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Clinical study

ATP1A3-related epilepsy: Report of seven cases and literature-based analysis of treatment response

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ABSTRACT

ATP1A3 related disease is a clinically heterogeneous condition currently classified as alternating hemiplegia of childhood, rapid-onset dystonia-parkinsonism and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss. Recently, it has become apparent that a remarkably large subgroup is suffering from often difficult-to-treat epilepsy. The aim of the present study was to assess the prevalence and efficacy of commonly used anti-epileptic-drugs (AEDs) in patients with *ATP1A3* related seizures. Therefore, we performed a retrospective study of patients in combination with a systematic literature-based review. Inclusion criteria were: verified *ATP1A3* mutation, seizures and information about AED treatment. The literature review yielded records for 188 epileptic *ATP1A3* patients. For 14/188 cases, information about anti-epileptic treatment was available. Combined with seven unpublished records of *ATP1A3* patients, a sample size of 21 patients was reached. Most used AED were levetiracetam (n = 9), phenobarbital (n = 8), valproic acid (n = 7), and topiramate (n = 5). Seizure reduction was reported for 57% of patients (n = 12). No individual AEDs used (either alone or combined) had a success rate over 50%. There was no significant difference in the response rate between various AEDs. Ketogenic diet was effective in 2/4 patients. 43% of patients (n = 9) did not show any seizure relief. Even though Epilepsy is a significant clinical issue in *ATP1A3* patients, only a minority of publications

Abbreviations: AHC, alternating hemiplegia of childhood; AED, anti-epileptic drug; AZA, acetazolamide; BTX, botulinum toxin; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss, CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; d, days; DZP, diazepam; EEG, electroencephalography; EOEE, early onset epileptic encephalopathy; FLU, flunarizine; GTCS, generalized tonic clonic seizure; hrs, hours; IED, interictal epileptic discharge; Int. Dis., intellectual disability; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; mos., months; MAF, minor allele frequency; MDZ, midazolam; MRI, magnetic resonance imaging; MTS, mesial temporal sclerosis; NCSE, nonconvulsive status epilepticus; NGS, next generation sequencing; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRO, propranolol; RDP, rapid-onset dystonia parkinsonism; SE, status epilepticus; STM, sulthiame; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid; wks., weeks; yr., years.

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provide any information about patients' anti-epileptic treatment. The findings of treatment effectiveness in only 57% (or lower) of patients, and the non-existence of a clear first-line AED in *ATP1A3* related epilepsy stresses the need for further research.

1. Introduction

ATP1A3 encodes the α3 Na^+K^+-ATPase and is mainly expressed in neuronal cells. Variants in *ATP1A3* are primarily associated with three, clinically considered distinct, syndromes: Alternating hemiplegia of childhood (AHC), rapid-onset dystonia-parkinsonism (RDP) and CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss). Concomitant epileptic seizures may occur in patients with *ATP1A3* related disorders. While some studies claim that 50–80% of all published AHC-cases have a history of seizures [1], a more recent publication reported a lower percentage (26.1%) [2]. Despite the heterogeneity of *ATP1A3* related seizures, some common characteristics have become apparent: An early onset of age, of mainly drug resistant seizure types, ranging from focal or generalized tonic, tonic-clonic, to myoclonic attacks, often initiated by triggers such as stress, excitement, extreme temperatures, water exposure, physical exertion, and lighting changes [3]. Even though epilepsy in *ATP1A3* patients is described as often pharmaco-resistant, data on treatment responses are still rare.

To expand our knowledge about different antiepileptic therapies and their outcomes, we present seven *ATP1A3* patients with clinical data, seizure history, and treatment, as well as the results of a performed systematic literature-based review, to delineate treatment response of antiepileptic drugs or ketogenic diet in *ATP1A3* related seizure disorder.

