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Review article

Porphyria attacks in prepubertal children and adolescents

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ABSTRACT

Context: The clinical and laboratory features of dominant acute hepatic porphyrias (AHPs) in prepubertal children and adolescents have not been well established.
Objective: To evaluate clinical and laboratory features of AHPs in prepubertal children and adolescents compared to adults.
Data sources: OVID (Embase Classic+Embase and MEDLINE), Scopus, and Google Scholar.
Study selection: Studies describing symptomatic children or adolescents (<18 years old) with increased urinary porphobilinogen were included.
Data extraction: Two reviewers independently extracted the data, with a third reviewer arbitrating discrepancies.
Results: 100 studies were included describing 112 patients (26 prepubertal children and 86 adolescents). Differences were found between prepubertal children and adolescents regarding sex distribution (female-to-male ratio: 1:2 vs. 4:1), clinical manifestations, and concomitant clinical manifestations.
Limitations: There was variation in the methods used to diagnose porphyria attacks across studies, and some elements of the quality of individual studies were unclear.
Conclusions: Prepubertal children with AHPs and porphyria attacks presented with distinct demographic and clinical characteristics from adolescents and adults. Nearly two-thirds of the affected children were males, and about half had a concomitant medical condition that can constitutively upregulate hepatic δ-aminolevulinic acid synthase-1. Adolescents were comparable to adults in almost all respects.

Contents

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1. Introduction

Acute hepatic porphyrias (AHP) are rare, life-threatening genetic disorders resulting from enzyme deficiencies in the heme biosynthetic pathway. The most prevalent forms are autosomal dominant conditions, namely acute intermittent porphyria (AIP, OMIM: 176000), hereditary coproporphyria (HCP, OMIM: 121300), and variegate porphyria (VP, OMIM: 176200). Mutation carriers are predisposed to developing attacks of neurovisceral symptoms, including abdominal pain, vomiting, constipation, seizures, behavioral changes, and muscle weakness. These attacks are triggered by factors that upregulate hepatic δ-aminolevulinic acid synthase-1 (ALAS1), the first and rate-limiting enzyme in heme biosynthesis, leading to excessive accumulation of the porphyrin precursors δ-aminolevulinic acid (ALA) and porphobilinogen. Some common triggers are infections, surgery, medications, caloric restriction, stress, smoking, alcohol, and hormones. The diagnosis is established by significantly elevated urinary porphobilinogen (UPBG) levels in the presence of symptoms [1].

AHPs predominantly affect adult females of childbearing age, but the pediatric onset of AHPs may be underestimated, considering the average delay of 15 years from the onset of symptoms to the porphyria diagnosis [2]. In the US Porphyria Consortium longitudinal study, 5% of patients diagnosed with AHP as adults reported that symptoms started during childhood [3]. Diagnostic delay may be particularly devastating for children with AHP who can be misdiagnosed with refractory forms of more common diseases (e.g., epilepsy) and be chronically treated with porphyrinogenic medications, increasing their risk of permanent neurological deficits and death [4]. Therefore, pediatricians should become familiar with AHPs and consider them in children and adolescents with apparently refractory or atypical presentations of more common conditions.

Nevertheless, the pediatric onset of AHP remains poorly understood. While two previous reviews suggested a slight male predominance and an increased risk of seizures in children compared to adults, these reviews have several limitations [3,5]. Kaplan and Lewis [5] reviewed cases published between 1892 and 1986 without confirming the adequacy of porphyria diagnosis. We reevaluated 53 cases (<18 years) included in their review and found that the diagnosis of porphyria was inadequately established based solely on elevated urinary porphyrins in 45.3% of them (see supplements). This finding is nonspecific and can be seen in many other more common conditions (e.g., liver disease, anemia, diabetes, CYP450 inducers) [6]. A subsequent review by Balwani and colleagues[4] examined 15 cases published between 1986 and 2016 only from PubMed. We searched multiple databases and identified 64 additional cases published in the same period, indicating that around 77% of the existing evidence was not evaluated in that review.

Here we present a systematic review and meta-analysis of studies reporting porphyria attacks in prepubertal children and adolescents published between 1892 and 2020. We aimed to summarize the clinical and laboratory characteristics of pediatric patients with AHPs and compare them with those of adult patients.

2. Methods

2.1. Protocol and registration

The systematic review protocol was registered in PROSPERO (crd.york.ac.uk/prospero) and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) statement [7].

