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ABSTRACT

Background: Pyridoxine monotherapy in PDE-ALDH7A1 often results in adequate seizure control, but neurodevelopmental outcome varies. Detailed long-term neurological outcome is unknown. Here we present the cognitive and neurological features of the Dutch PDE-ALDH7A1 cohort.
Methods: Neurological outcome was assessed in 24 patients (age 1–26 years); classified as normal, complex minor neurological dysfunction (complex MND) or abnormal. Intelligence quotient (IQ) was derived from standardized IQ tests with five severity levels of intellectual disability (ID). MRI's and treatments were assessed.
Results: Ten patients (42%) showed unremarkable neurological examination, 11 (46%) complex MND, and 3 (12%) cerebral palsy (CP). Minor coordination problems were identified in 17 (71%), fine motor disability in 11 (46%), posture/muscle tone deviancies in 11 (46%) and abnormal reflexes in 8 (33%). Six patients (25%) had an IQ > 85, 7 (29%) borderline, 7 (29%) mild, 3 (13%) moderate, and 1 severe ID. Cerebral ventriculomegaly on MRI was progressive in 11. Three patients showed normal neurologic exam, IQ, and MRI. Eleven patients were treated with pyridoxine only and 13 by additional lysine reduction therapy (LRT). LRT started at age <3 years demonstrated beneficial effect on IQ results in 3 patients.
Discussion: Complex MND and CP occurred more frequently in PDE-ALDH7A1 (46% and 12%) than in general population (7% and 0.2%, Peters et al., 2011, Schaefer et al., 2008). Twenty-five percent had a normal IQ. Although LRT shows potential to improve outcomes, data are heterogeneous in small patient numbers. More research with longer follow-up via the International PDE Registry (www.pdeonline.org) is needed.

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Abbrevations

α-ASAA	aminoadipic semialdehyde
AASS	aminoadipic semialdehyde synthase
CP	cerebral palsy
DQ	developmental quotient
GDD	global developmental delay
ID	intellectual disability
LRD	lysine reduction diet
LRT	lysine reduction therapy
MND	minor neurological dysfunction
nr	number
PA	pipecolic acid
P6C	piperideine-6-carboxylate
PDE	pyridoxine-dependent epilepsy
PLP	pyridoxal 5′-phosphate

1. Introduction

Pyridoxine-dependent epilepsy (PDE-ALDH7A1) is a rare epileptic encephalopathy. Recent estimated incidence based on international genomic data is 1:64.352 births [1]. In the Netherlands, the estimated incidence is around 1:276.000, primarily based on clinical criteria. This would mean that every three years, two children in the Netherlands are born with PDE-ALDH7A1 [2]. PDE-ALDH7A1 classically presents early with seizures at neonatal age (onset <1 month of life), or late with an onset of seizures >1 month [3]. In addition to epileptic seizures, patients can suffer from multiple symptoms, such as irritability, restlessness, crying, and emesis for several hours before clinical seizures [3,4]. Later on, cognitive problems may arise irrespective of severity of epilepsy [5]. Neurological outcome is not known in detail and only case reports have been published [6–11]. Commonly described Magnetic Resonance Imaging (MRI) abnormalities vary from corpus callosum agenesia/hypoplasia, ventriculomegaly, cerebellar hypo- or dysplasia to more unspecific findings [12,13].

PDE-ALDH7A1 is caused by deficient enzyme activity of α-aminoadipic semialdehyde (α-AASA) dehydrogenase or antiquitin, due to autosomal recessive mutations in the *ALDH7A1* gene [14]. As a result, lysine catabolism is impaired which leads to accumulation of intermediates proximal to the deficient enzyme, such as α-AASA and piperideine-6-carboxylate (P6C) which are in equilibrium with one another. P6C inactivates pyridoxal 5′-phosphate (PLP), the active form of pyridoxine [15]. Pyridoxine (vitamin B6) treatment compensates for the PLP deficit and leads, in most patients, to adequate seizure control. However, treatment with pyridoxine does not prevent the accumulation of these neurotoxic intermediates. Despite adequate seizure control by pyridoxine, more than 75% of the patients show global developmental delay (GDD) and/or intellectual disability (ID, intelligence quotient (IQ) < 70). [13]· This is possibly the result of the accumulated neurotoxic intermediates. To overcome this problem, lysine reduction therapy, which includes a lysine- or protein-restricted diet (substrate reduction) and/or arginine supplementation (competitive inhibition of lysine over the blood brain barrier) to the existing pyridoxine supplementation, is recommended for patients who do not have a normal neurocognitive profile [6].

Observational studies of lysine reduction therapies (LRT) in combination with pharmacological doses of pyridoxine have shown variable beneficial effects. These effects include decrease in intermediates pipecolic acid (PA), α-AASA, and P6C; improvement or maintenance of seizure control, subjective developmental improvement, and objective cognitive assessments in many study subjects, but not all [10,12,15–19]. Early initiation of treatment has been postulated beneficial [16]. However, evidence is limited and more studies are needed.

The present cross-sectional study aims to demonstrate the detailed neurological and cognitive outcome and the MRI findings of the brain in patients of the Dutch PDE consortium.