2. Methods

2.1. Patients and families

We collected data for seven unrelated patients (four from Thailand, three from Austria/Germany). Their shared characteristics were pathogenic *ATP1A3* variants and epileptic phenotypes. Ethical approval was obtained by the ethical review boards of both participating universities (IRB Chulalongkorn University, Thailand (No. 054/60) and LMU Munich, Germany (No. 18–232)). After patients and parents gave their consent, blood samples were collected. Genetic testing was performed by either Sanger sequencing (patient 3, 4, 5) or whole exome sequencing (patients 1, 2, 6, 7). Direct Sanger sequencing was performed to verify the results of patients 1 and 2. Variants were classified according to the criteria of the American College of Medical Genetics and Genomics [4].

2.2. Data collection procedures

For the literature search using PubMed, we first used the keywords 'ATP1A3 AND Epilepsy OR Seizure', followed by the single term 'ATP1A3′, to identify all cases appropriate for comparing with our patients. Additionally, records were found using PubMed Medical Subject Headings (MeSH). The filters applied were: Epilepsy (+genetics, +therapy) and Drug Resistant Epilepsy (+genetics, +therapy). If the abstracts of the matching papers mentioned patients with an *ATP1A3* mutation and associated epilepsy, we searched the full text of the paper for detailed information. If the case reports fulfilled the inclusion criteria, we gathered data for further analysis.

Data was last collected from PubMed on 26th of February 2019. After removing all duplicates of articles, we excluded papers that were not available in English or German language. Mandatory inclusion criteria were: 1. Verified mutation within *ATP1A3,* either fulfilling the criteria "pathogenic" or "likely pathogenic", according to the ACMG classification [4] 2. Seizures present and 3. Information on AED treatment available.

Further non-mandatory data extracted included: a) patient's gender and age at last follow-up, b) the phenotype, c) age at seizure onset, d) EEG findings, e) brain MRIs, f) intellectual disability/developmental status.

3. Results

3.1. Eligible studies

The free text term search for '*ATP1A3* AND Epilepsy OR Seizure' delivered 37 results while '*ATP1A3*′ yielded 217 additional matching studies.

After screening based on the inclusion criteria, we collected information on 188 *ATP1A3* patients with epileptic seizures, described in 17 publications. 174 cases had to be excluded due to insufficient data concerning antiepileptic treatment, so that we reviewed 14 suitable patients (7.4%) for seizure treatments and their effects. Combining these 14 *ATP1A3* cases with seven patients from our cohort, we obtained a sample of 21 patients for further investigation (Fig. 1).

3.2. Demographic data and seizure semiology

21 patients (10 males; age at publication: 9 mos. – 25 yr.; median: 7 yr.), first presenting with seizures at a median age of 2 months (0 – 156 mos.). All cases, which provided information about their patients' developmental status (n = 20) reported intellectual disability (100%). One case report did not include information about this variable. The median duration between onset of clinical manifestation and molecular diagnosis among our seven patients was 11 years (3–18 yr.). Within the entire cohort, documented seizure semiology varied from focal (n = 8), multifocal (n = 5) to generalized (n = 4) as well as mixed seizure patterns (focal/multifocal with secondary generalization) (n = 3). Eight of 21 patients (38%) experienced status epileptici (SE).

3.3. Response to AED

The most frequent used seizure medications were levetiracetam (LEV) (n = 9), phenobarbital (PB) (n = 8), valproic acid (VPA) (n = 7) and topiramate (TPM) (n = 5) (see Fig. 2). Seizure reduction was reported in twelve cases (57%). However, there was no standardized definition of what was considered a "significant reduction". Limited information was available for three patients, for whom it could not be stated to what degree the AEDs were responsible for seizure reduction (patient 6), and how sustainable the improvement was (patients C and M). Sulthiame (STM) led to moderate seizure reduction in patient C, but information on the long-term efficacy was not reported. Similarly, betamethasone led to seizure freedom in patient M, but therapy was omitted after four weeks

