Death in Epilepsy (SUDEP) and half of the patients died due to respiratory failure (15/30, 50%) or possible SUDEP (3/30, 10%). Three patients (10%) died from severe cardiomyopathy, liver failure and gastrointestinal bleeding, respectively. The cause of death was unclassified in nine patients (30%). Autopsies were rarely performed and the true cause of death remains unknown for the majority of patients.

Significance

Our data indicate an increased risk of premature death in patients with PIGA-CDG when compared to most monogenic developmental and epileptic encephalopathies.

Highlights

- Patients with PIGA-CDG have a high risk of early mortality.
- Most patients (26/30, 86%) died before the age of 20 years.
- Age at death ranged from 15 days to 48 years of age.
- There were no definite Sudden Unexpected Death in Epilepsy (SUDEP) events and half of the patients died due to respiratory failure (15/30, 50%) or possible SUDEP (3/30, 10%).
- Cardiomyopathy was also a cause of death.
- We identified both an overall and a SUDEP-specific mortality rate in PIGA-CDG patients.

Deciphering the premature mortality in PIGA-CDG – an untold story

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Glossary

CDG = congenital disorder of glycosylation; GDD = global developmental delay; GPI-AP = glycosylphosphatidylinositol anchored protein; PIGA = phosphatidylinositol glycan class A protein; SUDEP = sudden unexpected death in epilepsy

Introduction

Congenital disorders of glycosylation (CDG) are a group of genetic disorders with impaired synthesis and attachment of glycans to glycoproteins and glycolipids, and impaired synthesis of glycosylphosphatidylinositol (GPI)[1]. GPI is a glycolipid that is synthetized and transferred to proteins in the membrane of the endoplasmic reticulum[2]. Biogenesis of GPI anchored proteins (GPI-APs) is a conserved post-translational mechanism in eukaryotes and is important for attaching proteins to the cell membrane and for protein sorting, trafficking, and dynamics[2,3]. It also plays an essential role in embryogenesis, immune responses and neurogenesis[4-6]. GPI synthesis and GPI-anchored protein (GPI-AP) modifications are mediated by at least 31 genes and pathogenic loss-of-function variants in 22 of these genes have been associated with neurological impairments including seizures, global developmental delay (GDD) and multiple congenital anomalies[7] [http://www.iembase.org/nosology/n-browse.asp].

The first step of GPI anchor biosynthesis is catalyzed by PIGA (phosphatidylinositol glycan class A) which is the catalytic subunit of the GPI-N-acetylglucosamine transferase complex. Pathogenic germline variants in *PIGA* are associated with multiple congenital anomalies-hypotonia-seizures syndrome 2 (MIM 316818, MCAHS2) [8-29]. Patients share overlapping features such as epileptic seizures, congenital hypotonia, mild to profound global developmental delay (GDD), intellectual disability (ID), dysmorphic features and multiple congenital malformations[26]. Cardiac anomalies are rare and comprise minor structural abnormalities (e.g. atrial septal defects and valvular defects) cardiomyopathy, and arrhythmias. The only associated pulmonary manifestation described to date is a diaphragmatic hernia found in a single patient[26].

So far 84 live born patients have been published with GDD, seizures, and multiple congenital anomalies due to a hypomorphic germline *PIGA* variants[8-29]. A comprehensive analysis of epilepsy specific data including semiology and classification, degree of GDD, ID and congenital malformations was recently published[26]. All patients experienced epileptic seizures, with a median age of seizure onset at five months (ranging from 1 day – 60 months)[26]. Common seizure types included myoclonic and/or tonic seizures, often with apnea, sometimes evolving to bilateral tonic-clonic seizures[26]. Focal seizures were described in 38%, epileptic spasms in 23%, absences in 8%, atonic seizures in 4%, and gelastic seizures 1% of the patients[26]. Two patients were reported to have migrating focal seizures[26]. Fever-associated seizures were reported in 36% and status epilepticus was seen in 6% of patients[26].

A large number of patients with pathogenic *PIGA* variants die in early childhood[26]. A study clarifying the cause of death and conveying accurate information about the risk of death and potential preventive strategies in these patients is needed. This led us to evaluate the cause of death and to measure the PIGA-CDG specific mortality rate.

