Cellular and Molecular Biology ™ **55**, N°1, 19-22
DOI 10.1170/T833

ISSN 1165-158X
2009 Cell. Mol. Biol.™

AWARENESS IS THE NAME OF THE GAME: CLINICAL AND BIOCHEMICAL EVALUATION OF A CASE OF A GIRL DIAGNOSED WITH ACUTE INTERMITTENT PORPHYRIA ASSOCIATED WITH AUTISM

LUDER A.S.[1, 2], MAMET R.[3], FARBSTEIN I.[4] AND SCHOENFELD N.[3, 5]✉

[1]Department of Pediatrics and Genetics Service, Ziv Medical Centre, Safed;
[2]Faculty of Medicine, Technion, Haifa;
[3]National Laboratory for the Biochemical Diagnoses of Porphyrias, Rabin Medical Center, Beilinson Hospital, Petah Tikva;
[4]The Department of Child and Adolescent Psychiatry, Ziv Medical Center, Safed;
[5]The Department of Human Molecular Genetics and Biochemistry, The Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv; Israel
✉Nili Schoenfeld, National Laboratory for the Biochemical Diagnoses of Porphyrias, Rabin Medical Center, Beilinson Hospital, Petah Tikva, 49100 Israel; Tel: 972-3-9377710; Fax: 972-3-9377768;
E-mail: nschoenfeld@clalit.org.il

Received December 31th, 2008; Accepted January 17th, 2009; Published February 16th, 2009

Abstract – Neuroporphyrias, a heterogeneous group of metabolic diseases, are diagnosed less often than their true prevalence justifies. Lack of awareness of porphyrias and their protean clinical and biochemical manifestations, is the most significant hurdle to their recognition and diagnosis. These points are reflected in the unusual case reported here, which highlights the potential damage that inappropriate management may cause when the diagnosis is missed over a long period. We diagnosed heterozygous Acute Intermittent Porphyria (AIP) in a 15-y old girl, who first presented with autism at the age of 4 years. This phenotypic association has not been previously reported. In addition to the unrecognized phenotype, her normal urinary aminolevulinic acid and porphobilinogen, findings which are not compatible with symptomatic porphyria according to well established criteria, could also have led to a missed diagnosis of neuroporphyria. However, the diagnosis of AIP was established on the basis of a 64% reduction in erythrocyte hydroxymethylbilane synthase (HMBS) activity and the finding of a known causative AIP mutation (p.D178N). We therefore recommend that porphyria should be considered in autistic children especially when there is an atypical course or unexpected abreaction to medications. The biochemical and genetic data should be carefully evaluated in a specialized porphyria center.

Key words: Heme biosynthesis, protoporphyrin, tetrapyrrole, free radical; hydrogen peroxide.

INTRODUCTION

Porphyrias are inherited defects in the biosynthetic pathway of heme. Acute Intermittent Porphyria (AIP, OMIM #176000) is one of the four recognized acute porphyrias (neuroporphyrias) and is the commonest porphyria overall. It is caused by mono-allelic mutations in the hydroxymethylbilane synthase (*HMBS*) gene, and is inherited in an autosomal dominant manner with highly variable expression. The phenotype of AIP is extremely polymorphic and non-specific, and includes gastrointestinal, cardiovascular, neuro-psychiatric manifestations and others. Most patients present and are diagnosed between 18-45 years of age (8) a fact which reflects the important effects of hormonal changes associated with puberty and sexual maturity. However, AIP poses a considerable clinical diagnostic challenge and many patients are unrecognized, especially if they present with unusual phenotypes or outside the common age range. Often the deterioration associated with the unwitting administration of

Abbreviations: **AIP,** Acute intermittent porphyria; **ALA,** Aminolevulinic acid; **HMBS,** Hydroxymethylbilane synthase; **NP,** Neuroporphyria; **PBG,** Porphobilinogen.

porphyrogenic medications is the first diagnostic clue (2). We report here an unusual case of AIP associated with autism which illustrates these points.