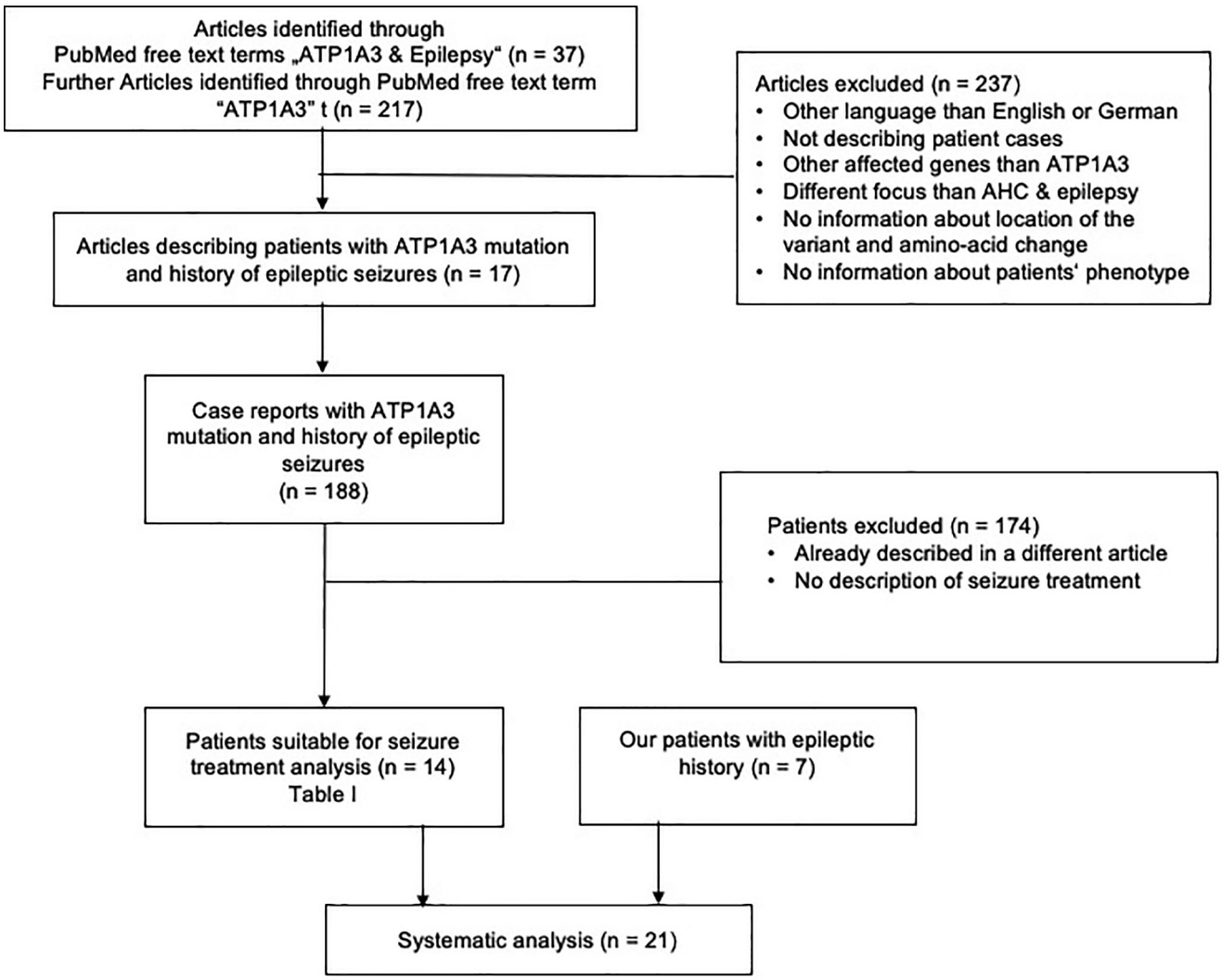

Fig. 1. Systematic review strategy.

due to non-compliance. In case of patient 6, it could not be stated to what degree the AED combination of VPA and PB was responsible for the seizure reduction since febrile seizures reported in childhood did not re-occur neither before nor after the termination of therapy.

In nine cases (43%) treatment effectiveness was reported in more detail. In 6/9 patients positive effects were achieved using a combination of different AEDs. The various AED combinations leading to treatment success are presented in Table 1. VPA as well as LEV proved effective as part of AED combinations in 3/9 patients. TPM, PB, carbamazepine (CBZ) and phenytoin (PHT) each successfully contributed to seizure reduction in two patients. Four patients were prescribed ketogenic diets (patients A, D, G, I). While two patients showed significant seizure reduction with either a combination of KD and AEDs (patient G) or KD only (patient A), the other two did not experience any seizure reduction through the implementation of KD (see Table 1). The prevalence of treatment effectiveness was slightly higher in our own patients (67%, 4/6) compared to the patients reviewed (50%, 5/12).