Methods

Literature search

We searched MEDLINE (PubMed) with the keywords epilepsy, GPI, GPI-AP or glycosylphosphatidylinositol-anchored protein in combination with *PIGA* or phosphatidylinositol glycan class A protein (last PubMed search: June 2020). Any relevant references in the assessed articles, which were not found in the MEDLINE search, were further investigated. Only articles written in English and published after 1980 were included to ensure optimal data collection. Only cases with a confirmed molecular diagnosis were included.

Study population

We reviewed all the reported patients with PIGA-CDG. In the literature one stillbirth[13] and two terminated pregnancies have been described[26]. In the case of the stillborn patient the intrauterine death was attributed to a placental abruption[13]. As we only included patients born alive these three cases were not included in our analysis. We also collected data on unpublished patients through an international network of Epilepsy and Genetics departments by asking members of the network if they recalled cases. We included both living and deceased patients.
The included cases entered the study at birth regardless of when the diagnosis of PIGA-CDG was confirmed.
All published cases were followed until time of death or until date of publication where non-deceased cases were censored. All unpublished cases were followed until time of death or June 1st 2020, whichever came first. Follow-up time was calculated as time between entry and exit regardless of date of diagnosis.

Data analysis and statistics

To evaluate the underlying causes of death in PIGA-CDG, we reviewed the patients' medical histories and obtained further details about the causes of death from the authors who initially had reported them. We also reached out to authors who reported patients that were alive at time of publication and requested an update. Feedback was only received for the patients 4, 5, 9, 12, 14 and 23 (confirmation by the authors regarding circumstances surrounding the patient's death).

Sudden unexpected death in epilepsy (SUDEP) was classified according the unified SUDEP classification by Nashef et al.[30]. Definite SUDEP was defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration above 30 minutes or seizures without recovery in between), in which postmortem examination did not reveal a cause of death. Definite SUDEP Plus was used, if a concomitant condition other than epilepsy was identified before or after death, if the death might have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of the terminal event did not prove the concomitant condition to be the cause of death. Probable SUDEP/Probable SUDEP Plus were defined as Definite SUDEP/Definite SUDEP Plus but without an autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death. Possible SUDEP was used when a competing cause of death was present. Near-SUDEP/Near-SUDEP Plus were used when a patient with epilepsy survived resuscitation for more than one hour after a cardiorespiratory arrest that had no structural cause identified after investigation. Not SUDEP was used when a clear cause of death was known. Unclassified cases were defined as cases with incomplete information available whereby it was not possible to classify the cause of death.

Mortality rates were estimated with a Poisson regression model and a Kaplan-Meier survival curve was estimated. All statistics were performed using SAS Enterprise Guide (version 7.1) (SAS Institute Inc., Cary, NC) and RStudio (Version 1.0.153) (RStudio, Inc., Boston, MA).

Ethics

The study was conducted in agreement with the Declaration of Helsinki and approved by the local ethics committees. All previously unpublished probands or, in case of minors, their parents or legal guardians gave informed consent. The clinical information was collected by interviewing families and/or from hospital records of the patients and their family members.

Results

We reviewed 88 live born patients with a pathogenic *PIGA* variant: 84 previously published[26-29] and four unpublished patients. Follow-up time was available for 86 patients and ranged from 15 days to 48 years (median 6 years) and in 78% of the patients the follow-up time was between 0 and 10 years (67/86). Of the included 88 patients, 30 patients were deceased (26 previously published patients[8,10,13,14,16,26] and four unpublished patients).
While the age at death ranged considerably - from 15 days to 48 years of life - half of the patients (15) died within the first two years of life (figure 1). In comparison, non-deceased patients were followed between 15 days and 11 years (median 6 years). In total, 18 patients died before the age of four years, including seven patients before the age of three months, two patients died respectively at the age of seven and eight years, six teenagers at the age of 12, 14, 15, 16 and 19 years and four adults at the age of 26, 33, 46 and 48 years (figure 1). Patients 2, 4, 5, and 20 were lost to follow-up, and consequently could not contribute to our knowledge on the cause of death. Therefore, the cause of death remained unclassified in 30%, while in 60% of all patients, death was either due to respiratory failure (15/30, 50%) or possible SUDEP (3/30, 10%), i.e. patients who died suddenly and unexpectedly, but where a competing cause of death was present. Almost all cases with respiratory failure or possible SUDEP occurred in infancy and we found that two out of three possible SUDEP cases (67%) occurred during the first year of life (figure 1). The clinical data of each patient are summarized in Table 1 and the cause of death is described below:

