



SCIENTIFIC LETTERS

Acute intermittent porphyria in a paediatric population in the region of Murcia: Phenotype and prevalence[☆]



Porfiria aguda intermitente en población pediátrica de la región de Murcia: fenotipo y prevalencia

Dear Editor:

Acute intermittent porphyria (AIP; MIM# 176000) is an autosomal dominant genetic disease with incomplete penetrance (10–15%) and variable expression. It is caused by a partial deficiency of the hydroxymethylbilane synthase (HMBS) enzyme resulting from mutations in the *HMBS* gene. Recently, a prevalence of 6.3 cases per million inhabitants has been reported for Spain,¹ but a higher prevalence is estimated for the Region of Murcia due to the founder effect of the c.669_698del mutation.²

It typically manifests as intermittent attacks of abdominal pain accompanied by other gastrointestinal, cardiovascular, neurological and/or psychiatric symptoms, and many precipitating factors are known, such as prolonged fasting or the consumption of alcohol or certain drugs (Table 1).

The prevalence of AIP in the paediatric population is unknown, symptomatic cases are exceptional, and the reported clinical manifestations are variable. Only one prospective study has been conducted, in Sweden, by Hultdin et al.³; it included 61 patients aged less than 18 years, of whom 10% experienced attacks (all experienced mild abdominal pain).

Although diagnosing AIP in children poses great challenges, this disease should be suspected in patients with nonspecific gastrointestinal, neurological and/or psychiatric manifestations, and should be included in the differential diagnosis of abdominal pain of unknown origin. When suspected, the preferred screening method is the Hoesch test (qualitative detection of PBG in urine), increasingly used in

Table 1 Precipitating drugs.

Aminoglutethimide	Barbiturates
Carbamazepine	Chloramphenicol
Clemastine	Clonidine
Co-trimoxazole	Danazol
Dapsone	Dihydralazine
Dimenhydrinate	Metamizole
Ergot derivatives	Erythromycin
Etamsylate	Ethosuximide
Etomidate	Griseofulvin
Ketoconazole	Meprobamate
Methyldopa	Sulphonamides
Methysergide	Nalidixic acid
Orphenadrine	Oxcarbazepine
Tolbutamide	Phenylbutazone
Phenytoin	Pyrimidone
Pyrazolone	Pyrazinamide

Spain as a result of the launching of the PAGORA project (Acute Porphyria Screening Protocol for patients with unexplained acute abdominal pain in the emergency department), to be followed by specific enzymatic or genetic testing. The management is based on removal of precipitating factors, symptomatic treatment and increased intake of carbohydrates in mild to moderate cases; there is evidence supporting the efficacy of the administration of hemin as haem arginate in severe cases,⁴ and recently Andreeva et al. have published a note about a research project on the use of genetic therapy in these patients (2014).⁵

We performed a retrospective review of the medical records of patients aged less than 18 years with a molecular diagnosis of AIP after the positive identification of a family history of AIP (affected parent) during the followup by the medical genetics department. We analysed the prevalence, phenotype and genotype of these cases.

We present the cases of nine patients, with a mean age at diagnosis of 7 years (Table 2). The prevalence is 28 cases per million inhabitants (total population under 18 years in Murcia, 320,698). The mean duration of followup after diagnosis was 23 months (range, 3–40 months), and according to the documentation, none of the patients experienced attacks during the followup. At age 2, case 9 experienced an episode of mild abdominal pain after the molecular diagnosis of AIP, so he was admitted to the hospital and diagnosed with pain

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Table 2 Summary of epidemiologic characteristics, phenotype and genotype of the cases.

Case	Age at diagnosis (years)	Sex	Associated anomalies	Affected parent	HMBS gene mutations
1	0.5	F		Father, asymptomatic AIP	c.669_698del
2	15	F		Father, asymptomatic AIP	c.669_698del
3	1	F	IUGR	Mother, symptomatic AIP	c.669_698del
4	1.5	M	VACTERL association	Father, asymptomatic AIP	c.669_698del
5	8	F		Father, asymptomatic AIP	c.669_698del
6	12	M		Father, symptomatic AIP	c.669_698del
7	9	F	Sideroblastic anaemia and language delay	Father, asymptomatic AIP	c.669_698del
8	7	F	Language delay	Mother, symptomatic AIP	c.669_698del
9	16	M		Mother, asymptomatic AIP	c.76C > T

of unknown origin (urine PBG was not measured to assess for a possible attack).

Four cases (45%) presented with associated abnormalities. Cases 7 and 8 presented with language delay. Case 7 also suffered from sideroblastic anaemia caused by a homozygous c.683G > T mutation in the *SLC25A38* gene. Case 5 had multiple congenital anomalies compatible with VACTERL association (imperforate anus with rectovesical fistula, lumbar hemivertebrae, superior vena cava draining into the coronary sinus, polycystic left kidney and left grade 5 vesicoureteral reflux).

Case 4 (history of intrauterine growth restriction [IUGR]; birth weight, 1630 g below first percentile) had significant growth retardation at age 3 years (weight and height below first percentile).

The mother of case 4 was diagnosed during pregnancy. She had an acute attack during gestation and required intravenous administration of haem. The child was delivered by emergency C-section due to IUGR and maternal preeclampsia at 36 weeks gestation.

To conclude, the results of our study support the hypothesis that there is a high prevalence of AIP in children in our region due to the founder effect of the c.669_698del mutation: 28 cases per million inhabitants. All patients were asymptomatic at diagnosis and remained so during followup (with a possible unconfirmed attack in case 9), which may be due to the young age of the population under study (7 years). We found a high rate of associated abnormalities (language delay, multiple congenital anomalies, etc.) that had not been reported previously, so additional follow-up studies need to be conducted on larger samples. Attacks during pregnancy could be a risk factor for IUGR in the newborn and hypertension in the mother, but this aspect is still being debated.⁶

Early diagnosis is essential in order to implement measures to avoid attack-precipitating factors, to address the chronic problems caused by the disease, and to provide adequate counselling to the family.

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