2.2. Search strategy, study selection, eligibility criteria, and risk of bias assessment

Studies were identified by searching OVID (Embase Classic+Embase and MEDLINE), Scopus, and Google Scholar (June 27, 2020; search in supplements), as well as by scanning reference lists of included articles. No limits were applied for language, and articles in languages other than Spanish and English were translated. Two reviewers (YAMP and CF) independently screened titles/abstracts, reviewed full-texts and extracted data, with a third reviewer (DAJC) arbitrating discrepancies. Studies were included if they described symptomatic patients 17 years of age or younger, with confirmed porphyria attacks (see diagnosis of porphyria attacks). The risk of bias within studies was assessed concerning the methods used to diagnose porphyria attacks adequately.

2.3. Data collection and study parameters

Data retrieved included demographics, medical history, clinical manifestations, laboratory tests, prescriptions, and hospital outcomes. Unreported information was considered absent or normal. Missing important information was requested from the authors.

2.3.1. Personal history

Pre-existing conditions were evaluated, including perinatal complications, congenital anomalies, unrelated epileptic disorders, chronic comorbidities, malnutrition, and recurrent inflammatory processes (e.g., infections and surgeries). The porphyrinogenic risk of medications received before porphyria diagnosis was evaluated with the aid of the Norwegian Porphyria Center and the American Porphyria Foundation drug databases (drugs-porphyria.org and porphyriafoundation.org/drugdatabase, respectively). In case of disagreement between these databases, the highest porphyrinogenic risk classification was chosen. Possible triggers for porphyria attacks were classified as infections, surgery, medications, caloric restriction, stress, smoking, alcohol, menstrual cycle, and decompensation of coexisting disease.

2.3.2. Definition of puberty and age groups

Patients were considered adolescents when any of the following features were described: 1) Tanner stage ≥II, 2) enlarged testicles in boys, and 3) breast development (thelarche) or menstruation in girls. When this information was absent, patients were classified as adolescents according to the average age of onset of puberty (≥10 years for girls, ≥11 years for boys) [8]. Otherwise, patients were considered prepubertal children. According to age, patients were classified as infants (<1 year), toddlers (1 to 3 years), preschoolers (4 to 5 years), school age children (6 to 9–10), early adolescents (10–11 to 14 years), and middle adolescents (15–17 years).

2.3.3. Diagnosis of porphyria attacks

Significant elevations of UPBG must be demonstrated to establish that a group of nonspecific clinical manifestations are caused by an attack of a dominant AHP. UPBG excretion is generally 20 to 200 mg/day (normal <4 mg/day) during porphyria attacks, which is pathognomonic for AIP, VP, and HCP [9,10]. UPBG should ideally be normalized per gram or mmol of creatinine to correct for concentration of the urine.

Significant elevations typically exceed 10 mg/g creatinine and more than 3 to 5-fold ULN [6,9–13].

In this review, a confirmed porphyria attack was defined by the presence of symptoms and quantitative UPBG levels of at least 4-fold ULN and 10 mg/g creatinine or 20 mg/l or day when creatinine in urine was not reported (assuming a normal concentration of the urine). An ULN of 4 mg/l or mg/day was used when the reference range was not reported. UPBG values were normalized to conventional units (mg/l = μmol/l * 0.226; mg/l = ug/l * 0.001; mg/g creatinine = μmol/mmol of creatinine * 2). Symptomatic patients for whom the diagnosis of porphyria attacks was based solely on positive screening tests (Hoesch or Watson-Schwartz tests) were classified as probable cases without definitive confirmation. These tests are useful because of their wide availability, simplicity, and low limit of detection (12 μmol/l). However, due to its low sensitivity and specificity, it is recommended to confirm the results on the same urine sample by quantitative methods [14–17].

2.3.4. Diagnosis of porphyria type

Porphyria types were determined using the following criteria [2]: 1) AIP: increased UPBG and little or no increase in total fecal porphyrins (TFP), decreased activity of hydroxymethylbilane synthase (also known as porphobilinogen deaminase and uroporphyrinogen synthase) or pathogenic/likely pathogenic variants in the *HMBS* gene. 2) HCP: increased UPBG and TFP (with copro III/*I* > 1.5 and copro III > proto IX), decreased activity of coproporphyrin oxidase or pathogenic/likely pathogenic variants in the *CPOX* gene. 3) VP: increased UPBG and TFP (with copro III/I > 1.5 and proto IX > copro III), increased plasma porphyrins with a fluorescence emission peak at 626 ± 2 nm, or pathogenic/likely pathogenic in the *PPOX* gene. The pathogenicity of all variants was reevaluated according to the standards of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [18]. Patients were classified as AHP when information about second-line laboratories was absent.

