Mini Review

Porphyria in Japan : The Past, Present, and Future

Masao KONDO[1)] and Tetsuya KUBO[2,3)]

[1)] Faculty of Human Life Sciences, Musashi Institute of Technology, 8-9-18, Todoroki, Setagaya-ku, Tokyo 158-8586, Japan, [2)] Faculty of Environmental and Information Studies, Musashi Institute of Technology, 3-3-1, Ushikubo-Nishi, Tsuzuki-ku, Yokohama 224-0015, Japan [3)]Department of physiology, School of Medicine, Showa University, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

Porphyrias are a group of disorders caused by inherited deficiencies in the activities of the enzymes of the heme biosynthetic pathway. Afflicted patients suffer either from neurological disturbances, cutaneous photosensitivity, or both. The first recorded case of porphyria in Japan was a patient with congenital erythropoietic porphyria (CEP), and was reported by Sato and Takahashi in 1920. Since then, 884 cases of porphyria have been diagnosed based on characteristic clinical and/or laboratory findings (502 males, and 375 females and 7 of unknown gender). The most recent data available is dated December 31, 2007. We analyzed these 884 cases on the basis of chronological occurance, age distribution, gender difference, geographical distribution, risk factors, initial diagnosis of acute porphyric patients, and prognosis. In this study, we discuss our findings and will also explain the difficulties in gathering reliable data for accurate epidemiological research.

Key words: Porphyria, Hepatic porphyria, Erythropoietic porphyria, Acute porphyria, Cutaneous porphyria

Introduction

Porphyrias are a group of disorders, which induce excess production of porphyrins, as well as cause their accumulation in the tissues [1,2]. They also increases the excretion of metabolites, as a result of inherited or acquired deficiencies in the activities of the enzymes of the heme biosynthetic pathway. There are 8 types of porphyria. Like other congenital metabolic disorders, this disorder is very rare, has attracted attention for a long time because of its specific symptoms, and was first observed by AE Garrod in 1923 [3], in his study *Inborn errors of metabolism*. Porphyria manifests a wide variety of symptoms, including cutaneous, psychoneurotic, gastrointestinal, and endocrine; endogenous and exogenous environmental factors influence the manifestation of these symptoms [4]. Therefore, acute porphyria may be fatal because of false and/or delayed diagnosis. A poor prognosis may be anticipated. Therefore, it is important that we have accurate knowledge of porphyria. In this report, we outline the past, present, and future of porphyria related research.

Results and Discussion

1. Classification of porphyria. (Fig.1)

Heme biosynthesis involves 8 enzymes [5], and the absence of just one leads to an arrest of heme production and then mortality. In other

Address,Akabane-nisi,Kitaku,Tkyo115-0055, Japan
Received 04/09, 2009

Porphyrin metabolism	Enzyme	Porphyria
Glycine＋Succinyl-CoA		
↓	ALA syntase (ALAS)	
ALA		
↓	ALA dehydratase (ALAD)	ADP
PBG		
↓	PBGD deaminase (PBGD)	AIP
HMB		
↓	UPgenⅢsynthase (UROS)	CEP
UPgenⅢ		
↓	UPgen decarboxylase (UROD)	PCT,HEP
CPgenⅢ		
↓	CPgen oxidase (CPO)	HCP
PPgenⅨ		
↓	PPgen oxidase (PPO)	V P
PPⅨ		
↓ Fe^{2+}	Ferrochelatase (FeC)	EPP
Heme		

Fig. 1 Heme biosynthetic pathway and porphyrias

ALA；δ -aminolevulinate、PBG；porphobilinogen、HMB；hydroxylmethylbilane
UP；uroporphyrin、CP；coproporphyrin、PP；protoporphyrin

words, reduction in enzyme activity as a result of abnormalities in enzyme-encoding genes can induce excessive production of porphyrin metabolites in porphyria. Massive accumulation of such metabolites in the tissues can have various clinical manifestations through phototoxic reaction and the generation of active oxygen. Porphyria types can be classified according to the clinical symptoms (cutaneous or acute), organs affected (erythropoietic or hepatic), or enzymes affected, but no harmonization of these classifications has been attempted.

