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Pyridoxine-dependent epilepsy (PDE-ALDH7A1) in adulthood: A Dutch pilot study exploring clinical and patient-reported outcomes

L.A. Tseng [a,b], L. Teela [c], M.C. Janssen [d], L.A. Bok [e], M.A.A.P. Willemsen [b,f], R.F. Neuteboom [g], L. Haverman [c], S.M. Gospe Jr [h,i], C.R. Coughlin 2nd [j], C.D.M. van Karnebeek [a,b,k,*]

[a] Department of Pediatrics, Emma Children's Hospital and Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[b] On behalf of United for Metabolic Diseases, Amsterdam, the Netherlands
[c] Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Reproduction and Development, Amsterdam Public Health, Amsterdam, the Netherlands
[d] Department of Internal Medicine, Radboud Centre for Mitochondrial and Metabolic Medicine, Radboud University Medical Center, Nijmegen, Gelderland, the Netherlands
[e] Department of Pediatrics, Máxima Medical Center, Veldhoven, the Netherlands
[f] Department of Pediatric Neurology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, the Netherlands
[g] Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands
[h] Departments of Neurology and Pediatrics, University of Washington, Seattle, WA, USA
[i] Department of Pediatrics, Duke University, Durham, NC, USA
[j] Section of Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[k] Department of Human Genetics, Amsterdam Reproduction and Development, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Background: Little is known about pyridoxine-dependent epilepsy due to α-aminoadipic semialdehyde dehydrogenase deficiency (PDE-ALDH7A1) in adulthood, as the genetic basis of the disorder has only been elucidated 15 years ago. This creates a knowledge gap for physicians, pediatric patients and their parents, which was aimed to address in this study using clinical data as well as patient-reported outcome measures (PROMs) for the patient's perspective.
Methods: Dutch, genetically confirmed PDE-ALDH7A1 patients ≥18 years were eligible for inclusion. Clinical data were collected as well as PROMs (PROMIS item banks Anxiety, Depression, Anger, Physical Functioning, Cognitive Functioning, Cognitive Abilities, Ability to Participate and Satisfaction with Social Roles).
Results: Ten out of 11 patients agreed to participate (91% response rate). Seizure control at last follow up (median age 25.2 years, range 17.8–29.8 years) was achieved with pyridoxine monotherapy in 70%, 20% with adjunct common-anti epileptic drugs and 10% did not obtain complete seizure control. Neurologic symptoms were present in all but one patient (90%) and included tremors, noted in 40%. Neuro-imaging abnormalities were present in 80%. Intellectual disability was present in 70%. One patient (10%) attended university, three maintained a job without assistance, five maintained a job with assistance or attended social daycare, and one patient never followed regular education. The cohort scored significantly lower on the PROMIS Cognitive Functioning compared to the general (age-related) population. Distribution of scores was wide on all PROMIS item banks.
Discussion & conclusion: Outcomes of this young adult cohort are heterogeneous and individualized approaches are therefore needed. Long-term seizure control with pyridoxine was achieved for almost all patients. Neurologic symptoms were noted in the majority, including tremors, as well as neuro-imaging abnormalities and intellectual disability, additionally reflected by the PROMIS Cognitive Functioning. PDE-ALDH7A1 patients scored comparable to the general population on all other PROMs, especially regarding Ability to Participate and Satisfaction with Social Roles this may indicate a positive interpretation of their functioning. The aim is to expand this pilot study to larger populations to obtain more solid data, and to advance the use of PROMs to engage patients in research and provide the opportunity for personalized care.

* Corresponding author at: Department of Pediatrics, Emma Children's Hospital, Room H7-254, Location AMC, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
E-mail address: c.d.vankarnebeek@amsterdamumc.nl (C.D.M. van Karnebeek).