2.3.5. Other parameters

Tachycardia and systemic arterial hypertension were defined by age [19,20]. Hyponatremia was categorized as mild (a ≤ 135), moderate (Na = 125–130), and profound/severe (Na < 125) [21]. Severe porphyria attacks were defined by the presence of significant hyponatremia (serum Na ⟨130), seizures, or paresis [22]. Otherwise, they were considered mild.

2.4. Data synthesis and analysis

Proportions of clinical manifestations were compared between prepubertal children and adolescents using the Fisher's exact or chi-square tests as appropriate. The median age at diagnosis was compared using the Mann-Whitney test. When feasible, a one-sample proportion test was used to compare proportions of clinical manifestations in prepubertal children and adolescents with theoretical relative frequencies of the same manifestation in adults [23]. Two-sided *p*-values <0.05 were considered statistically significant. Analyzes were performed using Stata Statistical Software, V.14 (College Station, TX: StataCorp LP.).

3. Results

3.1. Study selection and characteristics

168 full-text articles published between 1892 and 2020 were assessed for eligibility, of which 101 met the inclusion criteria (Fig. 1). One case was described in two distinct reports [24,25], so the case was counted only once and the information was retrieved from both articles.

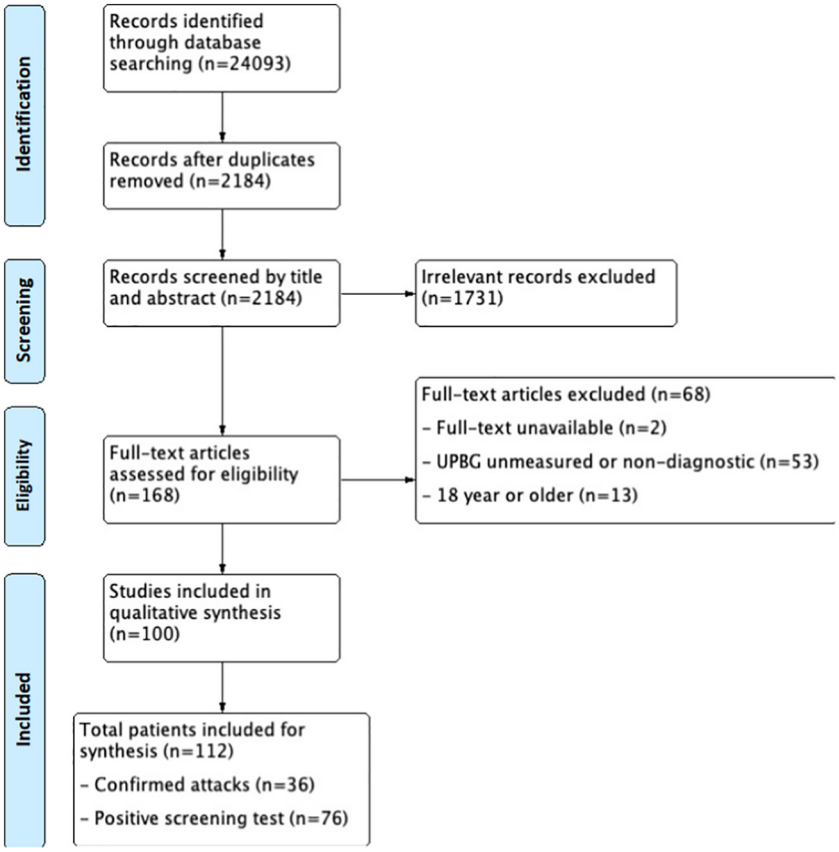

Fig. 1. Study selection flow diagram.

