NEUROLOGICAL MANIFESTATIONS OF ACUTE INTERMITTENT PORPHYRIA

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Abstract – Acute intermittent porphyria (AIP) is an inherited metabolic disease due to a deficiency of the hydroxymethylbilane synthase in the haem biosynthesis. It manifests with occasional neurovisceral crises due to overproduction of porphyrin precursors such as aminolaevulinic acid (ALA) which is released from the liver to the circulation. The majority of the acute attacks manifest as a combination of abdominal pain, mild mental symptoms and autonomic dysfunction mainly due to vagal insufficiency. However, both acute peripheral neuropathy and encephalopathy may develop if an acute attack proceeds especially due to administration of porphyrinogenic drugs. Acute porphyric neuropathy is predominantly motor and associates with a history of abdominal pain and dysautonomia, CNS involvement and mild hepatopathy. Other features include preservation of achilles reflexes while global hyporeflexia and neuropathic or myalgic pain. The pathogenesis of porphyric neuropathy is complex but overproduction of ALA via direct neurotoxicity, oxidative damage, and modification of glutamatergic release may initiate the neuronal damage. Acute encephalopathy manifests as a combination of mental symptoms, seizures, SIADH, but rarely focal CNS deficits. Posterior reversible encephalopathy syndrome (PRES), which has been found in patients' MRI during an acute attack with severe encephalopathy, could explain the pathogenesis of encephalopathy and seizures in AIP. Neurological manifestations are unspecific and careful interpretation of abnormal excretion of porphyrin precursors should be done before the symptoms can be related to inherited acute porphyrias and not to secondary porphyrinuria. Currently the prognosis of neuropathy and encephalopathy in AIP is good even in severe attacks, but physicians should be aware of a potentially fatal outcome of the disease.

Key words: porphyria, acute intermittent poprhyria, neuropathy, encephalopathy, MRI, PRES

INTRODUCTION

Acute intermittent porphyria (AIP) manifests with occasional acute attacks due to overproduction of porphyrin precursors (porphobilinogen, PBG and delta-aminolevulinic acid, ALA) in the liver.

Abbreviations: AIP, acute intermittent porphyria; **ALA,** aminolaevulinic acid; **CNS,** central nervous system; **CSF,** cerebrospinal fluid; **CT,** computed tomography; **DW,** diffusion-weighted (magnetic resonance imaging); **GABA,** gamma aminobutyric acid; **HMBS,** hydroxymethylbilane synthase; **MRI,** magnetic resonance imaging; **PBG,** porphobilinogen; **PNP,** peripheral neuropathy, polyneuropathy; **SIADH,** syndrome of inadequate secretion of antidiuretic hormone

PBG and ALA are released massively to the circulation and ALA, which is a neurotoxic compound (Figures 1 and 2), is the most potential candidate to cause autonomic dysfunction and mental symptoms in these patients (39). In a protracted attack, acute peripheral neuropathy (PNP) or acute encephalopathy may occur (28,34,63,68,75)
The neurological manifestations of acute porphyria are polymorphic (Table 1) and can easily be neglected. Thus, the current estimate that only 5-17% of symptomatic patients would have a neurological impairment (56,85), is probably too low. Since the mortality of an acute

attack is still high (~10%) especially in undiagnosed patients (63), the correct diagnosis and treatment at the early phase of an acute attack are crucial in order to prevent progression of neuropathy and encephalopathy (56). In some cases, however, similar neurological manifestations associated with secondary porphyrinuria have been misdiagnosed as acute porphyria (13,30,65,78) and thus, careful interpretation of adequate biochemical analyses must be performed before the diagnosis of an inherited acute porphyria can be established (64).

ACUTE ATTACKS

An acute attack is a neurovisceral crisis manifesting as a combination of signs and symptoms listed in Table 1. The severity of each symptom and the combination of the symptoms vary among patients, and their co-occurrence together with abdominal pain should suggest acute porphyria (39). Currently many patients with acute porphyria are diagnosed with a mutation analysis at their symptom-free stage, and acute attacks can be treated properly already at the early phase preventing progression of an acute attack to more severe polyneuropathy and encephalopathy (39,56). Thus, the majority of patients with diagnosed AIP have acute attacks which manifest as a combination of abdominal pain, mild mental symptoms and autonomic dysfunction without PNP or focal CNS impairment (56) (Table 1).