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1. Introduction

Little is known about the clinical outcome of pyridoxine-dependent epilepsy due to α-aminoadipic semialdehyde (α-AASA) dehydrogenase deficiency (EC 1.2.1.31; PDE-ALDH7A1) in adulthood. This creates a difficult situation in the pediatric clinic, as parents' and families' questions regarding the future of their child cannot be properly answered. PDE-ALDH7A1 is a disorder of lysine catabolism, where the deficient enzyme α-AASA dehydrogenase causes an accumulation of several diagnostic biomarkers such as pipecolic acid, α-AASA and piperideine-6-carboxylate, which leads to inactivation of pyridoxal-5-phospate, a co-factor for more than 140 enzymes in the body [1,2]. This secondary PLP depletion causes seizures, which can be controlled with high doses of pyridoxine. However, more than 75% of patients suffer an intellectual developmental disorder and other neurologic and behavioral symptoms. Brain abnormalities and systemic and non-specific symptoms are frequent [1,3–5] A neurodegenerative course during childhood has also been observed but the adult course remains unclear [6,7]. Later presentations are atypical, less known and thus poorly recognized, despite the availability of named biomarkers.

Although initially described over 60 years ago, the natural history from adolescence to adulthood is still relatively unknown [8]. Until the elucidation of the genetic and biochemical basis in 2006 [1], the diagnosis of PDE was only made clinically, based on intractable neonatal seizures responding only to pyridoxine [9]. Since then, it has become easier to diagnose this disorder, leading to a relatively large, currently pediatric population. Also, until recently, etiologic evaluations for rare disease phenotypes were often less rigorous in adult than pediatric patients. The advent of exome sequencing has changed this and now rare disease diagnoses, such as PDE-ALDH7A1, are also made in atypical and adult phenotypes. Finally, PDE-ALDH7A1 patients in adulthood may get lost to follow up due to the fact that seizures are often well controlled with low doses of pyridoxine [10], not requiring any changes in management for years, or due to transition into adult care. This is especially untoward given the therapeutic options for this condition, which include lysine reduction therapies. A lysine-restricted diet reduces substrate intake thus lowering the accumulation of neurotoxic metabolites [11]. However, adherence to this diet may be challenging when patients are not used to this diet from a young age. Another lysine reduction therapy is arginine supplementation, which competes with lysine for transportation over the blood-brain-barrier, thus lowering lysine and neurotoxic metabolites [12]. Lysine restricted therapies have mainly been studied in pediatric patients where they can improve neurodevelopmental outcome [4,11,13]. What the effect of these therapies is in adult patients is yet unclear.

To address this highly relevant knowledge gap of adult outcomes in PDE-ALDH7A1, we collected clinical data and performed a pilot study using patient-reported outcomes measurements (PROMs) for adult patients with PDE-ALDHA1 in the Netherlands. We have focused on their epilepsy and neurocognitive status, the occurrence of other neurologic symptoms, neuro-imaging and treatment. To gain insight in the patients' perspectives on their wellbeing, we have collected PROMs using Patient-reported Outcomes Measurement Instruments System (PROMIS®) [14]. The advantage of PROMIS is that it focusses on person-centered measures with regards to mental, social and physical health, by using Item Response Theory (IRT), where difficulty and varying power of items are taken into account when a domain score is calculated. An advantage of IRT is the use of computer adaptive testing (CAT), which presents questions based on their previous answers. This way, the questions better adapt to the abilities of the candidate, which leads to a reduced questionnaire burden [14,15].

2. Methods

2.1. Patients & procedures

Patients living in the Netherlands with molecularly confirmed PDE-ALDH7A1 and age $\geq$ 18 years were approached between February 2021 and July 2021 to participate in this study. These patients have been previously described in literature (Table 1). Patients were approached by their treating physician for participation in this study. If patients and/or parents/caregivers agreed to participate, they received personal log in codes to access the questionnaires on a PDE specific research website (www.pde.hetklikt.nu), and consent was obtained prior to the start of the questionnaires. This study was approved by the Medical Ethical Committee of the Amsterdam UMC, location AMC (W20_364 # 20.404). Data were processed in a de-identified manner. For patients with intellectual disability, parents/caregivers of the patient were asked to complete the questionnaires 'by proxy'.