2. Methods

2.1. Subjects

To the clinicians of the Dutch PDE-ALDH7A1 consortium, 28 genetically confirmed PDE-ALDH7A1 patients are currently known. Two siblings died due to therapy-resistant status epilepticus (at 5.2 years and at 3.4 years). Of the remaining 26 patients, two patients were unable to participate due to practical reasons. As a result, 24 patients with PDE-ALDH7A1 were included (age range 1–26 years; separate ages at the time of our study are presented in the column 'Neur' between brackets in Table 1). Thirteen patients were also described previously in the study of Bok et al. [13] (references included in Supplementary Table). The genetic and perinatal data are presented in the same Table. The first column represents the case numbers of the patients (similar in Table 1), to which will be referred in the following paragraphs.

In collaboration with the clinicians of the Dutch PDE-ALDH7A1 consortium, the neurological and neurocognitive examinations were conducted between February 2018 and May 2018. Parents and children older than 12 years of age, when mentally competent, provided written informed consent in accordance with the Declaration of Helsinki. The procedures were approved by the Medical Ethical Committee of the UMCG (METc2016/287). Data were processed in de-identified fashion.

2.2. Measurements

Neurological evaluation consisted of two standardized, age-specific neurological assessments. If the child was between 18 months and 4 years old the neurologic examination of Hempel was performed [20]. The reliability of this examination is satisfactory (κ 0.62–1.00) [21]. If the child was >4 years of age, the examination of Hadders-Algra was used, with a good reliability (κ 0.71–0.83) [22]. The assessments were video recorded and scored "blindly" in retrospect by LKvA, MS, MAMOL, and TK together and by RJL independently. Then, results were pooled and in case of differences discussed until consensus was reached. All test items of the assessments were divided into eight domains of dysfunction: posture and muscle tone, reflexes, involuntary movements, coordination and balance, fine manipulative ability, associated movements, sensory function, and cranial nerve function. Criteria for the presence of a dysfunctional domain were met when multiple signs of dysfunction were present. The neurological results were classified as neurologically normal, complex minor neurological dysfunction (MND) or neurologically abnormal. Prepubertal neurologically normal means: 0, 1 or 2 deviant domains; after the onset of puberty 0 deviant domains or deviancy of the posture and muscle tone domain, the reflexes domain, and/or the involuntary movements domain, i.e. a non-optimal yet normal form of brain function. Prepubertal complex MND means: the presence of more than two deviant domains at childhood; after the onset of puberty deviancy in the coordination domain and/or fine manipulative ability domain [22]. The patients of ≤10 years were considered prepubescent, the others (all ≥13 years) as pubescent or post-pubescent. Complex MND represents a clinically relevant form and can be considered as a distinct form of perinatal acquired brain

Table 1
Overview of treatment, neurological and cognitive outcomes and MRI results of patients with PDE-ALDH7A1.

		Treatment						Outcomes		
Nr	Age at study	Average B6 dose until study[a]	LRD age start - stop	Arginine age start - stop	Arginine dose	Compliance LRD and arginine	Anti seizure medication	Neur *(age)*	IQ/DQ *(age)*	MRI/MRS *(age)*
	years	*mg/kg/d or mg/d*	*years*	*years*	*mg/kg/d*			*years*	*years*	*years*
1	1	11.6**	0	0	150	Good		cMND *(1½)*	72 *(2)*	WMA *(0)*
2	2	9.5**	0-?	1-?	150	Unknown	LVT	A *(2½)*	30 *(2½)*	CCA L-CeP NAA VMe WMA *(½)*
3	3	14.6	0	0	160	Good		N *(3)*	76 *(3)*	SEC VMe *(½)*
4[a]	6	7.4		6	150	Good		N *(6)*	70 *(6)*	CCA MCM VM *(8)*
5	6	12.4	2	3	250	Good		cMND *(6)*	91 *(4)*	S *(1½)* Atr CCA VM *(6)*
6	6	2.9		6	250	Good#		cMND *(6)*	83 *(6)*	CrP *(1)*
7	6	22.3		6	250	Good		cMND *(6)*	56 *(6)*	CCA VMe WMA *(1)*
8	7	7.4	2	4	150	Good		cMND *(7)*	100 *(7)*	CCA VM *(9)*
9	8	4.2	2–4	4-5 + 7-7	150	Moderate		N *(8)*	69 *(8)*	L-HP L-VM L>R-WMA *(7)*
10[a]	8	5.5		8	150	Good		N (8)	107 (8)	N *(10)*
11	8	14.3						N *(8)*	117 *(2½)*	N *(6½)*
12	10	17.4						N *(10)*	62 *(6)*	CCA MCM VM WMA *(4)*
13	13	7.8		11	250	Good		N *(13)*	71 *(12)*	CCA GP VM *(½)*
14[b]	13	6.1		10–12	150	Good	ESM + CBZ	cMND *(13)*	58 *(12)*	CCA Dys *(3)*
15	14	1.8	12–14	12–14	150	Good		N *(14)*	51 *(14)*	L>R-VM *(1)*
16[b]	15	7.4						cMND *(15)*	53 *(12)*	CCA WMA *(11)*
17	16	3.1**					CBZ	cMND *(16*	49 *(5)*	CCA GP VM *(½)*
18	20	200 mg/d						A *(20)*	50 *(7)*	3rd *(½)* CCA L-Ce VM *(1)*
19[c]	23	60 mg/d **						cMND *(22)*	106 *(12)*	CCA MCM VM *(12)*
20[d]	25	50 mg/d						A *(25)*	50 *(12)*	CCA Cort L-VM WMA *(8)*
21	25	100 mg/d						N *(25)*	86 *(20)*	N *(15)*
22	25	100 mg/d						cMND *(25)*	71 *(17)*	N *(½)*
23[c]	25	60 mg/d						N *(25)*	80 *(16)*	CCA *(15)*
24[d]	26	50 mg/d						cMND *(26)*	77 *(13)*	WMA *(16)*