2. Diagnostic criteria of porphyria. (Table1)

Porphyria, which manifests as a variety of symptoms, is often falsely diagnosed. The disease is diagnosed on the basis of clinical symptoms, blood examination, liver function tests, gene diagnosis, enzyme diagnosis, biochemical diagnosis, and pathology. Biochemical quantification of blood and fecal/urine porphyrins and its precursors (ALA and PBG) is the most effective way of achieving a differential or definitive diagnosis [6]. Because an examination for porphyrin is never done as part of a general clinical checkup, the delay in the diagnosis of porphyria that commonly results, often markedly impairs patients' quality of life. There are a limited number of institutions that conduct examinations for porphyrin, and no international diagnostic criteria currently exist. Therefore, measurement is often done by a small number of specialists on the basis of different diagnostic criteria, and this can lead to confusion. This situation illustrates the fragility of healthcare policies for rare diseases in our country. Urgent countermeasures are required to address this problem.

3. Porphyrias reported in Japan from 1920 to 2007. (Table2), (Fig 2)

From the time of the first case of congenital erythropoietic porphyria (CEP) as reported by Sato et al. in 1920 [7] though to December 2007, a total of 884 cases have been reported by individual researchers or in *Igaku Chuo*

Table 1. Classification of porphyrias

Porphyrias			Enzyme	Inheri-	Clinical features		Biochemical signs
Classifi-cation		Condition	defect	tance	Skin	Neurologic	Porphyrins and its precursors
Erythropoietc	Cutaneous	Congenital erythropoietic porphyria (CEP)	UROS	Recessive	+++	−	UP I (Urine, Blood)
		Erythropoietic protoporphyria (EPP)	FECH	Dominant	+～++	−	FP (Blood)
		Hepatoerythropoietic porphyria (HEP)	UROD	Recessive	+++	−	UPⅢ(Urine)、ZP (Blood)
Hepatic		Porphyria cutanea tarda(Familial)(f-PCT)	UROD	Dominant	+～+++	−	UPⅢ(Urine)、isoCP (Feces)
		Porphyria cutanea tarda(Sporadic)(s-PCT)	UROD	Unknown	+～+++	−	UPⅢ(Urine)、isoCP(Feces)
	Acute	Variegate porphyria (VP)	PROX	Dominant	+～++	++	ALA, PBG, UpⅢ(Urine)、PP、XP (Feces)
		Hereditary coproporphyria (HCP)	CPO	Dominant	−～++	++	ALA, PBG, CPⅢ (Urine)、CP (Feces)
		Acute intermittent porphyria (AIP)	PBGD	Dominant	−	++	ALA, PBG (Urine)
		ALAD deficiency porphyria (ADP)	ALAD	Recessive	−	++	ALA (Urine)

FP; Free erythrocyte protoporphyrin、ZP；Zinc cherated protoporphyrin

Table 2. Porphyrias reported in Japan from 1920 up to 2007

	CEP	HEP	EPP	ADP	AIP	HCP	VP	PCT	AP	Total
Year	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)	Total (M:F:U)
1920-1955	12 (3:9:0)	0	0	0	2 (0:2:0)	0	0	0	8 (2:6:0)	22 (5:17:0)
1956-1965	4 (2:2:0)	0	2 (2:0:0)	0	35 (7:28:0)	0	9 (1:8:0)	3 (3:0:0)	11 (3:8:0)	64 (18:46:0)
1966-1975	10 (5:5:0)	1 (1:0:0)	22 (12:10:0)	0	65 (13:51:1)	21 (3:17:1)	17 (5:12:0)	42 (39:3:0)	7 (2:5:0)	185 (80:103:2)
1976-1985	3 (2:1:0)	3 (2:1:0)	37 (26:11:0)	0	31 (4:26:1)	1 (1:0:0)	11 (0:11:0)	147 (141:5:1)	10 (3:7:0)	243 (179:62:2)
1986-1995	4 (2:2:0)	0	43 (29:14:0)	0	31 (4:27:0)	4 (3:1:0)	9 (1:8:0)	73 (60:12:1)	13 (3:9:1)	177 (102:73:2)
1996-2005	1 (1:0:0)	2 (1:1:0)	60 (37:23:0)	1 (0:1:0)	27 (6:21:0)	11 (3:8:0)	8 (3:5:0)	46 (42:4:0)	5 (2:2:1)	161 (95:65:1)
2006-2007	1 (0:1:0)	0	17 (12:5:0)	0	2 (1:1:0)	2 (2:0:0)	1 (1:0:0)	7 (7:0:0)	2 (0:2:0)	32 (23:9:0)
Total	35 (15:20:0)	6 (4:2:0)	181 (118:63:0)	1 (0:1:0)	193 (35:156:2)	39 (12:26:1)	55 (11:44:0)	318 (292:24:2)	56 (15:39:2)	884 (502:375:7)
Year*	1920	1972	1964	1979	1932	1966	1962	1957	1962	

M, male; F, female; U, unknown gender; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; HEP, hepatoerythropoietic porphyria; ADP, δ-aminolevulinate dehydratase porphyria; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; VP, variegate porphyria; AP, acute porphyria of undefined origin; PCT, porphyria cutanea tarda. *, Year when the 1st case was reported

Zasshi. In recent years, there have been a decreasing number of porphyria reported, possibly because physicians have become less interested in the disease. The actual number of patients with porphyria may therefore be several times higher than the reported figure, and the estimated population of genetic carriers is presumed to be several tens of times higher than the number of cases.