2.2. Clinical outcomes

2.2.1. PDE registry

Clinical data of the Dutch PDE-ALDH7A1 patients are stored in the international PDE registry, an online accessible REDCap database, including data on mutation analysis, clinical history, specified seizure onset (age in days), therapeutic delay (days), age and seizure control at last follow up, use of additional anti-epileptic medications, neurologic symptoms, magnetic resonance imaging (MRI) results, formal neurodevelopmental test results and behavioral abnormalities. The PDE Registry was approved by the UBC Children's and Women's Research Ethics Board of the Children's & Women's Health Centre of British Columbia (H14-01832). The Medical Ethical Committee of the Máxima Medisch Centrum, Veldhoven (METC 2014-69) approved the PDE registry study, which was subsequently approved by the Medical Ethical Committee of the Amsterdam UMC.

2.3. Measures

2.3.1. PDE-questionnaire

A self-conducted PDE-ALDH7A1 specific questionnaire was administered to collect additional clinical data and consisted of dichotomous, multiple choice and free-response format questions with regards to demography (gender, current age), disease onset (seizure onset, start treatment, diagnosis), current treatment (pyridoxine, adjunct lysine reduction therapies, dosages), highest obtained level of education and current occupation. Level of education was categorized based on the Dutch comparison of the International Standard Classification of Education (ISCED) 2011: lower education (until lower secondary education), intermediate education (upper secondary and post-secondary non-tertiary) or tertiary education (short cycle tertiary until doctoral or equivalent) [16].

2.3.2. PROMIS

Seven Dutch versions of PROMIS instruments were administered. Four item banks were administered as CAT: CAT v2.0 - Physical Function (e.g., are you able to exercise for an hour?), CAT v1.0 - Anxiety (e.g., I felt anxious), CAT v1.0 – Depression (e.g., I felt helpless) and CAT v2.0 - Satisfaction with Social roles & Activities (e.g., I am satisfied with my current level of family activities). For three item banks, a CAT was not available and short forms were provided: SF v1.1 – Anger 5a (e.g., When I was frustrated, I let it show), SF v2.0 - Cognitive Function (e.g., I have trouble forming thoughts) and SF v2.0 - Cognitive Function Abilities (e.g., I have been able to think clearly). PROMIS instruments use a recall-period of seven days and are scored via a five-point Likert scale (e.g., 'never'- 'always'). Additionally, one item regarding Ability to Participate in Social Roles and Activities (Global09) was included from the PROMIS Global Health (e.g., In general, please rate how well you carry

Table 1
Overview of clinical characteristics of PDE-ALDH7A1 adult patients.