a,b,c,d = siblings; 3rd = third ventriculostomy; A = abnormal outcome; Atr = frontal atrophy; CBZ = carbamazepine; CCA = corpus callosum anomaly; Ce = cerebellar and caudal vermis hypoplasia; CeP = hyperintensity left middle cerebellar peduncle; Cort = cortical injury of sulcus centralis; cMND = complex minor neurological dysfunction; CrP = hyperintensity of cerebral peduncles; Dys = cortical dysplasia; ESM = Ethosuximide; GP = hyperintensity at globus pallidus; HP = hippocampal atrophy with atrophic collateral white matter; L = left; LRD = lysine restricted diet; LVT = levetiracetam; MCM = mega cisterna magna; N = normal outcome; NAA = decreased n-acetylaspartate at MRS; Neur = neurologic outcome; Nr = case number; R = right; S = ventriculoperitoneal shunt; SEC = subependymal cysts; VM = ventriculomegaly; VMe = ventriculomegaly + enlargement of peripheral cerebral spinal fluid spaces; WMA = white matter abnormalities.

[a] Pyridoxine dosages in mg/kg/day for patients below 18 years, in mg/d for patients above 18 years; ** no average known, dose at time of study; #twice a day arginine.

dysfunction, which is likely to be associated with structural abnormalities of the brain [23]. The complex MND findings are reproducible (see the κ mentioned above), yet do not encompass cerebral palsy (CP) features, like a pathologic foot sole response and/or spasticity. Neurologically abnormal implies the presence of a distinct neurological syndrome such as CP, ataxia, and/or dystonia. CP patients were scored using the Gross Motor Function Classification Scale (GMFCS) II, III, IV, and V) [24].

Cognitive and therapeutic data were collected through a questionnaire and interview. Intelligence was assessed with several intelligence tests: the Wechsler Preschool and Primary Scale of Intelligence-Third Edition-Dutch adaptation (WPPSI-III-NL) (n = 8), the Wechsler intelligence scale for children-Third Edition-Dutch adaptation (WISC-III-NL) (n = 9), the Wechsler Preschool and Primary Scale of Intelligence revised (WPPSI-R) (n = 1), the Wechsler Intelligence scale for children revised (WISC-R) (n = 1), and the Snijders-Oomen non-verbal intelligence test (SON-R) (n = 2) [25–29]. Three children were too young for a formal IQ test (one was 1 year and the others 2 years old, nr 1, 2, and 11, Supplementary Table). In two patients (nr 1 and 11) a Bayley Scales of Infant and Toddler Development (BSID)-III NL test was done [30]. The BSID-III NL is a motor score, which correlates with cognitive development. The third patient (nr 2) was scored according to the 'van Wiechen' developmental test which is based on the development of healthy full-term-born children which gives a rough estimation of development [31]. Of course, both the BSID–III–NL and the 'van Wiechen' test are not as precise as formal IQ tests. According to the World Health Organization and DSM-IV criteria, IQ was divided in 5 groups: normal (IQ > 85), borderline intellectual disability (ID) (IQ 71–85), mild ID (IQ 51–70), moderate ID (IQ 36–50), and severe ID (IQ < 36) [32,33].

Biochemical results were collected before and after the start of LRT, if determined. Because we hypothesized that LRT started at younger age may have a more beneficial effect, we selected six patients who started with LRT below the age of three years (nr 1, 2, 3, 5, 8, 9) to analyze in more detail.

The results of routinely performed MRI and MR Spectroscopy (MRS) were considered and reviewed by a neuroradiologist. Results were in line with the radiology reports and/or published data [13].

2.3. International PDE registry

The international PDE registry was established in 2014 by the PDE consortium (www.pdeonline.org) [15]. Study data from the PDE Registry are collected and managed using REDCap electronic data capture tools hosted at British Columbia Children's Research Institute (BCCRI) [34,35]. The international 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) and subsequently by participating partners. For the Netherlands, the study was approved by the Medical Ethical Committee of the Máxima Medisch Centrum, Veldhoven (METC 2014–69). The Medical Ethical Committee of the University Medical Center Groningen and Amsterdam UMC supported this approval. Data on birth history, diagnosis, and treatment of the Dutch PDE-ALDH7A1 patients were collected from the international PDE registry. Therapeutic delay was defined as the time between seizure onset and long-term (minimum of three consecutive months) pyridoxine treatment.

2.4. Data analysis

Descriptive statistical procedures were performed using Statistical Package for the Social Sciences (SPSS), version 25.0. We summarized continuous variables as mean and SD, or median and range. Mann Whitney *U* test was applied for comparison of not normally distributed data and Cohen's kappa for calculation of the interobserver agreement.