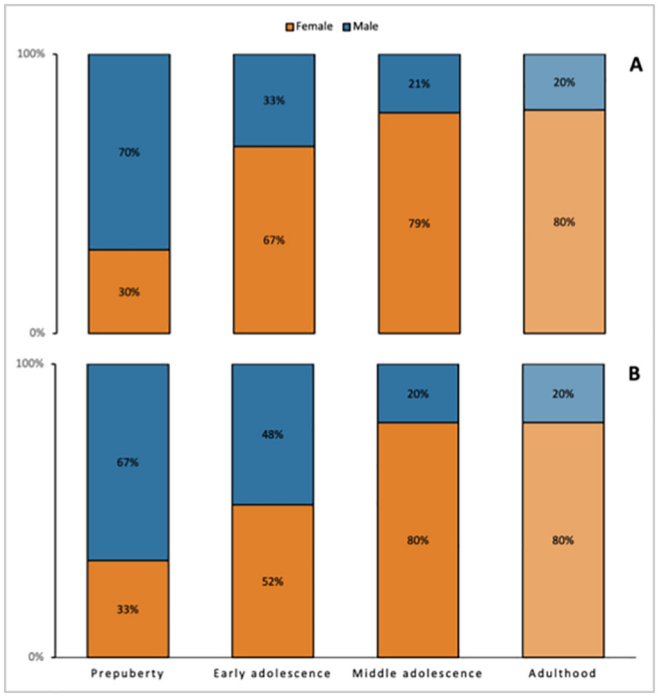

Fig. 2. Sex distribution of porphyria attacks by age stage (**A**: Confirmed attack; **B**: Positive screening).

The included reports represented 35 countries based on affiliations. Overall, reports of patients with confirmed attacks were published more recently (median: 2005, min-max: 1956–2020) than those of patients with positive screening (median: 1995, min-max: 1955–2020). Characteristics, risk of bias, and references of evaluated studies are available in the supplements.

3.2. Patients

36 patients with confirmed porphyria attacks (10 children, 26 adolescents) and 76 patients with positive screening were identified (18 children, 58 adolescents). No significant differences were observed in the proportions of children (28% vs. 23%) and adolescents (72% vs. 77%). There was a predominance of males over females in children of both groups, while the opposite was observed in adolescents. The female-to-male ratio progressively increased from prepuberty to early and middle adolescence (Fig. 2).

The median age at diagnosis was 9 years (IQR: 0.75, min-max:4–10) in children and 15 years (IQR: 3.5, min-max:11–17) in adolescents with confirmed attacks, while the same was 7 years (IQR: 3.75, min-max:1–10) in children and 14 years (IQR: 4, min-max:10–17) in adolescents with positive screening (Fig. 3A). Men were significantly younger than women at the time of diagnosis in both groups (Fig. 3B). Overall, 2.6% of patients were infants/toddlers ($n = 3$), 4.4% were preschoolers ($n = 5$), 17.8% were in school age ($n = 20$), 37.5% were early adolescents ($n = 42$), and 37.5% were middle adolescents (n = 42).

Table 1
Clinical manifestations.

	Confirmed				Positive screening			
	Adolescent		Children		Adolescent		Children	
	n	%	*n*	%	*n*	%	*n*	%
Severe attack	17	63	8	66.7	44	77.2	13	68.4
Abdominal pain	25	92.6	8	66.7	51	89.5	14	73.7
Dark/Reddish urine	19	70.4	9	75.0	34	59.6	12	63.2
Vomiting/Nausea	17	63	9	75.0	29	50.9	11	57.9
Hyponatremia[a]	17	63	7	58.3	23	40.4	3	15.8
Hypertension[a]	16	59.3	8	66.7	29	50.9	2	10.5
Tachycardia	14	51.9	6	50.0	24	42.1	6	31.6
Seizures	9	36.4	7	58.3	32	56.1	8	42.1
Altered consciousness	11	40.7	5	41.7	25	43.9	8	42.1
Muscle weakness	8	29.6	6	50.0	32	56.1	10	52.6
Constipation	9	33.3	2	16.7	20	35.1	5	26.3
Hyporeflexia	8	29.6	4	33.3	21	36.8	8	42.1
Psychiatric manifestations	7	25.9	3	25.0	21	36.8	7	36.8
Anxiety	3	11.1	0	0.0	2	3.5	3	15.8
Hallucinations	3	11.1	1	8.3	14	24.6	1	5.3
Irritability	3	11.1	1	8.3	7	12.3	5	26.3
Depression	0	0.0	1	8.3	6	10.5	0	0.0
Dysesthesia	3	11.1	0	0.0	3	5.3	3	15.8
Visual disturbances	3	11.1	0	0.0	1	1.8	1	5.3
Cutaneous lesions	1	3.7	2	16.7	7	12.3	2	10.5

Based on two-sided chi-square tests with an alpha level of 0.05, there is a significant difference between prepubertal children and adolescents in the positive screening group (Hyponatremia: $p = 0.02$ and hypertension: $p < 0.01$)