Case	1*	2*	3	4	5	6	7	8	9	10
Literature	10, 19–21	10, 19–22	10, 19–22	10, 19–22	10, 19–26	10, 19–22	10, 19–22	10, 19–22		27
Gender	Female	Female	Female	Female	Male	Female	Male	Female	Male	Male
Mutation analysis	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.834G>A; c.834G>A	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.834G>A; c.1432 T>A (p. Cys478Ser)	c.1279G>C (pGlu427Gln); c.1279G>C (p. Glu427Gln)	c.1483G>A p. (Ala495Thr); c.1483G>A p. (Ala495Thr)
Clinical history	prematurity (35 + 6), asphyxia, strabismus	None	Pes planus, scoliosis	Strabismus requiring surgery	Pes planus	Pes planus, vitamin B12 deficiency after gastritis	Premature birth (35 + 5) with asphyxia, metabolic acidosis, liver/kidneyfailure, respiratory insufficiency and lung bleeding. At age six months he had a hydrocephalus requiring ventriculostomy. Strabismus requiring surgery	unilateral cataract, carpal tunnel syndrome, vitamin B12 deficiency, neuralgia back and legs; MRI worn down vertebral discs	At age 5 months he had his first VP-shunt, which was removed two months later because of an infection. At 10y a progressive hydrocephalus was requiring VP-shunt.	possible asphyxia at birth, hypogonadotropic hypogonadism
Presentation										
Seizure onset	0 d	2 d	1 d	4 d	9 d	0 d	0 d	5 months	128 days, after vaccination	15 d
Pyridoxine delay	4 d	7 d	2 d	3 d	0d	116 d	3 d	30 days	9 days	16 years
Treatment										
Current type of treatment	pyridoxine monotherapy (50 mg)	pyridoxine monotherapy (50 mg)	pyridoxine monotherapy (150 mg)	pyridoxine monotherapy (200 mg)	pyridoxine monotherapy (60 mg)	pyridoxine monotherapy (100 mg)	pyridoxine monotherapy (200 mg)	Pyridoxine (100 mg) + arginine supplementation	pyridoxine monotherapy (200 mg) + risperidone + levetiracetam	pyridoxine 200 mg + valproic acid
Neurology										
age at last follow up	27.9y	29.8y	18y	19y	25.2y	28.5y	23.3 y	28.2y	17.8y	19.9y
Seizure history	breakthrough seizures as a child	breakthrough seizures as a child	no seizures since start pyridoxine	no seizures since start pyridoxine	no seizures since start pyridoxine	no seizures since start pyridoxine	no seizures since start pyridoxine	no seizures since start pyridoxine	unclear, potential abscence-like periods. No fulminant seizures for years	no seizures since start pyridoxine
Neurological assessment	Intellectual disability. Cerebral palsy, insecure movements	Problems with longer periods of concentration and automation, delayed processing speed. No motor abnormalities.	Intellectual disability. Mildly abnormal coordination, normal muscle tone	Psychomotor delay, learning disability. No spasticity	No cognitive issues. Walking in straight line sometimes bit wobbly. Tremor both hands, sometimes uncontrollable	Verbally a bit slow, has to think hard	Intellectual disability. Mild dysarthria, divergent eye stand. Abnormal fine motor function. Coordination mildly abnormal. Mild tremor of hands	Normal	Severe intellectual disability and autism. Speaks some single words, and uses sounds for communication. Hands/arms: tremor disturbing eating and drinking. Is able to walk around without major motor abnormalities. Severe autism prevents further formal exam	Intellectual disability. Tremor of hands

(*continued on next page*)

Table 1 (*continued*)

Case	1*	2*	3	4	5	6	7	8	9	10
MRI (age)	corpus callosum anomaly, cortical injury of sulcus centralis, left ventriculomegaly, white matter abnormalities (8y)	white matter abnormalities (16y)	corpus callosum anomaly, white matter abnormalities (11y)	corpus callosum anomaly, hyperintensity globus pallidus, ventriculomegaly (0.5y)	corpus callosum anomaly, mega cisterna magna, ventriculomegaly (12y)	normal (0.5y)	third ventriculostomy, 1y corpus callosum anomaly, left cerebellar and caudal vermis hypoplasia, ventriculomegaly (0.5y)	normal (15y)	CT cyst fourth ventricle. Ventriculomegaly after VP shunt was removed (0.8y)	changes due to prolonged seizures, possibly reflecting meningitis (16y)
Neurodevelopment										
Last formal neurodev test (age)	WPPSI (12.5y)	WISC-R (12.5y)	WISC-III (12y)	Son-R (5y)	WISC-III (12.5y)	WISC-III (17y)	SON-R (7y)	WISC-III (17y)	unknown	Weschler non verbal (15y)
FSIQ (VIQ; PIQ)	Developmental age 5.5-6y. Verbal 7y. Previous IQ <50 (9y)	77(80;78)	53 (unk;unk)	IQ <50, reference age of 2y	106 (114;96)	71 (72;76)	developmental level of 3:10y	86 (91;84)	IQ < 50	55
Behavioral abnormalities	Autistic traits	None	None	None	None	None	None	None	severe autism	Behavioral problems (not specified), concentration problems, not adequately responding to answers
Highest educational level	Lower	intermediate	Lower	Lower	tertiary	intermediate	Lower	intermediate	never followed regular education or obtained an educational level	Lower
Occupation	Social day care	Maintains a job without assistance	Social day care; job with assistance	Job with assistance	In university	Maintains a job without assistance	Job with assistance	Maintains a job without assistance	Social day care	Job with assistance
General comments	siblings	siblings							Older sibling (brother) died in the first week of life due to an unexplained incident necessitating resuscitation.	refugee, medical history from before age 14y limited
PROMIS										
Age PROMs completed by who	28.1y parent	30y self	18.2y parent	19.6y parent	25.7y self	28.5y Together with parent	23.3y parent	28.5y self	18y parent	19.9y Parent with social worker