Patients 1, 9, 12-16, 21-24, and 26-29 died from respiratory difficulties. All patients had a severe to profound GDD and refractory epilepsy. Patient 1 had an intractable epilepsy and died at the age of two years. Patient 9 suffered from progressive respiratory problems due to hypotonia and autonomic dysregulation. At the age of 2.5 years he experienced apnea-induced asystole and required resuscitation, dying from cardiac arrest several hours later[14]. No further data were available. Patients 12-16, and 20 had an intractable epilepsy and all died within the first 3 years of life. Patient 14 was alive when initially published by Kato et al.[10] but died at the age of 21 months due to a pneumonia. Patient 22 died of respiratory failure at 33 years of age. Patient 23 was known to have a ventricular hypertrophy and an atrioventricular block. He died at the age of 3.4 years[16]. An autopsy was not conducted. According to the corresponding author, the patient had a pneumonia and multi-organ failure leading to the cardiac arrest. Patient 24 died of aspiration pneumonia at seven years of age[15]. Patients 26 and 27 were the first patients described in the literature with PIGA-CDG[8]. Both sibs had early infantile epileptic encephalopathy (Ohtahara syndrome) and both died around three months of age due to respiratory failure. Autopsies were not conducted, and we were unable to obtain further data. Patients 28 and 29 were described in 2015 by Fauth et al.[13]. Both patients had intractable epilepsy with neonatal onset. Patient 28 was diagnosed

with an early infantile epileptic encephalopathy (Ohtahara syndrome) and died at age 15 days due to respiratory insufficiency after extubation. We obtained additional data on patient 29. He suffered from a profound GDD, intractable epilepsy and had recurrent pneumonia. He died at the age of three months due to respiratory failure following a pneumonia. There was no neurological deterioration prior to his death.

Patients 6, 10, and 11 died suddenly and unexpectedly at home. Patient 6 suffered from profound GDD and refractory epilepsy. He died at the age of 12 years. Patients 10 and 11 had refractory epilepsy but the degree of neurological impairment and the cause of death were not described in the publication[20]. According to the corresponding author both patients died at home at two months of age. No further data were available. These three patients were classified as possible SUDEP.

Patients 3 died from gastrointestinal bleeding. He suffered from a severe GDD and refractory epilepsy and died of a bleeding gastric ulcer at the age of 26 years.

Patient 7, who in spite of an otherwise attenuated neurological phenotype compared with the other deceased patients, developed severe cardiomyopathy contributing to premature death at age 19. Patient 25 was also diagnosed with a cardiomyopathy (ventricular hypertrophy) in addition to the profound GDD and refractory epilepsy. His condition was described to worsen progressively[15], although it is not clear whether he also had neurological deterioration. He died of liver failure at 16 years of age. It was not possible to obtain further data.

The cause of death in patient 2, 4, 5, 8, 17-20, and 30 remained unclassified. Patients 2, 4, 5, 8, 17, and 30 suffered from a severe-profound GDD and six of them had refractory epilepsy[23]. No further information was available. The time of death was known in all nine patients, but the precise cause of death remains unknown.

We have previously published a large cohort of patients with pathogenic *PIGA* (NM_002641.3) variants. 42 different variant sites emerged: 34 missense variants, 4 splice site variants, and 4 truncating variants[26]. Amongst the deceased patients 16 different variant sites emerged (table 1): 12 missense variants (17 patients), 3 splice site variants (nine patients) and 1 truncating variant (four patients). The four most common variants (c.-63+1G>A, c.356G>A; p.(R119Q) , c.849-5A>G, and c.1234C>T; p.(R414*)) were found in 53% (16/30) of the deceased cases. The variants c.356G>A; p.(R119Q) and c.1234C>T; p.(R414*) were observed in 70% (7/10) of the children who died within the first year of life. All four deceased children with the c.1234C>T; p.(R414*) variant site died of respiratory failure, while the cause of death in the deceased children with the c.356G>A; p.(R119Q) variant site was respiratory failure in two cases and possible SUDEP in two cases. Our data suggest that patients with the missense variant c.356G>A; p.(R119Q) in addition to variants causing haploinsufficiency (such as nonsense and splice-site variants) are at the highest risk of a premature death. According to the literature eight patients have been published with the p.(R119Q) variant[29] and in addition we identified a new patient (patient 16). Four of the nine patients (44%) died during the first three years of life (table 1)[26]. A detailed overview of the seizure classification and semiology has been previously published[26].