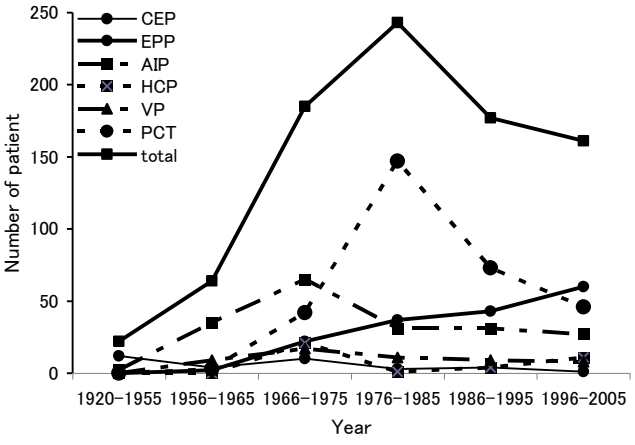

Fig 2. Porphyrias reported in Japan from 1920 up to 2005

The few hundred patients with the most intense cutaneous manifestation of CEP have been reported all over the world [8], whereas only 35 of these types of patients have been reported in Japan. Almost no cases have been reported in Asian countries other than Japan. Porphyria must exist in these developing countries, so improvement of techniques for the definitive diagnosis and understanding of porphyria is needed there.

4. Precipitating factors, initial diagnosis, and prognosis of porphyria.

The factors that had precipitated the development of clinical symptoms are strong ultraviolet light in the case of erythropoietic protoporphyria (EPP); long-term alcohol intake in the case of porphyria cutanea tarda (PCT); and phenobarbital and other agents, pregnancy, menstruation, delivery, and other types of stresses in the case of acute porphyria, in which daily lifestyle factors play important roles [4]. Many porphyria are not diagnosed properly during initial medical examinations or hospital admissions. The initial diagnoses of these porphyria cases, as summarized in Table 3, include various neurologic, gastrointestinal, and dermatologic disorders. Especially acute porphyria is often falsely diagnosed, and thus

Table 3. Initial diagnosis of acute hepatic porphyrias (%)

	AIP	VP	HCP	AP	Total
Acute abdomen	48	53	48	63	51
Ileus	25	13	8	17	19
Appendicitis	15	0	4	10	10
Psychogenic disorders (hysteria)	15	0	0	0	8
Pancreatitis	9	8	4	3	7
Epilepsy	2	0	24	7	6
Hyperemesis gravidarum	6	4	4	7	6
Acute peptic ulcer	4	0	4	7	4
Liver dysfunction	4	4	4	0	3
Neuropathy	3	4	0	0	2
Guillain-Barre syndrome	2	8	0	0	2
Ovarian volvulus	2	0	0	3	2
Ectopic pregnancy	2	0	0	0	1
Gallstone	1	4	0	0	1
Subacute opticoneuropathy (SMON	2	0	0	0	1
Kidney/Ureter stones	1	0	0	0	1
Myelopathy	1	0	0	0	1
Photodermatosis	0	4	4	0	1
Others	1	0	4	0	1

frequently results in fatal outcomes. Porphyria is often incorrectly identified as acute abdominal pain or ileus; about one-fourth of patients undergo laparotomy after a false diagnosis. These outcomes indicate that physicians have an inadequate understanding of porphyria and need to be educated accordingly.

5. The past, present, and future of porphyria.

The world's first porphyria case was reported by Schultz in 1874 [9]. Since then, clinical investigations and biochemical research to clarify the causes of porphyria have always been conducted in parallel, thus enabling significant investigatory progress. Specifically, biochemical investigations into porphyrin began with an analysis of the chemical structure of each porphyrin body by Fischer in 1915 [10]. The heme biosynthetic pathway was discovered in the 1940's [11]. Then, between 1963 and 1964—in the era of enzymological research—δ-aminolevulinate syntase (ALAS) activity was demonstrated to be abnormally induced in patients with acute intermittent porphyria (AIP) [12]. This era was followed by the current one of gene diagnosis and therapy. Around the beginning of the time of enzymological research—in the mid 1960's—Japan's first cases of various disease subtypes, including PCT, variegate porphyria (VP), hereditary coproporphyria (HCP), and EPP, were reported one after another. The number of case reports increased accordingly (Table 2).