*= siblings, CT = computed tomography, FSIQ = full-scale intelligence quotient, MRI = magnetic resonance imaging, mg = milligram, PIQ = performance IQ, PROMs = patient-reported outcomes measurements, PROMIS = Patient-reported Outcomes Measurement Instruments System, VIQ = verbal IQ, y = year.

out your usual activities and roles). Total scores were calculated by transforming item scores into a T-sore ranging from 0 to 100, with higher scores represent more of the construct. Scores of all patients as a group were compared to validated scores of the Dutch population (age 18–30 years, available for PROMIS anxiety, depression, physical functioning and Satisfaction with Social roles and Activities; age ≥ 18 years for Global Health; Global09 (personal communication C.B. Terwee, June 18, 2021 and August 26, 2021), or to validated scores of the US population (age 18–34 years; PROMIS anger, age > 18 years for cognitive functioning and cognitive functioning abilities) [15,17]. Symptoms were scored mild, moderate or severe when scores were deviant 0.5 SD, 1.0 SD or 2.0 SD respectively compared to the mean of the norm score. This scoring was relevant for all PROMIS except for Satisfaction with Social Roles & Activities, which uses a scale that ranges from very low to very high. Scores ±1.0 SD from the mean are considered average, ±1.0 SD to 2.0 SD from the mean is low or high, and scores ± more than 2.0 SD from the mean is very low/very high [15,18].

2.4. Statistical analysis

Analyses were performed using IBM SPSS statistics 26.0. Descriptive statistics were used to describe the characteristics of the cohort. In case of non-normality, median and interquartile ranges were provided. Comparison of sample scores with mean norm data was performed using one-sample *t*-tests. A *p*-value ≤ 0.01 was considered as statistically significant. A lower threshold was used as we did not correct for multiple testing.

3. Results

3.1. Patient characteristics & clinical outcomes

At the time of this study, 30 PDE-ALDH7A1 patients were known in the Netherlands, of which 11 were ≥18 years of age. One adult patient did not respond to the invitation, while ten agreed to participate (response rate of 91%).

Six patients (60%) were female and seven patients (70%) harbored the homozygous common Dutch founder mutation c.1279G>C (p.Glu427Gln). Neonatal seizure onset occurred in eight patients (80%), the onset of the remaining two patients was at 4 and 5 months of age. The median therapeutic delay was 5.5 days (IQR 48.8 days, range 0–16 years). All patients were treated with pyridoxine (range 50 mg/day – 200 mg/day). One patient was treated with adjunct arginine supplementation, two patients with adjunct common anti-epileptic medications and one patient was on risperidone for behavioral problems. Patient characteristics are provided in Table 1.

3.1.1. Seizures status and neurologic status

Clinical outcomes of all included patients are additionally provided in Table 1. All patients were seizure free at last follow up (median age 25.2 years, IQR 9.4 years, range 17.8–29.8 years). 20% had breakthrough seizures as a child. Since the introduction of pyridoxine, seven patients have been seizure free, two patients obtained complete seizure control with adjunct common epileptic drugs and one patient had persistent recurrent seizures.