The *PIGA* mortality rate, calculated over a total of 669 person-years was 44.9/1000 person-years (95% CI 28.7–70.0). In the present study, the autopsy rate was 6%, no cases of definite or probable SUDEP or death due to status epilepticus

were identified, and 30% of all deaths were unclassified. The risk of dying from respiratory failure was 22.4/1000 person-years (95% CI 12.5–40.1) while the risk of dying of possible SUDEP was 4.5 (95% CI 2.2–9.2). Three patients (10%) died of severe cardiomyopathy, liver failure and gastrointestinal bleeding, respectively. The probability of survival at three years of follow-up was 80% (95% CI 71%–89%) while the probability of survival at ten years of follow-up was 73% (95% CI 62%–83%) (figure 2).

The phenotypical spectrum in PIGA-CDG ranges from a mild to moderate DD, treatable epilepsy, lack of dysmorphic features, and no organ malformations in the milder end of the spectrum to profound DD/ID, treatment-refractory epilepsy, dysmorphic features, and multi-organ malformations in the most severe end of the spectrum[26]. While 9/88 (10%) patients born alive belonged to the milder end of the spectrum[26-29], only 1/30 deceased patients (3%) belonged to this part of the spectrum. This suggests that deceased patients could typically be allocated to the severe end of the spectrum. The calculated mortality rate ratio between patients with a mild and severe phenotype was estimated to 3.4 (95% CI 0.5–26.3), p-value: 0.23. Although not statistically significant it indicates a more trend towards an increased mortality rate in patients with severe involvement.

Discussion and conclusion

This paper highlights a high early mortality, mainly due to respiratory failure, for PIGA-CDG patients. This should raise awareness amongst pediatricians, child neurologists, epileptologists and geneticists in order to improve healthcare and life expectancy for these patients.

As in other retrospective studies, there are certain potential limitations in the data collection. The first is that 26/30 patients had already been published and that 15/26 published patients came from other research groups (Table 1). Published cases may tend to include more severe and/or novel presentations and may not reflect a representative sample of affected patients. Although exome sequencing is widely available, patients belonging to the milder spectrum of PIGA-CDG may not yet have been offered genetic testing. Since very few of these patients have died so far it is possible that the mortality rate would have been lower if more of them had been detected. As patients with a milder phenotype are expected to live longer, the slope on the Kaplan-Meier survival curve is expected to decrease if more of such cases were included in the study population. Restricting entry to the date of confirmed diagnosis would result in a bias too as potential follow-up time in patients diagnosed late in life would be unused in the analysis thereby increasing the mortality rates and the slope on the Kaplan-Meier survival curve.

The second limitation concerns the obtainment of data from the available literature. We faced the problem of having limited access to clinical data including the cause of death in 9/30 patients. Although we reached out to the corresponding authors almost 30% of cases remained unclassified in regard of the cause of death. When patients die unexpectedly at home without any information regarding the circumstances at death, and an autopsy is not conducted, it may be difficult to classify the cause of death properly. This results in an underestimation of the causes of death and more patients may have died from causes such as SUDEP and cardiomyopathy. Further data on the circumstances of death in these children are needed to clarify the cause of death and convey accurate information about the risk of death and potential preventive strategies.

We compared the mortality of PIGA-CDG to other less multi-organ-system epileptic encephalopathies such as Dravet syndrome, *SCN8A* and *UGP2* but also to other genes in the GPI-anchoring pathway. These are all multi-organ-system epileptic encephalopathies. We found that a mortality rate and a SUDEP rate are available only for a minority of monogenic epilepsies such as Dravet syndrome[31]. Strikingly, our results suggest an almost three times higher mortality rate in PIGA-CDG than in Dravet syndrome (15.84/1000 person-years (98% CI 9.01-27.85))[31] while it may potentially be comparable to other DEEs[32]. This highlights the need for further studies of both mortality and SUDEP rates in DEEs. While the rate of possible SUDEP found in our population was higher than the SUDEP rate in most other epilepsy populations[33], including those with an *SCN8A*-deficiency (2.84/1000-person-years (98% CI 2.81–2.87))[34], it was below what has been found in Dravet syndrome (9.32/1000-person-years (98% CI 4.46-19.45)[31]. The SUDEP rate was based on three cases of possible SUDEP who died at a much earlier age (between two and three months) (figure 1) than observed in other encephalopathies known to pose a high risk of SUDEP: *SCN1A*-related Dravet syndrome[31], *SCN8A*-related DEE[34], and *KCNT1*-related epilepsy in infancy with migrating focal seizures[35]. A limitation to interpreting this finding is that the burden of seizures and the overall neurological status at the time of death was unknown in those three patients. Therefore, it was not possible to ascertain whether death occurred in the context of a severe but stable condition or if these patients had an unstable neurological status contributing to their demise. Due to possible competing causes we chose to classify these patients as possible SUDEP. The SUDEP rate could potentially also have been underestimated due to a high number of unclassified causes of death.