Laboratory biochemical findings may also be misleading or ambiguous. It is well accepted that AIP is diagnosed biochemically on the basis of increased urinary aminolevulinic acid (ALA) and porphobilinogen (PBG) levels rather than on the basis of decreased HMBS activity (3). The patient, in the case reported here, presented with normal excretion of ALA and PBG even during clinical exacerbations. The diagnosis was based solely on markedly decreased erythrocyte HMBS activity, and this was later confirmed by DNA analysis. Further conclusions which might be drawn from this case are discussed.

CASE PRESENTATION

The patient, the only child of unrelated southern Indian "Cochin" Jews, was born after an uneventful pregnancy and delivery, and had grown and developed normally in the first two years. Following a series of severe middle-ear infections treated with various drugs, she developed severe behavioral disturbances with regression, which accelerated after her third birthday following an elective surgery and a CT scan under general anesthesia.

At age 4 she was diagnosed by a senior psychiatrist with autism and was referred for genetic and metabolic evaluation at tertiary hospital, where she underwent extensive investigation. No evidence of a genetic, metabolic or other identifiable neurological disorder was found. Because of marked irritability, violent tantrums and uncontrollable crying she was evaluated by a child neuro-psychiatrist, who started her on fluvoxamine maleate (*Favoxil*©) to which was added thioridazine (*Melleril*©) with poor effect. Persistent enuresis was treated with desmopressin acetate (*Minirin*©). The treatment was continued for many years but her clinical and neuro-psychiatric state continued to deteriorate.

At age 14, the patient had no speech, had frequent extreme and unpredictable mood swings and was often violent. She was presented for re-evaluation, which included brain MRI, repeat blood and urine metabolic studies, skin fibroblast studies for mitochondrial electron transport chain, pyruvate dehydrogenase complex and mtDNA evaluation, catecholamine metabolism and CSF studies for neurotransmitter abnormalities. None provided diagnostic information. Fragile X and Rett syndromes were also excluded.

At age 15 she had menarche, following which she experienced further deterioration in her behavioral problems, particularly during the pre-menstrual days. There were outbursts of shrieking, violence, uncontrollable agitation and crying. She would clutch at her abdomen and although unable to talk, the distinct impression was that she was suffering from abdominal pain. She was sleeping poorly and losing weight. A gestodene/ethinylestradiol oral contraceptive (*Harmonet*©) was prescribed in order to moderate her hormonal cycles but unexpectedly this was followed by further severe deterioration characterized by acute abdominal pain, vomiting and stupor, which required hospitalization.

Neuroporphyria (NP) was suspected. The patient was referred to the Israeli National Laboratory for the biochemical diagnoses of porphyrias. In accordance with its standard initial evaluation procedure employed for a newly suspected porphyria patient (11), the following six tests were performed: urinary ALA, PBG and porphyrins, fecal porphyrin profile (including coproporphyrin III/I isomeric ratio), plasma fluorometric scan and erythrocyte HMBS activity. As shown in table 1, urinary ALA and PBG were found to be at the borderline-upper levels of normal, however, HMBS activity was markedly reduced to 36% of normal. The results of all the other tests were within the normal range (not shown). Similar findings were observed in the patient's asymptomatic mother (table 1), while no exceptional findings were observed in the father. It is noteworthy that the patient's urinary ALA and PBG were not elevated, not only in quiet phases, but also on two separate occasions of clinical exacerbation, which occurred during pre-menstrual periods. Thus the diagnosis of Acute Intermittent Porphyria (AIP) was established solely on the basis of reduced HMBS activity, and was confirmed by DNA analysis (Zentrallabor, Stadtspital Triemli, Zurich, Switzerland). Both the patient and the mother were found to be heterozygous for the mutation p.D178N in the *HMBS* gene (Table 1), a mutation which has been previously described as causative of AIP (10).