43% of patients (n = 9) did not show any seizure relief. Lack of seizure relief was associated with the following AEDs: LEV (n = 6), PB (n = 6), VPA (n = 4), CBZ/OXC (n = 4), TPM (n = 3), PHT (n = 2), clonazepam (CZP) (n = 2), lamotrigine (LTG) (n = 2), acetazolamide (n = 2), zonisamide (ZNS) (n = 1).

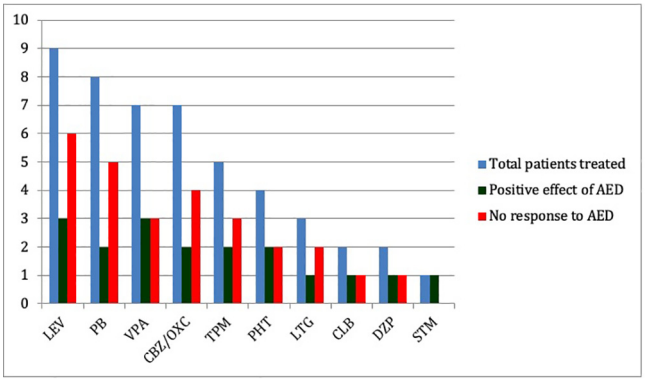

Fig. 2. Treatment effectiveness of several AEDs showing positive effects.

3.4. Neurophysiological data

EEG correlates were seen in 16/21 subjects (76%). Typical findings included ictal and interictal epileptic discharges (e.g. spikes and waves), showing either focal or generalized patterns, as well as recordings of diffuse background slowing on hemispheric or global levels, indicative of encephalopathies. Detailed findings are listed in Table 1.

Table 1
Clinical Data of the 21 cases with ATP1A3- related epilepsy.