Before comparing the mortality in PIGA-CDG with that in other genes involved in the same pathway one should know that GPI synthesis is a multi-step pathway[7]. In the case of most genes involved, only a small number of patients have been published[7]. The largest cohorts of patients belong to PIGA-, PIGN-, PIGV- and PGAP3-CDG[7]. Although there is a phenotypical overlap including severe-profound DD, congenital hypotonia, and structural organ damage, this does not apply to the premature mortality[38]. One example is the published cohorts of PIGN- and PGAP3-CDG patients. Both encompass around 30 patients, but in published cohorts of PGAP3-CDG and PIGN-CDG patients, the mortality rate was 9% (3/33)[37] and 60% (18/30)[36, 38-41], respectively. One possible explanation is that patients in the severe spectrum of PIGN-CDG have a Fryns syndrome phenotype with major organ damage including a congenital diaphragmatic hernia[41]. Natural history studies are needed to better understand these differences.

The highest risk of premature death in PIGA-CDG was due to respiratory failure, especially during the first three years of life when it was the cause of death in 69% (11/16) of all deaths. As respiratory failure was the most common cause of death and since pulmonary malformations are an uncommon feature of PIGA-CDG, we argue that the severe congenital hypotonia and muscle weakness may play an important role. These are also recurrent features in PIGA-CDG[26] and were present in all patients that died from respiratory failure (table 1). Patients with hypotonia, muscle weakness and a severe to profound motor delay are at risk of respiratory insufficiency but may potentially survive into adolescence and adulthood with optimized supportive care. Furthermore, we did not identify a single genetic variant, but ten different variants, causing death due to respiratory failure.

The three most frequent genetic variants found in the deceased children were c.356G>A; p.(R119Q), c.849-5A>G, and c.1234C>T; (p.R414*) comprising 69% (11/16) of all deaths including 55% (6/11) of all deaths due to respiratory failure. PIGA-CDG arises from a loss-of-function variant and missense variants are expected to produce more gene product than haploinsufficiency variants. Since protein truncating variants or splice-site variants produces little or no gene product one would expect a more severe phenotype. It remains unknown why the c.356G>A; p.(R119Q) variant is frequently associated with a premature death. One possible explanation could be that this particular variant causes more loss of function than other missense variants or that there is a high number of patients with this variant. Functional testing such as western blotting may be useful to further explore this finding.

In a systematic review from 2017, Marques et al.[42] showed that some 20% of CDG exhibit heart disease, which mainly included pericardial effusion, cardiomyopathy, arrhythmias and structural abnormalities. The majority of cardiac malformations in PIGA-CDG are mild encompassing atrio-septal defect, patent foramen ovale, atrial septal aneurysm, bicuspid aorta valve, mildly dilated ascending aorta and first-degree atrio-ventricular block[8,13,14,16]. Interestingly our patient 7 died at home due to a severe cardiomyopathy. This patient was classified as a “developmental encephalopathy plus epilepsy” in addition to a moderate DD and a treatable epilepsy. His death was anticipated following a slow but steady physical decline. Besides the pathogenic *PIGA* variant, no other explanation was found for the cardiomyopathy in this patient. Cardiomyopathy was also diagnosed in patient 25 (previously reported as patient III-10[15] and patient 22 (previously reported as patient II-2[16])), although it was not described as the cause of death. The cardiomyopathy was identified in an autopsy in patient 25, while the procedure was not performed in patient 7 and 23. Therefore it is still unclear,whether and how the cardiomyopathy contributed to death in these two patients. One could speculate that the high and unexplained number of fatalities in PIGA-CDG could be linked to an underlying undetected cardiomyopathy. In several cardiomyopathies, myocardial fibrosis is a substrate for abnormalities in the cardiac conductive system such as ventricular arrhythmias[43]. A review from 2017[44] describing the pulmonary and cardiac autopsy findings in SUDEP patients, reported that focal interstitial myocardial fibroses was identified in approximately 25% of cases. It is also useful to highlight that normal ECG, echocardiography and/or Holter-monitoring do not rule out myocardial fibrosis.