3. Results

In the Netherlands, 28 patients with PDE-ALDH7A1 were born between January 1991 and January 2018. According to the Central Agency for Statistics, the total number of live births during this period was 5.088.353 in the Netherlands [36], resulting in a birth incidence of at least 1:181.726 as there may be prenatal death and missed diagnoses. In the present study, 24 PDE-ALDH7A1 patients were enrolled and examined. Nine were male (38%) and 15 female (62%). The majority of patients (n = 14) had the predominant mutation found in the Netherlands, i.e. c.1279G>C (p.Glu427Gln) in homozygosity, formerly known as c.1195G>C (p.Glu399Gln). The other 10 patients had different mutations (see Supplementary Table). All patients presented with seizures, 20 patients (83%) with neonatal seizures, 4 patients (17%, nr 6, 8, 11, 21) with infantile/late onset seizures, defined as beyond 2 months of age [37]. Nr 8 and 11 were presented in the study of de Rooy et al. as well [37]. Perinatally, one patient (nr 9) suffered of intracranial hemorrhage. Four were prematurely born; two of them had an Apgar score at 1 min < 7, one had solely such a low Apgar score (Supplementary Table).

3.1. Pyridoxine and adjunct lysine reduction therapies (LRT)

All patients received pyridoxine treatment. Their daily dose ranged from 50 to 300 mg/day (mean 140.4 mg, SD 69.6) or 0.6 to 16.7 mg/kg/day (mean 5 mg/kg/day, SD 4.1, Table 1). For 21 patients, the last year before the participation in this study, seizures were controlled with pyridoxine therapy with or without LRT. For the remaining three patients, they were seizure free with one or two anti-epileptic drugs added (Table 1).

In Table 1, therapy is described. Eleven patients (46%) had pyridoxine monotherapy and 13 additional (54%) LRT, 6 with (25%) arginine supplementation, 6 (25%) with both lysine-restricted diet (LRD) and arginine, and one with LRD and arginine sequentially. At the age of 4 years, patient nr 9 switched from lysine-restriction to arginine supplementation. Two patients (nr 9 and 14) had stopped arginine supplementation in the year before our study, nevertheless they were included within the adjunct therapy group. The age at initiation of LRT varied from 5 days to 12 years (see column Therapy in Supplementary Table). Reasons to stop lysine restriction were adherence problems (nr 9 and 15) and family's personal opinion that no improvement was noted (nr 14 and 15). For arginine, reasons included bad taste (nr 9, 14, 15) and lack of financial reimbursement (nr 14).

In 10 patients, α-AASA before and after start of LRT were reported. In all patients these α-AASA levels decreased after starting LRT (Table 2). Reduction rates (% decrease from upper limit normal) ranged from 20.0 to 81.8 (mean 63.9). The IQ's of the four patients (nr 3, 4, 8, and 10) with the highest reduction rates, ranged from 70 to 107 and all were neurologically normal except one. Of the two with the lowest reduction rates (nr 5 and 13), their IQ's were 71 and 91; one was neurologically normal and one patient had complex MND.

3.2. Neurological outcome

Of the 24 patients, 10 (42%) were neurologically normal, 11 (46%) showed complex MND, while 3 (12%) were neurologically abnormal (κ 0.75, Tables 1 and 3). Two patients who met the criteria of mild ataxia (according to a scale for the assessment and rating of ataxia [38]) were classified as complex MND; they were not able to walk in tandem but did not experience any inconvenience in daily life (nr 16 and nr 19). One of them also showed a tremor, just like three others (nr 19, 13, 21,23), although specific tremor tests were not done.

In comparison, in the Netherlands 7% of the children at regular primary school show complex MND and 0.2% of the general population CP [39,40]. Of the 3 neurologically abnormal patients, one showed mild unilateral CP, one mild bilateral CP (both GMFCS level II), and the last a severe bilateral, dystonic CP (GMFCS level V) with severe visual problems (nr 2, 18, and 20).

Patient nr 18 and 20 showing mild CP, were born asphyxiated (gestational age 35 + 2 and 35 + 6, respectively) and endured neonatal seizures with prompt cessation after pyridoxine administration. Patient nr 18 also suffered pulmonary hemorrhage and

Table 2
Biochemical data, reduction rate (% decrease from upper limit normal) before and after start of lysine reduction therapies (LRT).

Nr	α-AASA[a] before	α-AASA after	% reduction (mean 63.9)
3	58.0	13.3	77.1
4	8.5	1.7	80.0
5	6.0	4.0	33.3
6	12.4	4.4	64.5
7	Missing	11.1	–
8	20.3	3.7	81.8
9	37.6	11.9	68.4
10	6.2	1.7	72.6
13	135.0	108.0	20.0
14	11.8	3.3	72.0
15	3.3	1.0	69.7

Nr = number identical with the case numbers in Table 1, α-AASA = α-aminoadipic semialdehyde measured in urine in mmol/mol creatinine.

[a] Age related reference ranges for α-AASA in urine: newborn = 0–2 mmol/mol creatinine, <1 years of age = <1 mmol/mol creatinine, >1 year of age = 0–0.5 mmol/mol creatinine.

Table 3
Neurological outcome and dysfunctional domains.