3.3. Clinical manifestations, concomitant medical conditions, and triggers

Clinical manifestations did not differ significantly between children and adolescents with confirmed attacks (Table 1). However, abdominal pain was less common in children compared to adolescents (67% vs 93%), with a trend toward significance ($p = 0.05$). Compared to adults, abdominal pain was significantly less frequent in children ($H_0 = 95\%$, $p < 0.001$) while seizures were significantly more prevalent in children and adolescents ($H_0 = 20\%$, $p < 0.04$–0.001). The presence of hyponatremia was associated with a higher occurrence of seizures in children and adolescents of both groups. Systemic arterial hypertension was reported more repeatedly in children with confirmed attacks than in adults, with a trend toward significance (66.7% vs. $H_0 = 40\%$, $p = 0.05$). The clinical presentation of patients with confirmed attacks was generally quite similar to that of patients with positive screening, except

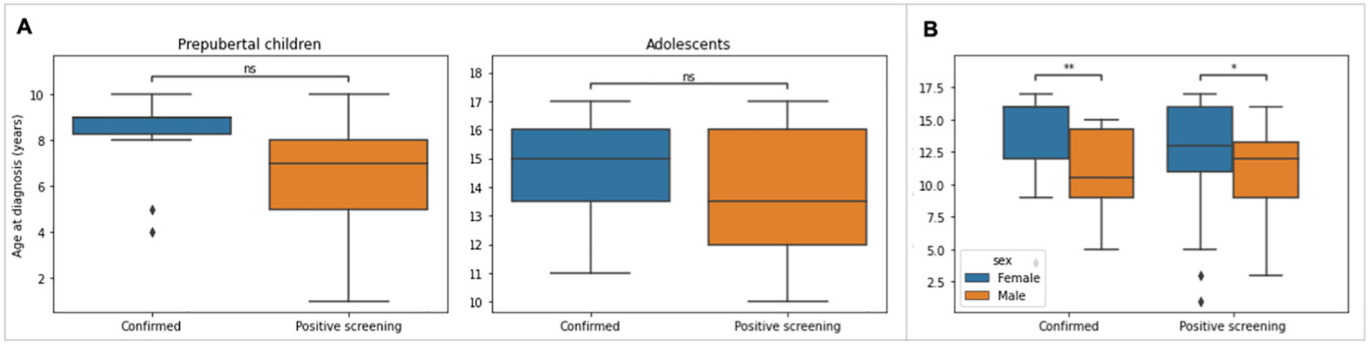

Fig. 3. A Age distribution in prepubertal children and adolescents. **B**: Overall age distribution by sex. ns = non-significant difference in Mann-Whitney test. $^*p < 0.05$.

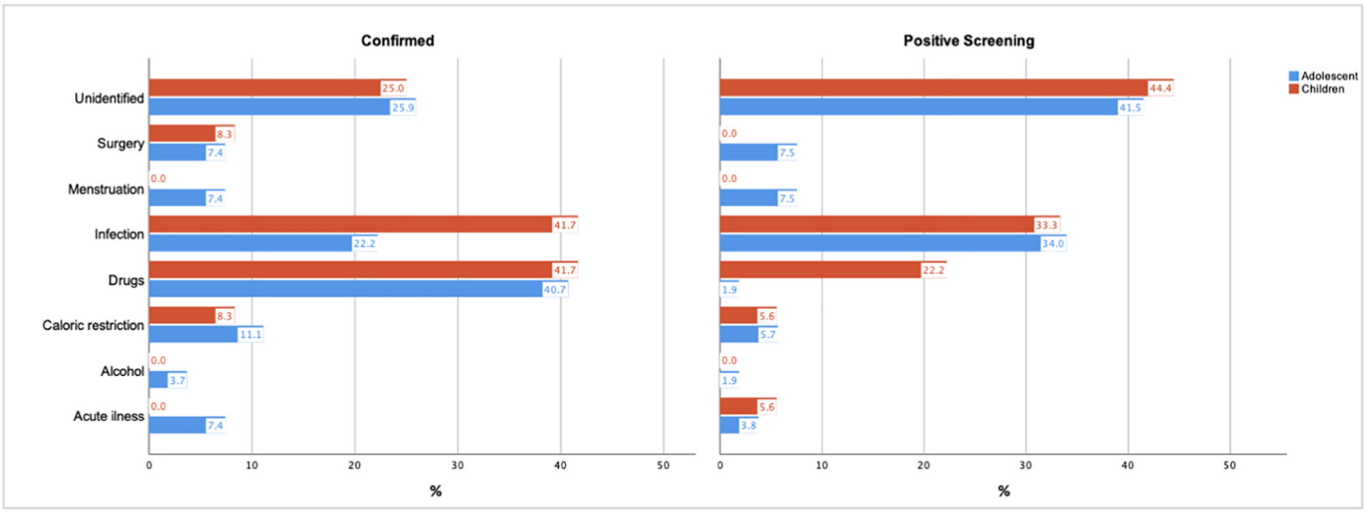

Fig. 4. Triggers of porphyria attacks in children and adolescents.