However, there has been little non-case-study research of the patients themselves, and little government action has been taken in our country. To be specific, the government has a poor appreciation of rare diseases and has invested little time or money in their research. A limited number of researchers have investigated porphyria out of a sense of curiosity, but there have been few patient-directed studies on porphyria. As a result, patients are forced to bear large medical expenses, without reliable therapy, for their entire lifetimes. Under such circumstances, because this disease has not yet been designated intractable, and uniform diagnostic procedures and therapy have not been established, many female patients refrain from marriage and childbirth in order to avoid passing their genes on to the next generation. Thus a form of unpardonable, self-inposel tradition of purification is now being handed down to future patients. The government needs to understand these issues so that patients can improve the quality of their lives and receive highly advanced medical treatment to relieve their symptoms. This will require a prompt overhaul of the current system.

6. Activities by a porphyria patient group.

In 1998, the Japanese porphyria patient group SAKURA Friends was formed by several volunteers. One of them, a CEP patient, established a homepage for porphyria patients (URL:http://www.sakuratomonokai.com/).
Since then, many patients have enrolled in this group, and its activities include distribution of a newsletter, medical consultation, drug information, and intercommunication. The content of the homepage has been improved. Currently, the group is actively involved in the approval process for new pharmaceuticals and in efforts to have porphyria designated a rare

disease. Portions of the articles of the patient group are given below.

1) Objectives

In the group, we strive for a complete cure of this syndrome of abnormal metabolism, through the support of research investigating the causes of disorders of porphyrin metabolism, early diagnosis, and the establishment of treatment. We also strive to promote mutual support and social contact among members in order to enhance knowledge about disorders of porphyrin metabolism and encourage optimistic daily care. Also, we aim to reinforce the medical system and promote social measures such as the improvement of patient welfare.

2) Our undertaking covers these topics:

1. Social contact and welfare among members
2. The publication of a bulletin
3. Medical care and medical consultation to promote a sound support system and information about health care centers
4. Support of the medical system
5. Publicity for the group
6. Exchange of information and experiences with organizations and groups in regard to disorders of porphyrin metabolism within and outside Japan
7. Other items, as considered necessary, for attaining the objectives of the group

---

The SAKURA TOMONOKAI is a meeting which the patients made, and an official name is called a Japan Porphyria Fundation. This meeting was born from a purpose to live brightly and forward like cherry blossoms every day.

Acknowledgment

This work has been supportwed in part by grants from the Japan Porphyria Fundation .

References

1. Sassa S. The hematological aspects of porphyria. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligson D, eds. Williams Hematology. 6th ed. New York, NY: McGraw-Hill; 2001:703-720.
2. Kauppinen R. Porphyrias. *Lancet* 2005; 365:241-252.
3. Garrod AE. Inborn errors of metabolism. Hodder & Stoughton. London, 1923.
4. Kondo M, Yano Y, Shirataka M, Urata G, Sassa S. Porphyrias in Japan:complication of all cases reported through 2002 (Review article). *Int J Hematol*, 2004:448-456.
5. Dailey HA. Enzymes of heme biosynthesis. *JBIC* 1997; 2:411-417.
6. Kondo M. Biological diagnostic technique of porphyria. *Jpn J Dermatol* 1997; 106:1-8.
7. Sato A, Takahashi H. Family anemia of a certain kind or an anemia of hemoglobinuria which is not yet reported. *Acta Paediatr Jpn* 1920; 239:47-48.
8. Kondo M, Yano Y, Urata G, Takamura N. Congenital erythropoietic porphyria in Japan: Complication of all cases reported through 2005. *Porphyrins* 2005; 14:69-84.
9. Schultz JH. Ein fall von Pemphigus leprosus, compliciert durch Lepra visceralis (thesis), Gleiswald, 1874.
10. Fischer H, Hilger J. Zur kenntnis der naturlichen porphyrine. II. Uber das Turacin, *Z Physiol Chem* 1923: 128:167-174.
11. Shemin D. The succinate-glycine cycle. The role of δ-aminolevulinic acid in porphyrin synthesis. *Porphyrin Biosynth Metab Ciba Found Symp*. Churchill, London 1955:4, 4-22.
12. Nakao K, Wada O, Kitamura T, Uono K, Urata G. Activity of aminolevulinic acid synthase in normal and porphyric human liver. *Nature* 1966; 210:838-839.