PIGA-CDG has only been known in the past decade but one important question that remains unanswered is why adult/elderly PIGA-CDG patients are not being identified and published. Recent studies examining large cohorts of genetically undiagnosed adults reported no subjects with PIGA-CDG[45-46]. One explanation is that they are no longer suffering from epilepsy and are therefore not being followed up or offered genetic testing. A gloomier explanation could be that they have passed away in childhood and adolescence. Although these limitations do not invalidate our main point, they will pose a challenge also in the study of other developmental and/or epileptic encephalopathies (DEEs). Natural history studies are needed to unravel some of these questions and could be considered in future studies.

Conclusion

Our data highlight a high early mortality, mainly due to respiratory failure, for PIGA patients when compared with most other monogenic developmental and epileptic encephalopathies, including those associated with other the genes involved in the production of the GPI-anchor. This study also emphasizes a need for future natural history studies to better investigate the DEE associated mortality.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Figure legends

Table 1. Causes and circumstances of death in patients with PIGA-CDG.

Figure 1. Early mortality. Age and cause of death are shown for 26 published and four unpublished patients with *PIGA*-deficiency. Age (in years) is the time of demise and is displayed on the x-axis while the y-axis shows the number of patients that have died.

Figure 2. Kaplan-Meier curve of survival probability for the PIGA-CDG cohort.

Caption

Figure 2. Risk of all-cause mortality for the PIGA-CDG patients. The Kaplan-Meier curve shows the risk of death from all causes for the PIGA-CDG patients. The probability of survival at three years of follow-up was 80% (95% CI 71%–89%) while the probability of survival at ten years of follow-up was 73% (95% CI 62%–83%).

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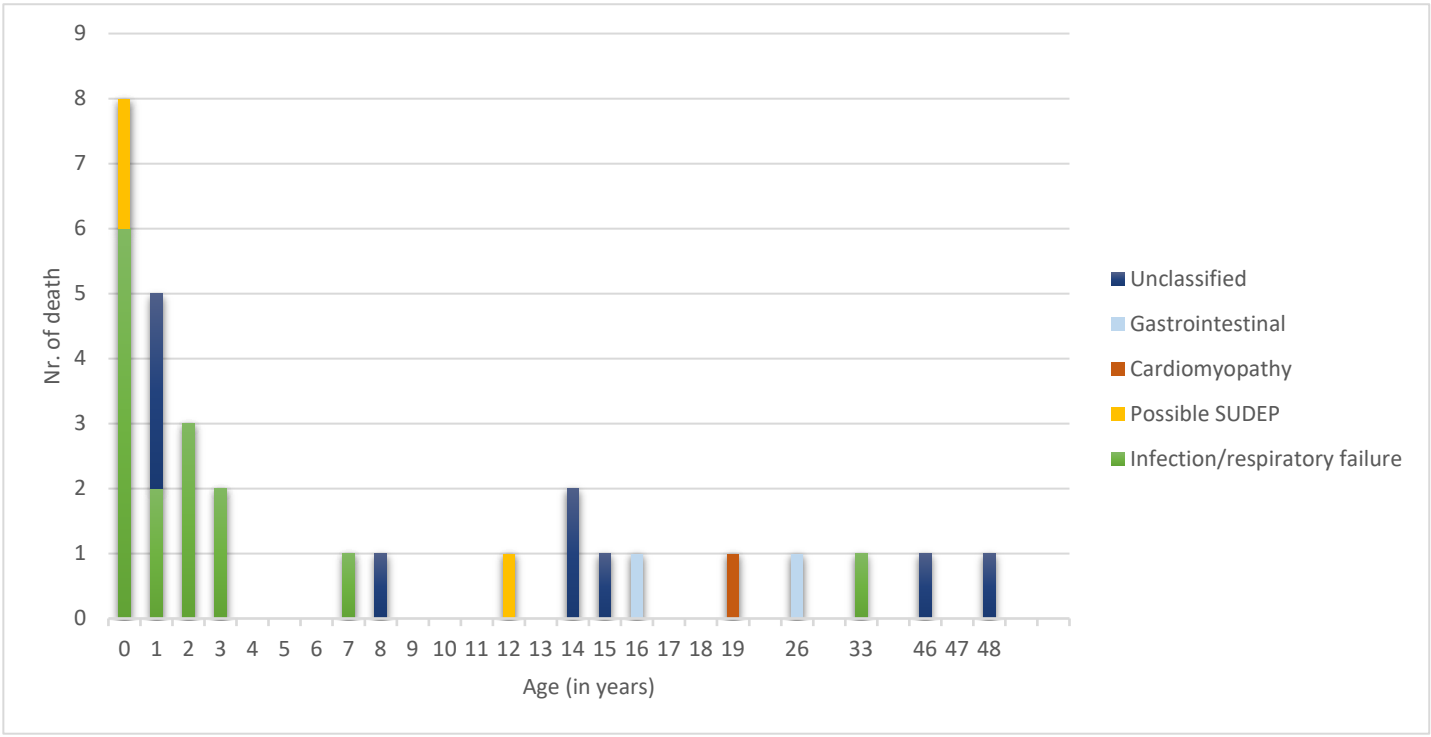
Figure 1. Early mortality. Age and cause of death are shown for 26 published and four unpublished affected subjects with *PIGA*-deficiency. A subjects age (in years) is at time of demise is displayed on the x-axis while the y-axis shows the number of subjects that have died.