Patient	Age/ Sex	Variant NM_152296.5	Phenotype	Age at seizure onset	EEG	MRI	Unsuccessful AEDs	Successful AEDs	Effect on Epilepsy	Int. Dis./Developmental status
A [27]	4y/m	c.2736_2738CTTdel p.Phe913del (likely pathogenic)	AHC, hypotonia, frequent focal epileptic seizures (not further specified)	2 d	Ictal EEG focal discharges left frontal area	Delayed myelination and high intensity in the white matter, esp. surrounding the anterior horn of the lateral ventricle, progressive bilateral brain atrophy	PB, multiple AEDs (not specified)	KD (since 1 1/ 3y) Combination therapy with unsuccessful AEDs	Seizure frequency reduced by 50% but still occurred daily	Int. Dis., no vocalization, respiratory failure postnatally, cardiac failure at 17d
B [3]	9 m/ m	c.1111G > A p. Gly371Ser (likely pathogenic)	AHC, GTCS, SE, apnoea, Choreic limb movements, hypotonia, unilateral nystagmus, eyelid myoclonia	1 d	IED both hemispheres alternatingly, disturbed background activity	MTS left	VPA, LEV, CZP	–	Persistence of seizures and occurrence of paroxysmal prolonged apnoea.	Int. Dis., facial dysmorphism, hypopigmentation, apnoea access with desaturation, severe delay of psychomotor acquisitions.
C [29]	2y1m/ f	c.2116G > C p. Gly706Arg (pathogenic)	Reoccurring apnoeic episodes resulting in cyanosis and desaturation → considered as focal epileptic seizures.	9 mos.	Left temporal theta seizure pattern	Normal	STM, OXC, LEV	STM reintroduced at 25 m monotherapy	Reduced the events moderately, loss to follow up after 25 m	No info about int. dis., delayed motor development
D [26]	16y/f	c.2224G > T p. Asp742Tyr (likely pathogenic)	Both epileptic (focal not further specified, generalized, myclonic) and nonepileptic neurologic spells, no AHC	6 wks.	Poor spatiotemporal organization, slowing of background activity and left frontotemporal slow waves and spikes.	Short corpus callosum and parieto-temporal atrophy.	KD, other AEDs (not specified)	–	No improvement, about five generalized seizures per month	Int. Dis., severe developmental delay, auto-aggressive bursts, permanent horizontal nystagmus and strabismus, hypotonia without ataxia and normal head circumference.
E [26]	6y/m	c.1036 T > C p. Cys346Arg (likely pathogenic)	Severe pharmaco-resistant multifocal epilepsy. Global hypotonia, no AHC	12 d	Seizure pattern right and left temporal frontal not lateralized	Normal	AEDs (not specified)	–	No improvement	Int. Dis., severe developmental delay
F [26]	4y/f	c.1825G > T p. Asp609Tyr (likely pathogenic)	Stereotyped neurological spells, characterized by dyspnoea, drooling, chewing, gaze deviation, unresponsiveness, hypotonia with small choreic movements of the hands, no AHC multifocal pattern	1 mos.	Interictal EEG: posterior slow waves with left predominance; Slow spike waves with right or left predominance.	Normal	Rectal DZP, other AEDs (not specified)	–	No improvement	Int. Dis., severe developmental delay: able to sit and crawl. No oral language, rudimentary nonverbal communication.
G [30]	2y7m/ m	trinucleotide deletion c.2266_2268delGAC p.Asp756del (likely pathogenic)	EOEE with late onset AHC (Hemi- and quadriplegic), Nystagmus, apnoea, hypotonia, Focal SE at onset and at two more episodes	2 mos.	Spikes and slow waves left fronto-temporal	Normal	CBZ, CZP, MDZ, TPM	(PB&VPA (<2m)) LEV, VPA, KD (>20 m) Combination therapy	Clinical and cognitive improvement, frequency of both epileptic and AHC manifestations significantly decreased. Daily/more → 16 m seizure free, then every 2–3 m	Int. Dis., severe global developmental delay
H [31]	10y/f	c.2443G > A p.Glu815Lys (pathogenic)	AHC, abnormal ocular movements, tonic and dystonic attacks, focal temporooccipital seizures, at 8y: GTCS, focal status epilepticus	20 hrs	Multifocal sharp and slow waves during sleep prevailing right frontotemporal	Hypoplasia of the anterior commissure and corpus callosum	VPA	FLU, TPM, DZP Combination therapy	Reduced frequency of paroxysmal attacks Focal seizures responsive to DZP, GTCS good clinical response to TPM, yet SE at 10y	Int. Dis., severe complex movement disorder characterized by choreo-dystonic and myoclonic features, global hypotonia, mental retardation, no