Following the establishment of the diagnosis of AIP all further use of drugs considered to be unsafe in acute porphyrias was avoided. The patient was begun on a high carbohydrate diet and her menstruation was controlled using triptorelin (*Decapeptyl*©). Small doses of haloperidol (*Haldol*©) were administered for aggression and agitation to good effect. She has also been treated with olanzapine (*Zyprexa*©) a serotonin 5-HT_2 and dopamine D_2 receptor antagonist used in porphyria for hypokinesis and tremor (5), also to good effect.

Currently, at the age of 20, she is doing relatively well and her quality of life has improved. She is attending occupational therapy, and working at a sheltered workshop, and is able to travel on a supervised bus with no problems. She is quiet, happy and cooperative, sleeping and eating well and she has regained her lost weight. Nevertheless, her neurological damage is irreversible and no significant intellectual change has been seen.

Table1. The Biochemical and the genetic findings in the patient in and her parents.

	Urinary ALA µmol/24h	Urinary PBG µmol/24h	RBC HMBS activity % of normal	Mutation analysis p.D178N
Patient	34.2±1.6 (n=5)	9.2±1.7(n=5)	36	+/-
Mother	41.2	13.3	44	+/-
Father	----	----	90	-/-
Normal	<38	<8.8	>70	-/-

DISCUSSION

Porphyria is a polymorphic syndrome biochemically and phenotypically. It therefore often escapes detection, sometimes for years, in an individual patient. Numerous reports have testified to the fact that psychiatric manifestations of porphyria are particularly heterogeneous and easily overlooked (1). The unexpected deterioration of a patient after treatment with a psychotropic drug may be the first clue to the diagnosis and a paradoxical reaction to such a medication should prompt investigation for porphyria (2). Although there have been isolated reports of mental retardation associated with homozygotic AIP and Variegate Porphyria (4,9), the importance of the case reported here is the presence of a previously unreported neuro-psychiatric symptom complex, childhood autism, associated with heterozygotic AIP. Of particular note is the unusually young age at which the disease became manifest. In retrospect, general anesthesia was twice administered to the patient (details unknown) and she was treated for years with a variety of medications, some of which (fluvoxamine, thioridazine and others), are considered unsafe for porphyria patients (13). These undoubtedly contributed to her severe problems. Nevertheless, porphyria was not considered and was not included in a broad investigation in a major tertiary centre.

Although in an isolated case a causal relationship between AIP and autism cannot be conclusively established, nevertheless the failure to find an alternate diagnosis despite thorough and repeated investigation, the progressive/periodic nature of her disorder, it's clear relationship to menses and to known porphyrogenic drugs and its marked improvement upon their withdrawal, all suggest that such a relationship is highly likely. We therefore suggest that evaluation for NP of pediatric patients with autistic syndrome, especially those with an atypical course or unexpected deterioration, should be considered.

Families of autistic patients are often desperate to find a specific genetic or metabolic cause for their child's tragedy. Scientific and popular publications contain many speculations as to inherited, psychological and environmental factors that may contribute to autism. There have been no previous published reports, before the current one, concerning porphyria and autism.

A recently published paper reported the findings of increased urinary coproporphyrin in 106 autistic and 163 developmentally abnormal children (7). Porphyrinuria is a non-specific phenomenon in many acquired and toxic states, unrelated to but often mistakenly confused with porphyria. The authors of this paper themselves related their findings to environmental heavy metal poisoning and did not make any suggestion of genetic porphyria. In fact, our patient, as with many other porphyric patients, did not exhibit porphyrinuria.

Biochemical diagnosis of NP frequently poses a real challenge. As this case clearly shows, ALA and PBG measurements may be inconclusive. The diagnosis in this case, as in another case previously described (12), was based solely on markedly reduced erythrocyte HMBS activity. This test is available only in specialized porphyria centers, and even in these, it is not always carried out, especially when patients present with normal urinary ALA and PBG. Hultdin et al.(6), in a population-based study in Sweden, showed that in children with AIP, symptoms and signs may differ from those of adults and that they may present with normal urinary ALA&PBG even during symptomatic periods.