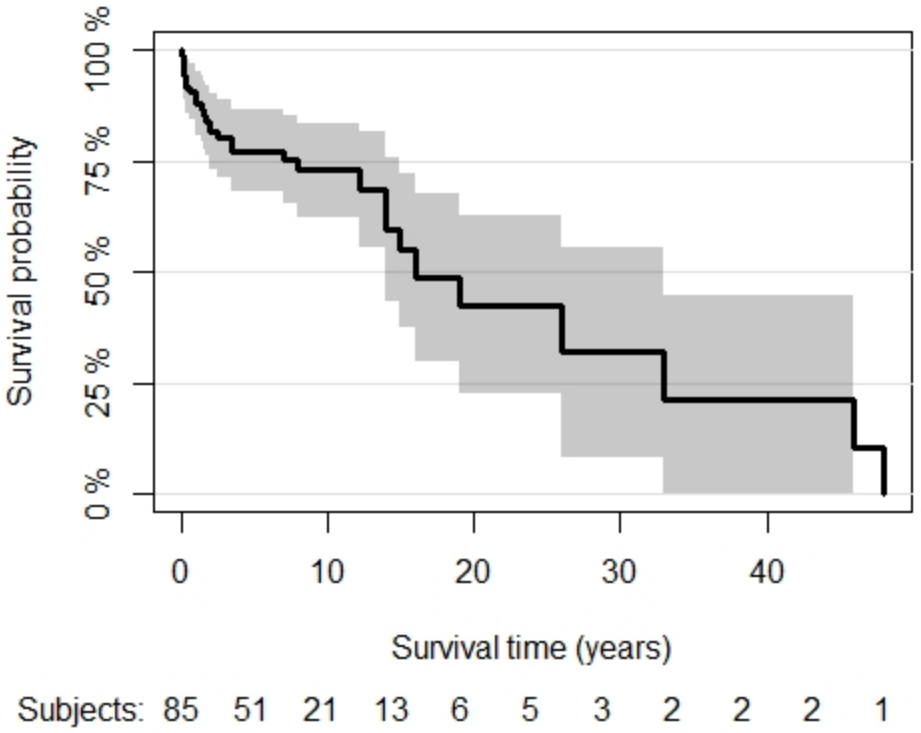

Survival probability
0 %
25 %
50 %
75 %
100 %
0
10
20
30
40
Survival time (years)
Subjects: 85 51 21 13 6 5 3 2 2 2 1

Table 1. Causes and circumstances of death in patients with PIGA-CDG.