Neurologic status was assessed as normal in one patient (10%). Abnormal motor function was noted in 6/10 (60%) with hand/arm tremors present in 4/10 patients (40%). Cerebral palsy was reported in one patient (10%). Coordination problems were reported in three patients (30%).

Neuro-imaging was abnormal in 80%. Corpus callosum anomalies and ventriculomegaly were noted in 50%, white matter abnormalities in 30% and other abnormalities in 60%.

3.1.2. Neurodevelopmental outcomes

Intellectual disability or cognitive function abnormalities was noted in seven patients (70%). All patients had a formal developmental test at pediatric age (median age 12.5y, IQR 6.5y). For nine patients (90%) a full-scale intelligence quotient (FSIQ) was provided, which was <85 in 7 patients (78%). Three patients had an IQ <50 (33%). The mean IQ score was 66 points (SD 20, range 50–106). Behavioral abnormalities were present in 3/10 patients (30%) and included severe autism, autistic traits and unspecified behavioral and concentration problems.

3.1.3. Level of education and occupation

One patient (10%) follows tertiary education and goes to university. Three patients (30%) obtained the intermediate level of education and maintained a job without assistance, five patients (50%) obtained the lower level education and either maintained a job with assistance or attended social daycare (daycare service for persons with disabilities). One patient (10%) never followed regular education and attended social daycare.

3.2. PROMIS

Of the ten participating patients, three patients completed the PROMs themselves (30%), one patient completed them together with their parents (10%) and for the remaining six patients their parents completed the questionnaires (60%). For two patients, parents reported that the questions included in the PROMs were not fully applicable to the abilities of their children (case 7 and 9). The median age of the patients at time of completing the PROMs was 24.5 years (IQR 9.25, range 18.0–30.3).

As a group, the PDE-ALDH7A1 adults scored significantly lower on PROMIS Cognitive Functioning (mean T score 38.9, $p = 0.009$). There was no significant difference on the other PROMIS (Table 2). The numbers of deviant scores per PROMIS item bank are listed in Tables 3a and 3b, which shows that on all item banks at least two patients scored in the mild, moderate or severe domains. T-scores of all other PROMIS item banks were widely distributed and are shown in supplementary figs. 1–7.

4. Discussion

In this study, we have focused on PDE-ALDH7A1 in adulthood, not only in terms of clinical outcomes but also on patient-reported outcomes. The high response rate of 91% shows that the adult PDE-ALDH7A1 patients are willing to be involved in research.

4.1. Clinical outcomes

Intellectual disability was present in 78% of this adult cohort, which is comparable to the literature, although a number of our patients has been reported previously [10,21,22]. It should be noted that not having an intellectual disability does not mean PDE-ALDH7A1 patients are

Table 2
Mean scores of PDE-ALDH7A1 adults versus norm scores.

PROMIS	N	Sample mean T score (SD)	Mean T score (SD)	*p*-value
Anxiety	10	56.5 (7.8)	52.1 (9.9)	0.104
Depression	10	49.5 (7.7)	52.1 (9.5)	0.324
Anger	10	50.0 (6.8)	52.4 (10.7)	0.286
Physical functioning	10	47.1 (11.7)	55.57 (9.7)	0.049
Ability participate	10	2.5 (1.3)	3.0 (0.9)	0.244
Satisfaction social roles	10	49.6 (8.2)	48.8 (7.8)	0.752
Cognitive functioning	10	38.9 (10.6)	50.0 (10.0)	0.009*
Cognitive abilities	10	45.9 (9.8)	50.0 (10.0)	0.219

One sample *t*-test ($p < 0.01$).
N = number of patients; SD = standard deviation.
* Significant values.

Table 3a
Number of PDE-ALDH7A1 adults with clinically relevant deviant scores on PROMIS item banks with range normal to severe.