Neurology Domains	Normal (n = 10)	Complex MND (n = 11)	Abnormal (n = 3)	Total
Coord	3 (30%)	11 (100%)	3 (100%)	17
Fma	2 (20%)	6 (55%)	3 (100%)	11
Posture	2 (20%)	6 (55%)	3 (100%)	11
Reflexes	1 (10%)	4 (36%)	3 (100%)	8
Invol mov	1 (10%)	2 (18%)	1 (33%)	4
Assc mov	0	1 (9%)	2 (67%)	3
Cranial n fx	0	1 (9%)	3 (100%)	4
Sens fx	0	1 (9%)	1 (33%)	2

Neurology = neurological outcome; coord = coordination and balance; fma = fine manipulative ability; posture = posture and tone; invol mov = involuntary movements; assc mov = associated movements; cranial n fx = cranial nerve function; sens fx = sensory function.

suffered from hydrocephalus at age 6 months. Patient nr 2 presented with neonatal seizures and suffered a status epilepticus at age 4 ½ months. Twice a thiopental coma was induced. During the first coma, pyridoxine was administrated intravenously without effect. During the second coma, about one week later, elevated α-AASA pointed towards diagnosis of PDE-ALDH7A1 and pyridoxine was continued. The mild CP in two patients was believed, at least in part, to be due to perinatal events. In the third patient, his severe dystonic CP seemed to be related to the intractable status epilepticus. Of the 24 patients, 17 (71%) had minor coordination problems, 11 (46%) had fine manipulative problems, 11 (46%) had posture and muscle tone problems, and 8 (33%) had reflex dysfunction. The other domains were rarely deviant (see Table 3). In 4 (17%) there was macrocephaly and in one child, with dystonic CP, who suffered status epilepticus twice, microcephaly (−3.5 SD, nr 24 in the Supplementary Table). The mean SD for head circumference was plus 0.9 (SD 1,5).

3.3. Imaging results

Of all 24 patients, magnetic resonance imaging (MRI) examinations of the brain were available for review with 14 patients having had at least one follow-up MRI. The MRI's were normal in 4 (17%). The others showed ventriculomegaly (n = 14, 58%, in 3 patients with associated enlargement of the peripheral cerebral spinal fluid spaces), corpus callosum abnormalities (n = 14, 58%), white matter abnormalities (n = 8, 33%), mega cisterna magna (n = 3, 13%), hippocampal atrophy (n = 1, 4%), unilateral cortical damage (n = 1), subependymal cysts (n = 1), caudal vermis and left cerebellar hypoplasia (n = 1), frontal cortical dysplasia (n = 1) or atrophy (n = 1), decreased N-acetylaspartate at magnetic resonance spectroscopy (n = 1), T2 hyperintensity of the globus pallidus (n = 1), the cerebral peduncles (n = 1) or the left middle cerebellar peduncle (n = 1). The 3 most common findings, i.e. ventriculomegaly, corpus callosum abnormalities, and white matter abnormalities, were often present in a combination of 2 or 3 of them (13 of the 19 (68%)).

The mean SD for head circumference was plus 1.5 in the group with ventriculomegaly (n = 13), with the exclusion of patient nr 2. He had a SD of −3.5 and all cerebral spinal fluid spaces were enlarged, assumedly because of cerebral atrophy secondary to prolonged status epilepticus. Twelve of the patients with ventriculomegaly (with or without enlargement of the peripheral cerebral spinal fluid spaces) had at least one follow-up MRI. In 11 patients this ventriculomegaly was progressive with age, in 1 patient (nr 3) not. She was the only patient who started with pyridoxine and LRT at neonatal age. All the others started with LRT at two years of age or later or had no LRT. Two patients (8%, nr 5 and 18) needed ventricular drainage or third ventriculostomy. In both the intervention was performed due to an increasing skull circumference up to 3.5 SD. Six patients had white matter abnormalities and had at least one follow-up MRI. In 5 patients these abnormalities were present at their neonatal MRI and remained stable over time. In 1 patient (nr 2) they appeared at his third MRI at 5 months of age, while he suffered a status epilepticus for the second time. Thereafter, pyridoxine had been started.

3.4. Cognitive outcome

Of 23 patients the IQ scores were collected, for one the DQ (patient nr 2, see Table 1 for all IQ/DQ).

The mean IQ was 72 (SD 22, range 30–117). Cognition was normal (IQ > 85) in 6 patients (25%), borderline ID (IQ 71–85) in 7 patients (29%), mild ID (IQ 51–70) in 7 patients (29%), moderate ID (IQ 36–50) in 3 patients (13%), and severe GDD (DQ < 36) in 1 patient (4%).

3.5. Comparison between neurological and cognitive outcome

Patients with complex MND had a mean IQ of 74 (SD 19) and the neurologically normal group a mean of 79 (SD 20). No significant difference was reached.

Overall, 3 patients were completely normal in terms of cognitive (IQ range 86–107), neurological, and MRI outcome at ages of 8, 8, and 25 years (nr 10, 11, and 21), two were treated with monotherapy, nr 10 started with LRT at the age of 8 years.

3.6. Relation between therapeutic modality and neurological and cognitive outcome

In the mono-therapeutic (i.e. only pyridoxine) group (n = 11), 4 (36%) were neurologically normal, 5 (46%) showed complex MND, and 2 (18%) patients showed CP like features. In the LRT group 6 (46%) were neurologically normal, 6 showed complex MND (46%), and 1 (8%) dystonic CP.

In the mono-therapeutic group mean IQ was 73 (SD 23, range 49–117), in the group with adjunct LRT (n = 13) mean IQ was 71 (SD 21, range 30–117).

We formed three groups: A. patients with LRT started <3 years of age, B. patients with LRT started ≥3 years and C. patients without LRT. We excluded the patients with perinatal adversities (prematurity, Apgar score <7, intracranial hemorrhage) and/or a therapeutic delay >30 days. The remaining patients in these three groups are presented in Fig. 1, regarding their neurocognitive outcome. The size of the circles is an indication of the % of patients (Fig. 1). All patients in group A (patients nr 3, 5, and 8), had an IQ > 70, one of them was also neurologically normal. The outcome in the other groups was more diverse. In more detail, patient nr 8 had a late onset of seizures at 3 months and started with pyridoxine at 3½ months. He suffered a speech delay of several months at the age of 2½ years before introduction of LRT. Four weeks after LRT he spoke sentences of 4–5 words. Patient nr 3 started with both pyridoxine and LRT at neonatal age. She was neurological normal and had an IQ of 76. According to the examiner and a parent she did not perform optimally because of cooperation issues during the evaluation, while at primary school she performs at an average level. All patients of group A showed abnormalities at the MRI.