NEUROLOGICAL MANIFESTATIONS DURING AN ACUTE ATTACK

Autonomic neuropathy

Autonomic neuropathy is responsible for the majority of the symptoms during an acute attack (Table 1). Abdominal pain, which is a hallmark of an acute attack, is considered to be the sign of autonomic dysfunction (51) due to splanchnic dysfunction (43) such as intestinal dilatation or spasm (14). The alternative mechanisms such as local vasoconstriction and intestinal ischemia have also been suggested (19,44). The exact mechanism of pain is still obscure (43) and even enteric ganglionitis/ganglionopathy (31) or sensory neuropathy could be involved. Tachycardia, which reflects the activity of the disease (69), is commonly associated with pain and occurs in combination with constipation, hypertension and bladder paresis. Orthostatic hypotension (75), diastolic hypertension (28,75) and diarrhoea (54,75) have occasionally been observed.

Vagus nerve demyelination, axonal loss and chromatolysis of sympathetic ganglion cell in autopsies (27,76) support the direct involvement of autonomic fibers and explain partly dysautonomic features. In addition, direct gut-spasmodic effect of ALA (14) could be mediated through recently recognised receptors (31).

During an acute attack abnormal parasympathetic cardiac reflexes have been demonstrated in eight AIP patients using the battery of standard Ewing's tests (22,43). The slightly abnormal result in the sympathetic sustained hand-grip test (43) is questionable, since it is uninformative in patients with motor PNP. Thus, the vagal insufficiency rather than sympathetic activation is more likely explanation for cardiac dysautonomia in AIP. The other signs of cholinergic insufficiency are constipation and bladder paresis. The mechanisms of these phenomena are currently quite speculative, since no appropriate bowel emptying or urodynamic tests have been reported in these patients. The origin of nausea and vomiting in acute porphyria is unknown (51). Both abnormal bowel motility and central mechanisms may be involved.

Reduced heart rate variability found in 23 patients with AIP in remission, (8) and abnormal response to Valsalva maneuver in 10 symptom-free patients with AIP (43) suggest mild chronic cardiac dysautonomia with cholinergic insufficiency (8). The tests of sympathetic function in those patients have been normal (8,43). In summary, autonomic neuropathy in acute porphyria manifests as acute pandysautonomia with predominance of parasympathetic insufficiency (43).

ACUTE PERIPHERAL NEUROPATHY

Acute PNP is the most common neurological complication of a severe acute attack (28,68,75) (Table 1). It manifests as diffuse muscle weakness, symmetrically distributed hyporeflexia and sensory loss (63,68) in combination with abnormal excretion of porphyrins and their precursors. Similar to other classical polyneuropathies, distribution of muscle weakness is symmetrical and evenly distributed in the proximal and distal muscle groups of the upper extremities. In the lower extremities the weakness is pronounced in the proximal muscles
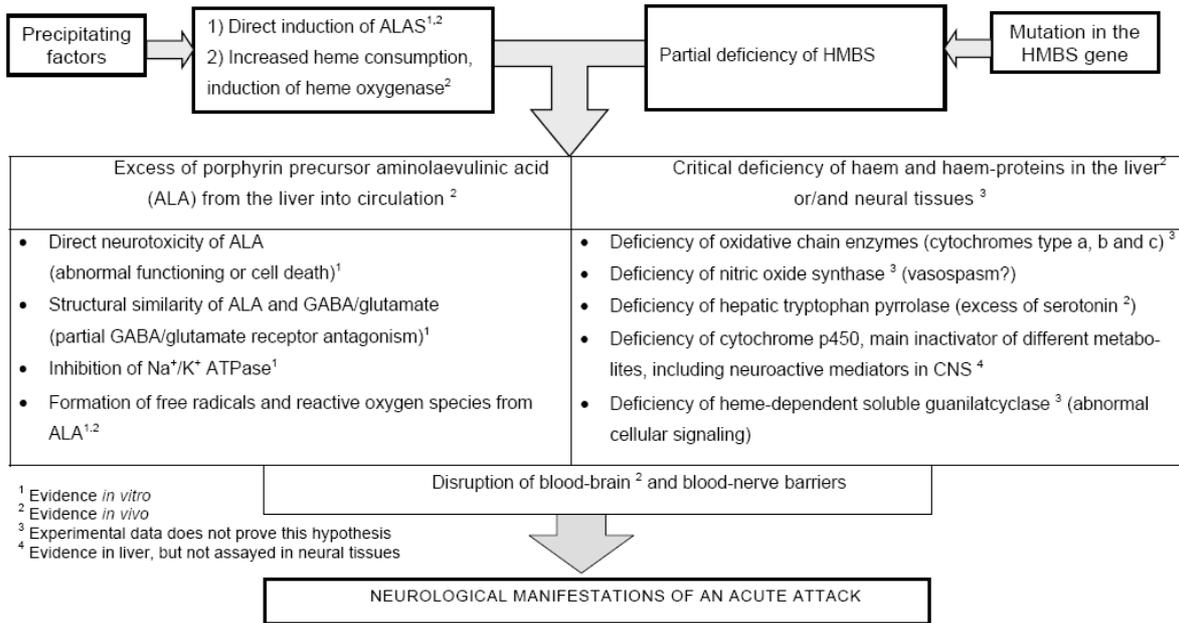
Figure 1. Pathogenesis of neurological impairment during an acute attack of AIP (Main hypotheses)
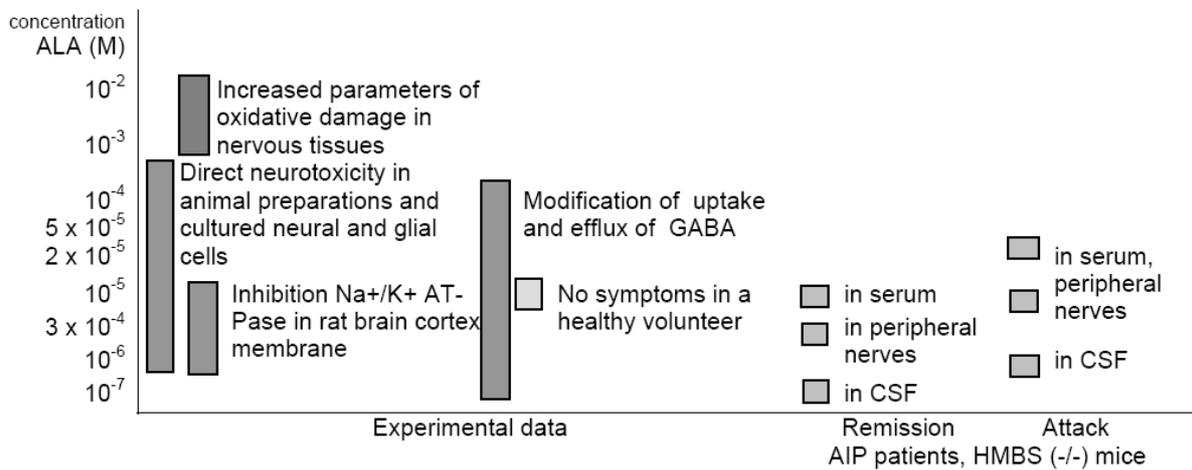
Figure 2. Comparison of ALA concentration detected in experimental models and AIP patients during an acute attack