for a significantly higher frequency of hyponatremia and systemic arterial hypertension in children.

The prevalence of concomitant medical conditions was similar in children and adolescents with confirmed attacks (40% vs. 35%). However, epilepsy and developmental delay were more common in children than in adolescents. When stratified by sex, concomitant medical conditions were more prevalent in prepubertal males (57.1%) than in prepubertal females (0%) and adolescents of both sexes (males: 38.1%, females: 28.6%). A similar but less marked situation was recognized in patients with positive screening (adolescent males: 11.1%, females, 22.7%; prepubertal females: 33.3%, males: 41.7%). Fig. 4 presents possible triggers of porphyria attacks in children and adolescents.

3.4. Porphyria diagnosis

UPBG was increased at least 10-fold ULN in 92% and 15-fold ULN in 89% of patients with confirmed attacks. Median UPBG was 92.1 mg/l (IQR = 66.5; min-max: 34.4–303.5) in prepubertal children and 65 mg/l (IQR = 86; min-max: 20–314) in adolescents (Fig. 5).

The porphyria type described in patients with confirmed attacks was AIP in 86.1% ($n = 31$), VP in 8.3% (n = 3), and HCP in 5.5% ($n = 2$). However, second-line testing to determine the porphyria type was only described in 77.8% ($n = 28$) of cases, corresponding to DNA analysis in 17.8% ($n = 5$, Table 2), enzymatic activity in 64.3% ($n = 18$), fecal porphyrins in 33.3% ($n = 12$), and plasma porphyrins fluorometric scanning in 21.4% ($n = 6$).

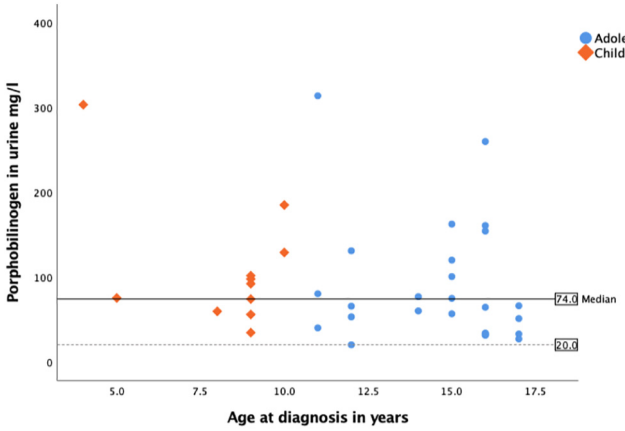

Fig. 5. UPBG during porphyria attacks in children and adolescents.

4. Discussion

This review examined the available evidence on the pediatric onset of AHPs published between 1892 and 2020. More than a third of the identified cases were excluded due to lack of biochemical evidence to support the diagnosis of a porphyria attack, which was based on an isolated urinary porphyrin elevation without UPBG evaluation or a small non-significant elevation of UPBG.

Our analysis corroborates that porphyria attacks are extremely rare before the onset of puberty, considering that our comprehensive search only identified ten symptomatic children in whom attacks were confirmed by a quantitative evaluation of UPBG. Furthermore, the number of prepubertal patients with a confirmed attack or positive screening was less than a third of the number of adolescents, reflecting the influence of sexual development on the appearance of porphyria symptoms. There is a trend toward prepubertal attacks predominating in males (70%, female-to-male ratio = 1: 2.3), unlike attacks during adolescence and adulthood that predominate in females. Kaplan and Lewis [5] reported a similar but less pronounced male predominance (57%, female-to-male ratio = 1:1.3) in patients younger than 15 years, which is probably explained by the inclusion of patients misdiagnosed with AHPs and a lack of distinction between prepubertal children and adolescents. We also found that the female-to-male ratio progressively increased from prepuberty to early and middle adolescence until reaching the expected values of adults (from ~1:1 to 4:1). These observations support that porphyria attacks are more common after the onset of puberty and in women, in part due to the effect of female sex hormones (especially progesterone) in increasing heme demand and inducing ALAS1 in the liver [34].