										vocalization
I [32]	5y/m	c.2443G > A p. Glu815Lys (likely pathogenic)	AHC, multifocal epileptic seizures, recurrent left-sided SE	2 yr.	Interictal EEG: bilateral IEDs; maximum frontal, slowing the left hemisphere	Bilateral MTS and a left-sided ischaemic lesion.	LEV, OXC, TPM, KD, VNS	–	No improvement, recurrent SE	Int. Dis., severe psychomotor disability
J [33]	17y/f	c.1747G > T p. Asp583Tyr (likely pathogenic)	Focal right motor seizures, generalized weakness, AHC, bradykinesia, apathy	3 mos.	IED left temporal	Normal		PB, CBZ Combination therapy	'Proved effective' (not specified)	Int. Dis., slight delay in motor and cognitive skills, psychotic ideation with auditory and visual hallucinations, and anorexic behaviour.
K [1]	16 m/f +	c.1073G > T p. Gly358Val (likely pathogenic)	Neonatal multifocal seizures, recurrent SE, nystagmus, disconjugate gaze, mouth and tongue movements, reduced responsiveness, continuous athetotic movements, postnatal microcephaly	4 hrs.	Multifocal seizures	Progressive atrophy, widening of cerebellar sulci, extensive gliosis	PB, other AEDs (not specified)	–	No improvement, Recurrent SE, death at 16 m	Int. Dis., death at 16 months of age - Report of autopsy: gliosis of: hippocampus, basal ganglia, increased microglia, normal myelination. Gliosis in cerebellum, brainstem and spinal cord
L [1]	4y/m	c.1088 T > A p. Ile363Asn (likely pathogenic)	Focal seizures with apnea, gaze deviation, and decreased, responsiveness, Dystonic spells, Alternating hemiplegia (at 4y), postnatal microcephaly	4 wks.	Diffuse slowing but no epileptiform discharges. (Right hemispheric electrographic seizure)	Normal	LEV, LTG, LZP	–	No improvement	Int. Dis., severe developmental disability
M [34]	25y/f	c.2401G > A; p. Asp801Asn (pathogenic)	AHC, mild form of epilepsy with focal seizures	2 mos.	IED temporo-occipital	N.A.	AEDs, (not specified), FLU, calcium channel blocker, Anti-migrainous drugs	Betamethasone Monotherapy	Complete aborted symptoms, relapsed after 4-week course → relapse of symptoms	Int. Dis., developmental delay
N [35]	5y/f	c.2267G > A p.Arg756His (likely pathogenic)	RDP, hypotonia, ataxia, dysphagia, partial complex, multifocal seizures arising from bilateral parasagittal regions	4 yr.	Normal	Normal	–	LEV Monotherapy	'Responded'	Int. Dis., severe developmental delay
1	7y/m	c.2552A > C, p. Gln851Pro (pathogenic)	AHC, tonic seizures, right and left focal clonic. NCSE at age 3 years and 4 months.	5 mos.	Normal at age 3y. Generalized rhythmic slow waves (during NCSE episode)	Normal	CBZ, LTG, TPM, FLU, LEV, PB, PHT, CZP, AZA	–	No improvement	Int. Dis., severe developmental disability
2	15y/m	c.2479A > T, p. Arg827Trp (pathogenic)	AHC, nystagmus, focal clonic seizures, tonic seizures, SE	11 mos.	Epileptiform discharge from left paracentral head regions	Right gliosis and cerebral atrophy	PHT, PB, LEV, VPA	–	No improvement	Int. Dis., severe developmental disability, hemiplegic/quadriplegic attacks
3	21y/m	c.410C > A, p. Ser137Tyr (pathogenic)	AHC, GTCS, hypomotor seizures, SE	13 yr.	Mild generalized encephalopathy. Intermitted slow bifrontal regions.	N.A.	ZNS, CLB, PB, chloral hydrate, AZA	PHT for SE, VPA, TPM Combination therapy	Reduced seizure frequency but did not prevent status epilepticus 2–3/years	Severe Int. Dis.,

(*continued on next page*)

Table 1 (*continued*)

Patient	Age/ Sex	Variant NM_152296.5	Phenotype	Age at seizure onset	EEG	MRI	Unsuccessful AEDs	Successful AEDs	Effect on Epilepsy	Int. Dis./Developmental status
4	16y/f	C.2429 T > G, p. Ile810Ser (pathogenic)	AHC, GTCS, Opsoclonus	5 yr.	Normal	Normal	PRO, TPM,	CBZ, (FLU for AHC) Combination therapy	Seizure free after age 5y	Severe Int. Dis., regression at 6w
5	7y/f	C.2401G > A, p. Asp801Asn (pathogenic)	AHC, GTCS, disconjugate eye movements	7 mos.	Normal	Normal	PRO	VPA, PHT Combination therapy	Seizure free for at least since 1y	Moderate Int. Dis.
6	19y/f	c.2401G > A, p. Asp801Asn (pathogenic)	Generalized hyperkinesia, Choreoathetosis, febrile seizures	2 mos.	Normal	Normal	(VPA, PB)	(VPA, PB) Combination therapy	Seizures only during childhood. Effect of AEDs not clear. Attacks didn't reoccur after stop of AEDs	Int. Dis., developmental delay, walking at age 11, only able to speak few words at age 19
7	22y/m	c.2332A > C, p.Thr778Pro (NM_152296.4) (likely pathogenic)	Generalized dystonia responding to BTX injections, regression of psychomotor development, generalized epileptic and also presumed psychogenic non-epileptic seizures	13 yr.	Normal	Dilated lateral ventricles	OXC, CLB with unknown effect - aborted	LEV, LTG, Combination therapy	No evidence of epileptic seizures during the past 3 years under a current AED combination of LTG and LEV (previous outcome of OXC not documented)	Int. Dis., severe developmental regression starting at age 13 years rapidly worsening over a period of 2.5 years, not able to speak