Two siblings (nr 4 and 10) revealed a subaverage (55) and low normal (87) IQ at ages 4 and 6 years of age. Patient nr 4 had his first seizure only once at the age of 3 years when the pyridoxine was used up and patient nr 10 had neonatal seizures and consequently at 3 months of age, they started with pyridoxine prenatally and at 6

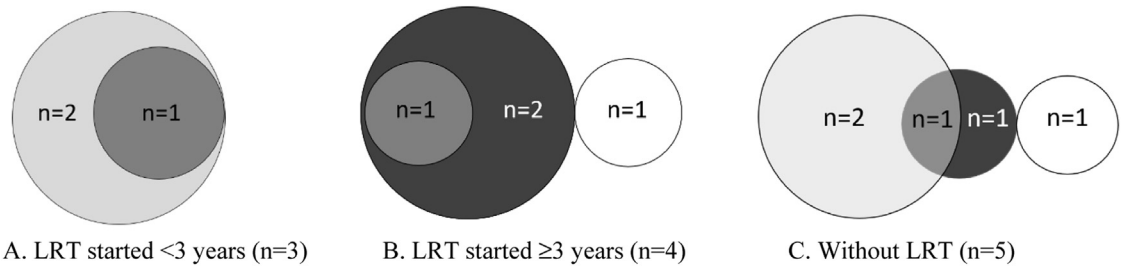

Fig. 1. Patients with PDE-ALDH7A1: A. LRT started <3 years, B. LRT started ≥3 years, or C. without LRT and cognitive and neurological outcome. Patients with neonatal adversities and therapeutic delay were excluded. The size of the circles indicates approximately the percentage of patients within one group. The different shades of gray represent patients with; white: IQ ≤ 70 & complex MND, light gray: IQ > 70 & complex MND, medium gray: IQ > 70 & neurologically normal, dark gray: IQ ≤ 70 & neurologically normal. Complex MND = complex minor neurological dysfunction, IQ = intelligence quotient, LRT = lysine reduction therapies, n=number.

months. After starting LRT, their IQ's improved to 70 and 107; this could also be due to more reliable testing at older age and once a language barrier was overcome. Patient nr 15 was administered LRT for 2½ years. Her IQ before and after 2 years of LRT was exactly the same. However, she was more attentive according to parents and schoolteachers; she stopped LRT after two years because she craved a normal diet and disliked arginine.

4. Discussion

This cross-sectional and retrospective cohort study presents the neurological and cognitive outcomes for our Dutch PDE-ALDH7A1 cohort. We studied 24 patients, their ages ranged from 1 to 26 years. This cohort is clinically quite heterogeneous; however, genotypically, it must be noted that half of our patients harbor the common Dutch founder mutation.

Of the 24 patients, 3 (13%) had normal cognitive (IQ > 85) and neurologic outcome and neuro-imaging; the vast majority suffer the neurocognitive sequelae of this debilitating epilepsy. We discuss our main findings and attempt to relate outcomes to genotype, clinical presentation, diagnostic and therapeutic delays, and initiation of adjunct therapies.

4.1. Neurological outcome

This is the first cohort study focussing on detailed neurological abnormalities in PDE-ALDH7A1 (Table 3). Complex MND or neurological abnormality are present in the majority of our cohort (60% vs 7% of the general Dutch population) [39,40] with almost half of our patients showing complex MND. In PDE literature, similar findings in coordination, fine motor, tone, and reflexes have been reported [6–11].

We propose three possible explanations here:

a) Inactivation of pyridoxal 5′-phosphate (PLP) leading to a pyridoxine deficiency [15]: Pyridoxine is a cofactor to >160 enzymes, most in the CNS, required for the biosynthesis of several neurotransmitters, including dopamine, which is of importance via the nigrostriatal circuitry for the coordination of movements [41,42]. Therefore, lack of pyridoxine may lead to these coordination problems.
b) Epileptic activity generated in PDE, especially at young age: We postulate that this leads to cortical and basal ganglial damage, compromising fine manipulative ability and tone/reflexes, reflecting function of widespread activity in the cerebral cortex and the cerebral cortex, basal ganglia, cerebellum, brainstem and spinal cord, respectively [22,43]. In case of intractable seizures, if pyridoxine introduction is delayed, CP seems to reflect the most severe spectrum (patient nr 2 and Jansen et al.) [44].
c) Ongoing damage by neurotoxic metabolites: We hypothesize that putative toxic intermediates are etiological to the presentation with complex MND at later age. This is corroborated by Dogan et al. who performed a magnetic resonance spectroscopy study, showing persistent decrease in the n-acetylaspartate (NAA)/choline ratio in 1 patient despite pyridoxine treatment [45]. This suggests ongoing neuronal damage. Further substantiation is illustrated by persistent elevated levels of α-AASA, PC6, PA and 2S,6S- and 2S,6R-oxopropylpiperidine-2-carboxylic acid (2-OPP), despite pyridoxine administration [6,15,44,46,47].