Concerning sex hormones, there are lower levels and practically no gender differences before the onset of puberty. Therefore, other factors are likely to drive pediatric activation of AHPs and its male predominance. We evaluated the prevalence of coexisting medical conditions that may contribute directly or indirectly to increasing heme demand or inducing constitutive upregulation of ALAS1 in the liver. Such a phenomenon can produce a lower threshold for the precipitation of attacks and increased susceptibility to common triggers [35]. Although not significant, prepubertal males had a higher burden of concurrent medical conditions (57%) compared to prepubertal females (0%) and adolescents of both sexes (28.6–38.1%). The same situation was detected in

Table 2
Genetic mutations identified in children and adolescents with alleged or confirmed porphyria attacks.

Type	Gene	Base change	Amino acid change	Interpretation	Ref
Missense	*CPOX*	c.404 T > C	p.V135A	Likely Pathogenic	[26]
	HMBS	c.962G > A	p.R321H	Benign	[27]
	HMBS	c.517C > T	p.R173W	Pathogenic	[28,29]
Nonsense	*PPOX*	c.1118G > A	p.W373X	Pathogenic	[30]
Insertion/Deletion	*HMBS*	c.966insA		Pathogenic	[31]
	HMBS	c.1084delT		Likely Pathogenic	[32]
Splice site	*HMBS*	IVS4-1G > A		Pathogenic	[3]
	HMBS	c.160 + 6 T > A		VUS	[33]

CPOX, Coproporphyrinogen oxidase; HMBS, hydroxymethylbilane synthase; PPOX, Protoporphyrinogen oxidase; Ref, Reference; VUS, Variant of uncertain significance.

patients with positive screening. The age of onset of attacks may also be influenced by genetic modifiers and the environment [36].

The incidence of seizures in children and adolescents in this review was higher compared to what is seen in adults and was positively associated with the presence of hyponatremia. These findings are consistent with observations in patients who suffered from posterior reversible encephalopathy syndrome and seizures during porphyria attacks, in whom hyponatremia occurred twice as often as expected for attacks in general [37]. Seizures and significant hyponatremia are indicative of a severe porphyria attack, which usually develops when hemin is not administered early. Thus, treatment delay is probably the main reason for the high occurrence of these manifestations in our review rather than an unknown distinctive characteristic of children and adolescents compared to adults. Most of the included reports described severe cases with prolonged hospitalizations and repeated exposure to porphyrinogenic drugs before suspecting a diagnosis of porphyria, which fostered the progression of neurological damage. In contrast, symptoms in patients with a known diagnosis of porphyria are quickly attributed to an attack and treated while they are still mild. A retrospective study in Israel found that the incidence of seizures in symptomatic patients with AHPs decreased from 50% before suspecting porphyria to 0% after diagnostic confirmation ($p < 0.001$) [38]. Similarly, a 5.1% lifetime prevalence of seizures has been found in Swedish patients with known AIP who have experienced porphyria attacks [39].

Hultdin et al. [40] reported that 10% of Swedish children with genetically confirmed AIP in a prospective study showed clinical evidence of an attack without excreting high concentrations of PBG in urine. However, the patients presented only mild and nonspecific symptoms (e.g., abdominal pain and nausea) that may have arisen from a cause other than porphyria. Conversely, our review found that children and adolescents with porphyria attacks exhibit significantly high UPBG levels similar to those of adults. This finding supports that UPBG is also a useful biomarker of porphyria attacks in the pediatric population. Interestingly, less marked UPBG elevations were seen below the age of 8 years and some patients with convincing evidence of an AHP (DNA analysis or reduced enzyme activity) had UPBG levels below 20 mg/l. These patients were excluded from the main analysis, but a very dilute urine sample due to high fluid administration may have caused falsely low UPBG levels. Allowing for this issue, UPBG should ideally be normalized per gram or mmol of creatinine in urine [6,10]. Besides, UPBG levels could have decreased following administration of dextrose before collecting urine samples or due to very poor handling of samples. UPBG may also be less elevated and normalize more rapidly in HCP and VP than in AIP. With this in mind, total fecal and plasma porphyrins can be measured in conjunction with UPBG to add sensitivity. They persist elevated for longer periods compared to ALA and PBG (specially in VP and HCP), which will help maintain porphyria as a differential diagnosis to be confirmed with subsequent UPBG measurements if consistent symptoms reappear [41].