On the above basis, we would like to suggest that the criteria employed for exclusion of symptomatic acute porphyria in children will differ from those that are well accepted in adults. Meaning, the diagnosis of NP (AIP, Variegate Porphyria, Hereditary Coproporphyria) in children may be established in patients who present with normal ALA and PBG. AIP may be diagnosed solely on the basis of reduced erythrocyte HMBS activity. The diagnosis of either Variegate Porphyria or Hereditary Coproporphyria may be based on characteristic fecal porphyrin profile and/or plasma scan. However, the diagnosis should always be confirmed by DNA testing, as in the case reported here.

Awareness is the name of the game; early diagnosis of NP may prevent irreversible damage. Unfortunately, in the present case, the diagnosis of AIP at 15 years of age, although improving her quality of life and preventing further deterioration, could not reverse existing neurological damage.

ACKNOWLEDGEMENT

We thank Dr X. Schneider-Yin and Prof E.I.Minder, Zentrallabor, Stadtspital Triemli, Zurich, Switzerland, for performing DNA mutation analysis.

REFERENCES

1. Burgovne, K., Swartz, R. and Ananth, J., Porphyria: reexamination of psychiatric implications. *Psychother Psychosom* 1995, **64**:121-130.
2. Ellencweig, N., Schoenfeld, N. and Zemishlany, Z., Acute intermittent porphyria: psychosis as the only clinical manifestation. *Isr J Psychiatry Rel Sci* 2006, **43**:52-56.
3. European Porphyria Initiative (EPI): http:// www.porphyria-europe.com , 2005.
4. Hessels, J., Voortman, G., van der Wagen, A., van der Elzen, C., Scheffer, H., And Zuijderhoudt, F.M., Homozygous acute intermittent porphyria in a 7-year-old boy with massive excretions of porphyrins and porphyrin precursors. *J Inherit Metab Dis* 2004, **27**:19-27.
5. Holroyd, S. and Seward, R.L., Psychotropic drugs in acute intermittent porphyria. *Clin. Pharmacol Ther*. 1999, **66**:323-325.
6. Hultdin, J., Schmauch, A., Wikberg, A., Dahlquist, G. and Andersson, C., Acute intermittent porphyria in childhood: a population-based study. *Acta Paediatr*. 2003, **92**:562-568.
7. Nataf, R., Skorupka, C., Amet, L., Lam, A., Springbett, A. and Lathe, A., Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. *Toxicol Appl Pharmacol* 2006, **214**:99-108.
8. Nordmann, Y., Puy, H., and Deybach, J.C., The porphyrias. *J Hepatol*. 1999, **30**:12-16.
9. Norris, P.G., Elder, G.H. and Hawk, J.L., Homozygous variegate porphyria: a case report. *Br J Dermatol*. 1990, **122**:253-257.
10. Puy, H., Deybach, J.C., Lamoril, J., Robreau, A.M., Da Silva, V., Gouya, L., Grandchamp, B. and Nordmann, Y., Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet*. 1997, **60**:1373-1383.
11. Schoenfeld, N. and Mamet, R., Individualized workup: a new approach to the biochemical diagnosis of acute attacks of neuroporphyria. *Physiol Res.* 2006,**55** Suppl 2:S103-8.
12. Schneider-Yin, X., Ulbrichova, D., Mamet, R., Martasek, P., Marohnic, C.C., Goren, A., Minder, E.I. and Schoenfeld, N., Characterization of two missense variant in the hydroxymethylbilane synthase gene in the Israeli population, which differ in their associations with acute intermittent porphyria. *Mol. Genet. Metab*. 2008, **94**:343-346.
13. The Norwegian porphyria center (NAPOS): The Drug Database for Acute Porphyria, http://www.drugs-porphyria.org , 2007.