AHC (alternating hemiplegia of childhood), AED (anti-epileptic drug), AZA (acetazolamide), BTX (botulinum toxin), CBZ (carbamazepine), CLB (clobazam), CZP (clonazepam), d (days) DZP (diazepam), EEG (electroencephalography), EOEE (early onset epileptic encephalopathy), FLU (flunarizine), GTCS (generalized tonic clonic seizure), hrs. (hours) IED (interictal epileptic discharge), Int. Dis. (Intellectual disability), KD (ketogenic diet), LEV (Levetiracetam), LTG (lamotrigine), LZP (lorazepam), m (months) MDZ (midazolam), MRI (magnetic resonance imaging), MTS (mesial temporal sclerosis), NCSE (nonconvulsive status epilepticus), OXC (oxcarbazepine), PB (phenobarbital), PHT (phenytoin), PRO (propranolol), RDP (rapid-onset dystonia parkinsonism), SE (status epilepticus), STM (sulthiame), TPM (topiramate), VNS (vagus nerve stimulation), VPA (valproic Acid), wks. (weeks), yr. (year).

3.5. Neuroimaging

Brain MRI data were available for 19 patients (90%). Hippocampal sclerosis was detected in five subjects (26%), while three of them additionally showed signs of widespread atrophy. With two more patients presenting atrophic observations in diverse areas, and one showing dilated lateral ventricles, the prevalence of pathological findings in neuroimaging was 42%. Four of five patients with hippocampal sclerosis on MRI had SE suggesting a significant correlation ($p = 0.019$, Chi^2-test).

4. Discussion

4.1. Treatment of epileptic seizures

Results of this literature and case review show that treatment responses to AEDs are only rarely reported in patients with *ATP1A3* related seizures, despite the high incidence and clinical significance of seizures in this syndrome. Thus, this systematic report combined with data of our own patients yielded only a few patients for analysis. No significant treatment response to seizure medication could be achieved in almost half of the cases (43%). By comparing our seven patients to the 14 cases reviewed, the prevalence of effective treatments was slightly higher in our patients. The difference (67% vs. 50%) should be interpreted cautiously given the small sample size. Among the most commonly used AEDs, the rates of successful trials within the cohort were never > 50%. VPA (3/3) and PHT (2/2) showed the strongest success ratios while LEV (3/6) and PB (2/5) performed most poorly. The partial efficiency of TPM (2/3) in seizure reduction corresponds with previous findings in literature. While there were consistent reports about reducing hemiplegic attacks in *ATP1A3* patients [5], there were both reports advocating for a seizure reduction in AHC patients through TPM [6], and others contradicting this finding [7].

As an alternative to standard AEDs, the positive effects of KD shown in patients A and G were in accordance with other AHC case reports [8–10]. While previous case reports only mentioned a positive effect on hemiplegic attacks in AHC patients, patients A and G also experienced a reduction of seizures. However, the results of two other KD trials covered in this review (patients D and I) do not necessarily underpin the hypothesis of KD being a first line anti-epileptic therapy in *ATP1A3* patients. Nevertheless, since KD was not been prescribed in any of our own seven patients, it represents a viable treatment option. Patient M's total relief from AHC related symptoms (including epileptic seizures) for four weeks through steroid therapy with betamethasone also gives cause to address this treatment option further. However, due to loss to follow-up, the long-term outcome of this therapy is unknown. Further, our findings confirm that although some drugs appear to be more effective than others, there is no single agent with explicitly higher potency for epileptic *ATP1A3* patients. From the present body of evidence it cannot be concluded whether this is due to the small number of subjects analysed in this review or due to the medical refractoriness of the disease.