Mutational analysis was available for nine patients. Anyaegbu et al. [27] informed a missense variant in *HMBS* (c.404 T > C) encoding p.R321H, which is seen in five different ethnic groups with a particularly high allele frequency in Caucasians (~2%), exhibits 122 ± 24% of the expressed wild-type activity in vitro, and has been classified as benign by four different submitters in ClinVar [42]. However, the fact that increased urinary ALA (135 mmol/24 h) and PBG (176.9 mg/24 h) concentrations were recognized in the patient suggests the presence of an unidentified second and pathogenic mutation. Two patients carried a missense variant encoding p.R173W [28,29], which occurs at CpG dinucleotides and replaces an arginine residue involved in critical salt bridges that stabilize interactions with the acetate and propionate side groups of the dipyrromethane cofactor in the active site [43,44]. This sequence change causes an almost total kinetic dysfunction associated with severe conformational instability [45]. The small insertion c.966insA resulted in the frameshift leading to the incorporation of 36 completely different residues and to premature truncation that produces an unstable protein structure and loss of enzymatic activity [31]. The small deletion c.1084delT mutation disrupted the stop codon and is predicted to result in aberrant splicing patterns and no-go decay of the transcript or a mutant HMBS protein with 180 amino acids more than the wild-type enzyme [32,46].

The strengths of this review stem from the comprehensive nature of the search and the strict criteria used for case evaluation, overcoming in depth and rigor the ones of the two preceding reviews [3,5]. The majority of existing cases of prepubertal porphyria attacks have likely been published given the extreme rarity of the condition. This review evaluated over 90% of cases reported in the western literature, allowing the estimation of a reliable denominator. It is also the first attempt to identify truly prepubertal children and discriminate them from adolescents, which is a fundamental aspect given the marked differences in levels of sex hormones with an important role in the pathogenesis of AHPs. Moreover, the fact that cases were analyzed separately based on the reported ascertainment method of UPBG provides an extra layer of clarity for the interpretation of results while decreasing the risk of bias due to misclassification of patients, allowing to identify strong congruent characteristics or focus on findings from confirmed attacks in instances of disagreement.

This review has several limitations that need to be considered when interpreting the results, including the small sample size of prepubertal children with confirmed seizures and several possible sources of misclassification bias. First, the methods used to assess urinary porphobilinogen vary widely across studies and it is not possible to be sure about the validity of results in all. UPBG should ideally be normalized per gram or mmol of creatinine in urine to correct for concentration of the urine. Falsely low UPBG could occur if the urine is very dilute and falsely raised UPBG could occur if the urine is very concentrated. Second, some patients were receiving antiepileptic drugs before the onset of neurovisceral symptoms, which are hydroxymethylbilane synthase inhibitors that can induce ALAS1 and produce an iatrogenic increase in the excretion of porphyrin precursors with neurovisceral symptoms similar to those of porphyria attacks [47]. Third, some patients may also have been misclassified as prepubertal children or adolescents because the average age of onset of puberty was used to define these groups rather than Tanner stage or hormone levels, and normal puberty

may begin between the ages of 8–13 years in girls and 9–14 years in boys [48]. Although uncommon, it is also not possible to exclude precocious or late puberty. Future studies may overcome these limitations by identifying children carrying AHP mutations and prospectively following them with appropriate assessment of sexual development and changes in porphyrin precursor levels. These studies would be important in understanding the natural history of AHPs and in determining whether prepubertal porphyria attacks are associated with an increased risk of recurrent or chronic symptoms.

5. Conclusion

Porphyria attacks are exceedingly rare before the onset of puberty. Affected children are more often males as opposed to affected adolescents and adults who are predominantly females. The sex distribution of prepubertal attacks seems to be in part explained by males having a higher burden of coexisting medical conditions with the potential to induce sustained overexpression of ALAS1. Abdominal pain is still a major symptom in the prepubertal age group, but it may be absent in around 20% of patients while it is almost invariably present in adolescents and adults. Adolescents are comparable to adults in most aspects of porphyria attacks. Pediatricians should consider AHPs in the differential diagnosis of children and adolescents with apparently refractory or atypical neurovisceral symptoms, regardless of the presence of abdominal pain or dark urine. Early diagnosis and treatment of porphyria attacks can prevent permanent neurologic complications and premature death.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2021.04.008.

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