Pre-, peri-, and neonatal adversities and neonatal neurological deviancy have been reported as causal factors [23], because of the small numbers we could not correct for this.

We strongly advocate to follow a diagnostic algorithm in case of neonatal seizures of unknown etiology [48,49]. Also, we support the inclusion of this metabolic epilepsy in newborn screening panels; the discovery of reliable biomarkers measurable by tandem Mass Spectroscopy makes this feasible [47].

4.2. Cerebral abnormalities

In this cohort, neuro-imaging revealed abnormalities in 83%, which is more than the 68% (of 19 patients with MRI results) reported by Mills and al [50]. We noted more often ventriculomegaly/hydrocephaly (58% vs 16%), corpus callosum anomalies (58% vs 21%), and white matter abnormalities (33% vs 5%). Mega cisterna magna incidences (13 vs 5%), hemorrhages (4% vs 11%), cerebellar abnormalities (8% vs 11%), and cortical atrophy (4% vs 11%) were rare [50]. In contrast to Mills et al. the MRI's in this study have all been reviewed by one neuroradiologist dedicated to neuroimaging in children. Results changed for 8 out of 11 patients who have been included in both previous literature and this study; therefore, a part seems to be due to misinterpretation. Another study focusing on brain abnormalities in PDE-ALDH7A1 was performed by Toldo et al. However, they only selected patients (n = 60) with PDE-ALDH7A1 mutations associated with brain malformations and excluded patients with normal MRI results [12]. The results of that study are therefore not comparable to ours. In addition, 11 of our subjects have been included in their review, four even twice (for references see Supplementary Table).

Multiple causes may account for the MRI findings: Structural brain abnormalities, such as corpus callosum hypoplasia and cerebellar malformations, may be due to the antiquitin dysfunction early in fetal life of glia cells causing neurogenesis and neuronal

migration abnormalities [44]. In addition, antiquitin is expressed in the choroid plexus and ependyma and is therefore thought to be involved in CSF formation, absorption, and circulation; possibly contributing to ventriculomegaly and hydrocephalus [44]. However, ventriculomegaly may also be caused by increased osmotic pressure, which may be due to the neurodegeneration resulting from the toxic products [51]. This hypothesis may be supported by the stable ventriculomegaly of patient nr 3, who had been on LRT since neonatal age, leading to a decrease in neurotoxic metabolites. She is the only patient showing a stable ventriculomegaly, however the follow-up duration was short, i.e. 5 months. Two patients required CSF drainage due to increased head circumference (up to 3.5SD) without reported clinical signs of increased cerebral pressure, but surprisingly, not all patients with ventriculomegaly had a SD $\geq$ 2 or vice versa. Lastly, epileptic activity may have an effect on these abnormalities [37,52]. This is illustrated by patient nr 2 on whom's MRI white matter abnormalities appeared after a status epilepticus at the age of 5 months.

In conclusion, there may be publication bias and observer bias with interpretation of MRIs of PDE patients. We advise that head circumference growth chart and signs of raised intracranial pressure should be monitored in PDE-ALDH7A1.

4.3. Neurological outcome and cerebral abnormalities

In the neurologically abnormal group of three patients, the MRI findings matched neurologic outcome. Two (nr 2 and 18) had cerebellar deviancies with coordination difficulties. In the total cohort, cerebellar abnormalities were present in 8%. Similar incidences have been noted in literature by Mills et al. and Perez et al. However, those studies did not include neurological outcome [50,53]. In general, coordination problems or other neurological findings in complex MND are not of such clinical significance to be classified as an ataxia (as was similar for two patients in this cohort (nr 16 and 19)) or another neurological diagnosis [22]. We hypothesize that unspecific MRI findings, such as white matter hyperintensities lead to complex MND symptomatology, as is corroborated by a literature review by Peters et al. which concludes that motor impairment without CP is related to white matter abnormalities [54].

To further unravel this, we advise to examine PDE-ALDH7A1 patients neurologically by standardized methods at regular intervals.

4.4. Cognitive outcome

Cognition was normal in 25% of this cohort (one not formally tested). In the other 75%, cognition varied between borderline ID to severe GDD. Our mean IQ of 72 (SD 22) is similar to the literature [13,53]. However, the review of Bok included subjects without genetically confirmed diagnosis and 13 of our subjects [13]. In contrast, in our study 13 patients started adjunct therapies. Even though mean IQ did not change, we do not think that this should mean that LRT is not effective on outcome, as anecdotal and subjective changes have been noted in some of our patients and literature [10,15–19]. The four patients with late onset, performed cognitively better with a mean IQ of 97. This is in line with previously published late onset patients, however two of our patients (out of four total) were in that study as well (see Supplementary Table) [37].

Not surprisingly, all neurologically abnormal patients had low IQ's. As noted earlier, our patient nr 2 and Jansen et al. presented the severe end of the spectrum, showing severe GDD [44]. In contrast, patient nr 10, with a therapeutic delay as well but an IQ of 107, had infrequent seizures which responded immediately to first line anti-seizure drugs. We consolidate the hypothesis that a late onset is positive for cognitive outcome. Neurological deviancy and/or intractable status epilepticus/seizures are unfavourable for cognition. We suggest that a sporadic case with infrequent, tractable seizures might have a good outcome, nevertheless a therapeutic delay.