There are singular, thorough reports of other drugs, such as aripiprazole, having significant effects on otherwise pharmacoresistant epileptic AHC patients [11]. However, since verification of the *ATP1A3* mutation was not given (report published before 2012), they were not listed in Table 1. Another report described improvement of hemiplegic attacks in a patient with AHC through oral ATP [12]. Since epileptic seizures were not explicitly described, and this was the only trial thus far, it cannot be concluded that oral ATP would also reduce *ATP1A3* related epileptic symptoms. Nevertheless, if large-scale trials confirm the efficiency for seizure reduction in *ATP1A3* patients, it may become a noteworthy treatment alternative.

4.2. Clinical findings

The correlation and sequence of SE and hippocampal sclerosis (MTS), implied by the Chi^2-test result, has already been the topic of vivid scientific discussion [13]. Although some studies failed to provide evidence for the existence of a strong correlation [14,15], the majority of recent publications points towards a considerable association. In rat models it has been demonstrated that provoked status epileptici led to reoccurring seizures, neuronal loss and subsequent gliosis within the hippocampus [16,17]. Other rat trials and human clinical data indicate that early life status epileptici suppress neurogenesis in the developing brain [18–21], and that a young age at seizure onset, as well as length of seizures, correlate with decreased hippocampal glucose metabolism in patients with MTS [22].

Putting the *ATP1A3* mutations in context, one may begin to construct a pathway of causality: Pathogenic genetic variants (such as in *ATP1A3*) predisposing for SE, SE damaging the mesial temporal lobe through different potential pathways (e.g. Olneys excitotoxic theory [23]) and finally the MTS as a consequence of these injuries, which increases the risk of reoccurring seizures through reduced GABA-mediated inhibition (loss of inhibitory neurons or missing excitatory input to these), or misdirected regeneration, that causes a novel recurrent excitatory circuit [24,25].

4.3. Demographic data

Both the median time of seizure onset at 2 months of age, as well as the overwhelming occurrence of intellectual disability amongst the cohort, stress the severity of epileptic symptoms and the need for targeted treatment. Further, the median time interval of 11 years between age of onset and genetic testing among our seven patients is high. This underlines that genetic testing should be performed earlier during the diagnostic work-up. Thus, stressful diagnostic interventions, such as brain MRIs with sedation, could be avoided and more targeted therapies may be introduced earlier.

4.4. Limitations

Although the seizure burden portrays a significant clinical issue in patients with *ATP1A3* mutations [1,26,27], only 7.4% of the identified 188 published cases provided information about AED treatment. Since a great proportion of patients had to be excluded, specific phenotypes might be over- or underrepresented in our cohort. Thus, the universality of this systematic reports' findings, combined with data from our own patients, is limited. Another general issue that occurred while investigating reports for effective treatments was the unclear degree of seizure reduction through AEDs. Phrases like 'seizures responded', 'significant', 'moderate reduction', or 'reduced frequency' are not as relatable as a numerical variable would be. One possible solution could be a mandatory classification of future case reports according to the CGI-I, in which the American Epilepsy Society characterizes a reduction of seizure frequency of 44% as a clinically meaningful cut-off point, while a reduction of 60–68% is regarded as 'very much improved' [28]. In case of patient 6, the degree of treatment response could not be detected, since febrile seizures reported in childhood did not reoccur neither before nor after the termination of therapy. Hence, the diagnosis of epilepsy and the effectiveness of treatment remain unknown.

5. Conclusion

Findings of this case study and literature review can be summarized in three main points: Firstly, the overwhelming number of publications concerning *ATP1A3* related epilepsy fail to provide information about seizure treatment. Secondly, the relevant treatment data is oftentimes nonnumerical and therefore unclear, and therefore insufficient for clearly rating individual AEDs' effectiveness. Finally, for almost half of the patients (43%) adequate seizure control was not achieved. The data presented implies that treatment solutions should be constructed tailored to patients' needs. Consequently, further studies with detailed treatment information and quantified effects are needed in order to address the health burden of epilepsy in the population with *ATP1A3*.

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