PROMIS	Within normal limits	Mild	Moderate	Severe
Anxiety	6 (60%)	1 (10%)	3 (30%)	
Depression	9 (90%)	–	1 (10%)	
Anger	8 (80%)	–	2 (20%)	
Physical functioning	5 (50%)	2 (20%)	2 (20%)	1 (10%)
Ability participate	5 (50%)	–	2 (20%)	3 (30%)
Cognitive functioning	2 (20%)	1 (10%)	6 (60%)	1 (10%)
Cognitive abilities	4 (40%)	2 (20%)	4 (40%)	

Mild = ± 0.5–1.0 SD from the mean, moderate = ± 1.0 to 2.0 SD from the mean, severe = ± more than 2.0 SD from the mean.

Table 3b
Distribution of scores on PROMIS item banks with range very low – very high.

PROMIS	Very low	Low	Average	High	Very high
Satisfaction with Social roles and Activities	–	2 (20%)	5 (50%)	3 (30%)	–

Very low/very high = ± 2.0 or more SD from the mean, low/high = ± 1.0 to 2.0 SD from the mean.
N = number of patients with deviant scores; SD = standard deviation; value within brackets is percentage of patients with the specific deviant score of the total cohort.

completely unaffected; in a recent study we have shown that 86% of a total cohort of 37 patients was affected when neurodevelopment was clinically assessed extensively over seven domains [26]. Comparably, in our study only one patient was assessed as neurologically normal with an IQ score within one standard deviation of the general population (86 points). Interestingly, the one patient attending university did have neurologic and neuro-imaging abnormalities (case 5). This may indicate that these abnormalities have a limited influence on cognitive outcome. It is unclear why this patient is so cognitively capable; while there was no diagnostic delay in this patient, it has been shown and recently validated that timing of pyridoxine does not have a clear influence on neurodevelopment [21,26] In terms of neurological features in this adult cohort, the relatively high incidence of hand/arm tremors is notable. We hypothesize that as PLP is a cofactor for many enzymatic reactions in the central nervous system, this secondary depletion might also affect enzymes involved in neurotransmitter synthesis which may be related to tremor pathophysiology. For example, an enzyme such as AADC (L-amino acid decarboxylase, EC 4.1.1.28) responsible for the conversion of L-dopa to dopamine. While L-dopa or dopamine levels have not been reported in PDE-ALDH7A1 patients, high levels of 3-*O*-methyldopa, a dopamine precursor, and low levels of homovanilic acid, a downstream metabolite of dopamine, have been noted in cerebrospinal fluid of PDE-ALDH7A1 patients, potentially suggesting an impaired enzyme within that route [28,29]. Another cause of these tremors and other neurologic features may be putative ongoing neurotoxicity of reactive intermediates such as α-AASA or other aldehydes oxidized by PLP, causing oxidative stress [30,31]. Further evaluation of these tremors and other neurologic features, as well as studies focusing on neurotransmitters may create more insights into this pathophysiology. Neuro-imaging was abnormal in 80% of patients. Unfortunately, the majority of these MRI's were from pediatric age. Longitudinal follow-up of MRI's of these patients would be very interesting as ongoing damage has been suggested and noted on neuro-imaging [6,10].

4.2. PROMIS

PDE-ALDH7A1 patients scored significantly lower on PROMIS cognitive functioning, which is in line with the described intellectual disability in this cohort and in PDE-ALDH7A1 in general. Patients did not score significantly lower on other PROMIS, such as participation in daily activities and satisfaction with social roles, which is a positive finding and therefore important to share with pediatric patients and their parents. However, individual differences need to be kept in mind, especially as the distribution of scores was wide on all PROMIS.