	Patient number	Case number of original report	cDNA change	Protein change	Degree of developmental delay	Age at demise	Treatment response	Cause of death	Autopsy performed	SUDEP diagnosis
Bayat et al., 2020	1	P1	c.-63+1G>C	-	Severe	2 years	Intractable	Respiratory failure	No	Not SUDEP
Bayat et al., 2020	2	P3	c.-63+1G>A	-	Severe	48 years	NA	Unknown	No	Unclassified
Bayat et al., 2020	3	P4	c.-63+1G>A	-	Severe	26 years	NA	Bleeding gastric ulcer	No	Not SUDEP
Bayat et al., 2020	4	P5	c.-63+1G>A	-	Severe	46 years	NA	Unknown	No	Unclassified
Bayat et al., 2020	5	P6	c.-63+1G>A	-	Severe	8 years	NA	Unknown	No	Unclassied
Unpublished	6	-	c.145G>A	p.(V49M)	Profound	12 years	Intractable	Unknown. Died suddenly and unexpectedly.	No	Possible SUDEP
Bayat et al., 2020	7	P13	c.242G>A	p.(R81H)	Moderate	19 years	Good	Cardio-myopathy	No	Not SUDEP
Bayat et al., 2020	8	P15	c.248T>C	p.(L83P)	Severe	15 years	Intractable	Unknown	No	Unclassified
Van der Crabben et al., 2013	9	III-1	c.278C>T	p.(P93L)	Profound	2.5 years	Intractable	Respiratory failure	No	Not SUDEP
Lin et al., 2018	10	ZY01	c.356G>A	p.(R119Q)	Profound	2 months	Intractable	Unknown. Died suddenly and unexpectedly	No	Possible SUDEP
Lin et al., 2018	11	ZY04	c.356G>A	p.(R119Q)	NA	2 months	Intractable	Unknown. Died suddenly and unexpectedly	No	Possible SUDEP
Bayat et al., 2020	12	P17	c.356G>A	p.(R119Q)	Profund	3 years	Intractable	Respiratory failure	No	Not SUDEP
Unpublished	13	-	c.356G>A	p.(R119Q)	Severe	12 months	Intractable	Respiratory failure	No	Not SUDEP
Kato et al., 2014	14	P5	c.355C>T	p.(R119W)	Profound	21 months	Intractable	Respiratory failure	Yes	Not SUDEP
Unpublished	15	-	c.391T>C	p.(P131L)	Profound	7 months	Intractable	Respiratory failure	No	Not SUDEP
Unpublished	16	-	c.391T>C	p.(P131L)	Profound	2 years	Intractable	Respiratory failure	No	Not SUDEP
Bayat et al., 2020	17	30	c.565A>G	p.(K189E)	Profound	14 years	Intractable	Unknown	No	Unclassified
Yang et al., 2018	18	III-5	c.849-5A>G	-	NA	1 year	Intractable	Unknown	No	Unclassified
Yang et al., 2018	19	III-10	c.849-5A>G	-	NA	18 months	Intractable	Unknown	No	Unclassified

Yang et al., 2018	20	IV-3	c.849-5A>G	-	NA	17 months	Intractable	Unknown	No	Unclassified
Yang et al., 2018	21	IV-4	c.849-5A>G	-	Severe to profound	2 months	Intractable	Respiratory failure	No	Not SUDEP
Bayat et al., 2020	22	P33	c.971G>T	p.(C324F)	Profound	33 years	Intractable	Respiratory failure	No	Not SUDEP
Tarailo-Graovac et al., 2015	23	II-2	c.989G>A	p.(S330N)	Profound	3,4 years	Intractable	Pneumonia and multi organ failure leading to cardiac arrest.	No	Not SUDEP
Swoboda et al., 2014	24	III-9	c.1030_1032del	p.(L344Del)	Profound	7 years	Intractable	Respiratory failure	Yes	Not SUDEP
Swoboda et al., 2014	25	III-10	c.1030_1032del	p.(L344Del)	Profound	16 years	Intractable	Liver failure	Yes	Not SUDEP
Johnston et al., 2012	26	IV-2	c.1234C>T	p.(R412*)	NA	3 months	Intractable	Respiratory failure	No	Not SUDEP
Johnston et al., 2012	27	IV-4	c.1234C>T	p.(R412*)	NA	2,5 months	Intractable	Respiratory failure	Yes	Not SUDEP
Fauth et al., 2015	28	P1	c.1234C>T	p.(R412*)	NA	0,5 months	Intractable	Respiratory failure	Yes	Not SUDEP
Fauth et al., 2015	29	P2	c.1234C>T	p.(R412*)	Profound	3 months	Intractable	Respiratory failure	No	Not SUDEP
Bayat et al., 2020	30	P38	c.1352T>C	p.(I451T)	Severe	14 years	Intractable	Unknown	No	Unclassified

Abbreviations:

NA = Not available; SUDEP = Sudden unexpectedly death in epilepsy.