4.5. Geno-phenotype correlations

For the 14 patients with the Dutch founder mutations, the clinical phenotype varied in cognitive and neurological outcome, however in all patients, MRIs were abnormal, with ventriculomegaly or corpus callosum anomalies in 64%. Mean IQ was slightly lower compared to the group with the other mutations (70 vs 76). Based on the current study, there is no evidence for a clear genotype-phenotype correlation. Previous studies suggested that there are 3 clinical groups 1. patients with complete seizure control with pyridoxine and normal developmental outcome; 2. patients with complete seizure control with pyridoxine but with developmental delay; and 3. patients with persistent seizures despite pyridoxine treatment and with developmental delay [55]. Further research is needed to elucidate this in larger numbers. *In vitro,* residual activity has been shown for missense mutations in a recombinant human antiquitin E.coli while null mutations showed a complete loss of function [56]. However, the assay is not very sensitive, and newer more appropriate models such as neuronal iPSCs are now available to recapitulate the disease and further delineate the impact of specific mutations on ALDH7A1 protein function as well as its downstream effects [57].

4.6. Therapeutic outcomes

Pyridoxine dose was prescribed in a reasonably large range (Table 1). According to the “consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to α-aminoadipic semialdehyde dehydrogenase deficiency”, by Coughlin and Tseng, 2020, the dosages (the average or at the time of study) of 11 of our 24 patients were below the recommended (i.e. infants 15–30 mg/kg/day, children and adolescents with an average of 20 mg/kg/day (range 5–30 mg/kg/day) of pyridoxine with a maximum dose of 500 mg per day, adults 200–500 mg per day) [58]. Nevertheless, the patients were seizure free the last year. Furthermore, pyridoxine itself can be neurotoxic and may therefore compromise neurological and intellectual outcome [59]. More precise data are necessary to come to solid conclusions about the optimal daily pyridoxine dose.

LRT lowered α-AASA with substantial reduction rates in 8 out of 10 patients, which is believed to be neurotoxic [10,12,15–19,60]. However, normal values were not achieved and the percentage of α-AASA reduction did not correlate with better outcomes. Others reported no correlation between α-AASA level and the severity of phenotype [16]. Nevertheless, LRT seemed to have a positive effect in a small subset of patients, with neonatal introduction of B6 or a late onset of seizures, especially if started early (Fig. 1). This is corroborated by Al Teneiji et al. [16] However, patients were still young, so longitudinal follow-up is required to make these conclusions more robust.

Furthermore, for diseases as clinically heterogeneous as PDE, with prenatal onset and with differing treatment initiation age and regimens, it is not possible to draw conclusions regarding the effect of therapy based on group comparisons. Therefore, each patient should be regarded as his or her own control and sibling studies with different ages at initiation of treatment are most ideal for establishing evidence-based conclusions. Clearly, an effective therapy is still needed and compliance issues must be overcome.

Aminoadipic semialdehyde synthase (AASS) upstream inhibition studies yield promising results in recent preclinical studies by Leandro et al. and preclinical gene therapy studies in cell, mouse and human brain cells are underway [61–63]. To conclude, early diagnosis and initiation of B6 and LRT is warranted.

4.7. Strengths and limitations

The strengths of this study are (i) inclusion of nearly all patients of the Dutch PDE-ALDH7A1 cohort, yielding a rather large study size, (ii) the applied detailed, standardized neurological techniques and (iii) the availability of standardized IQ tests and MRI findings. The main limitation is the lack of longitudinal results, possible confounding factors, and the clinical and genotypic heterogeneity as well as varying treatment modalities initiated at different ages. The common Dutch founder mutation may have introduced bias. Furthermore, the cohort size remains relatively small.

4.7.1. Future directions

To overcome this problem, an international database with solid uniform follow-up, and n = 1 study designs with personalized yet generalizable outcomes and novel statistical methods [64], are much needed. We welcome colleagues to join the International PDE Consortium, and to enroll patients into the International PDE Registry www.pde-online.org via RedCAP.

To standardize management and monitoring of PDE-ALDH7A1 patients, the International PDE-ALDH7A1 Consortium provides an updated Consensus Guideline based on a review of the literature and a Delphi consensus meeting. In summary, a diagnostic, therapeutic (for pyridoxine dose as well as LRT at three age groups) and treatment monitoring guideline is presented in detail, based on the best available evidence [58].

5. Conclusion

In the Dutch PDE-ALDH7A1 cohort, complex MND, CP, and cognitive problems were more often present in comparison to the general Dutch population. The frequencies of neurological and cognitive problems were similar to other reports of PDE-ALDH7A1 patients. Here for the first time, we report in detail on minor neurologic abnormalities, i.e coordination issues, and to a lesser extent of fine motor ability and posture/muscle tone. LRT may have an anecdotally beneficial effect on outcome, however more and earlier started treatments will be required to further optimize outcome.

To establish more robust conclusions regarding geno-phenotype correlations, the long term neurological and intellectual outcomes, and effect of different therapeutic strategies in PDE-ALDH7A1 patients, longitudinal follow-up studies with examination at regular intervals, using standardized neurologic and cognitive assessment methods are needed. Neuronal stem cells provide opportunities to delineate disease mechanisms and evaluate novel therapeutic interventions such as AASS upstream enzymatic inhibition. Finally, studies to enable inclusion in newborn screening panels for early detection and treatment are underway. Together with our patients and families, our consortium of clinicians and scientists continues to strive for P4 medicine (precision, participatory, predictive, preventive) [65].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2021.06.001.

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