4.3. General discussion

The most important finding of this study is the heterogeneity in both clinical and patient-reported outcomes and it remains unclear what causes this heterogeneity in phenotype. The majority of this cohort harbors the Dutch founder mutation, which has been shown to lead to complete inactivity of α-AASA dehydrogenase [1,32,33]. No genotype-phenotype relation has been established, which strongly suggests that there must be other mechanisms attributing to the phenotypic variety in PDE-ALDH7A1 [21,28]. Potential influencers of phenotype may include modifier genes, other genes that can affect the phenotypic expression of the primary locus [34], a second diagnosis (for example in the severely affected patients), epigenetics [35], environmental modifiers [36], brain damage due to seizures influenced by therapeutic delay, or rather a combination of those. The heterogeneity in outcomes and the complexity of disease mechanism shows that not all PDE-ALDH7A1 patients can be treated the same and demands a more personalized medicine approach.

4.3.1. Limitations

There are limitations to this study including its cross-sectional and retrospective design. Due to the relatively young median age of this cohort (25 years) we have not been able to establish a prognosis into advanced adult life. This may be due several reasons, including under-diagnosis, which may have led to patients expiring without pyridoxine treatment. Adult patients with a milder phenotype may still experience (infrequent) recurrent seizures without a diagnosis or adequate treatment. Another possibility may be that diagnosed patients obtain long-term seizure control on stable pyridoxine dosages, which decreases the urge to visit a physician on a regular basis and may have led to loss of follow up. While we were able to include almost all Dutch PDE-ALDH7A1 adults, the sample size is still limited and there may be ascertainment bias present. We aim to internationally expand this study to create greater patient numbers and validate the results generated with this pilot study. Lastly, we may have overestimated the generalizability of the PROMIS instruments and the cognitive function of our adult cohort. For the majority of the patients, their parents have completed the PROMs, which may have introduced bias such as overestimation of the actual burden of their children [37,38]. Intellectual disability is a feature in many IMDs, therefore it is likely that this problem may be encountered not only in PDE-ALDH7A1. PROMs adapted to lower cognitive functions may aid in this, although it will remain challenging below certain IQ scores. However, we were able to create insights in PDE-ALDH7A1 at the young adult age and have provided a baseline starting point from where we can conduct future studies. To evaluate the disease course into advanced adult life, follow up of the clinical features as well as the patient reported outcomes of this cohort is imperative.

4.3.2. Treatment recommendations

Recently established consensus guidelines addressed the management of adult PDE-ALDH7A1 patients. For those with incomplete seizure control, cognitive delay or behavioral abnormalities, adjunct lysine reduction therapies may be initiated and otherwise offered [39]. While subjective improvements have been noted in patients on these adjunct treatments, it is still largely unknown what they can do beyond the pediatric age. Recent studies show a neurocognitive benefit of early treatment initiation, although especially before the age of six months [13,22]. However, it may be that patients still benefit from these therapies at adult age, as in phenylketonuria (PKU) [40]. Dietary restriction is often too burdensome, difficult to start up and adhere to at the adult

age. Therefore, adjunct arginine supplementation is the treatment of choice; recently, three of our adult patients started with this therapy and efficacy will be evaluated. In this current study, all but one patient were treated with pyridoxine monotherapy. These outcomes may be used as baseline for comparison to future studies on adjunct LRT outcomes or other novel therapies.

5. Conclusion

In conclusion, outcomes of this young adult cohort are heterogeneous, emphasizing the phenotypic variety known to PDE-ALDH7A1 and showing the need for individualized care and management. Noteworthy is that in the majority of patients, adequate seizure control has been achieved ever since the introduction of pyridoxine at a young age. Neurologic symptoms are reported in the majority, including tremors, as well neuro-imaging abnormalities and intellectual disability, which is reflected in the patient-reported outcomes. Additional mental, social and physical health PROMs are on average comparable to the general population, albeit that individual scores range widely from normal to severe.

To follow-up on this current study, international collaboration is key to obtain greater patient numbers. PROMIS instruments are accessible online, which facilitates international participation. Parallel to this clinical data collection is ongoing via the PDE registry (www.pdeonline.org). With the use of PROMs, an opportunity is created to engage patients in care and research, and to pave the way for more personalized care with treatment and management tailored to the patient [41].

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2022.100853.

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