Table1. Clinical manifestations during an acute attack in different patient series

Signs and symptoms	Unselected patients with acute porphyria						Selected AIP patients with neuropathy or encephalopathy	
Series	(1)	(2)	(3)	(4)*	(5)†	(6)*	(7)	(8)
Number of attacks/patients	n=252	n=50	n=40	n=88	n=51/22	n=112/24	n=29/25	n=12
	%	%	%	%	%	%	%	%
I. Autonomic dysfunction								
Abdominal pain	85	94	95	95	96	97	100	83
Tachycardia (>80 per min)	28	64	80	85	79	38	96	92
Hypertension	40	54	36	55	57	74	52	67
Constipation	48	84	48	80	78	27	94	75
Vomiting and nausea	59	88	43	80	84	79	44	42
Bladder paresis	n.a.	n.a.	12	n.a.	n.a.	n.a.	54	33
II. Peripheral neuropathy								
Pain in the back and limbs	n.a.	52	50	70	25	n.a.	68	75
"Pareses" / "Muscle weakness"	42	68	60	50	8	10/46‡	100	83
Low/absent tendon reflexes	n.a.	54	29	n.a.	n.a.	n.a	97	83
Respiratory paresis	n.a.	10	9	20	0	n.a	55	67
Cranial neuropathy	n.a.	28	54	15	0	n.a	69	58
Neuropathic sensory loss	n.a.	38	26	25	n.a.	n.a	59	42
III. Encephalopathy								
Mental symptoms	55	58	40	40	19	1§	86	92
Seizures	10	16	20	20	1	5	21	33
Coma	n.a.	n.a.	10	n.a.	0	n.a	n.a.	25
Blurred vision	n.a.	6	6	n.a.	2	n.a	7	8
Babinski signs	n.a.	10	3	n.a.	n.a.	n.a	3	50
Nystagmus	n.a.	2	0	n.a.	n.a.	n.a	7	17
Cerebellar ataxia	n.a.	2	0	n.a.	0	n.a	0	8
IV. Metabolic changes								
Hyponatraemia	n.a.	25	26	61	32	31	28	42
Transaminases increased	n.a.	n.a.	13	n.a.	n.a.	n.a.	69	100
Pink/ Red/ Dark urine	n.a.	n.a.	74	90	90	n.a.	100	92

[1] (81); [2] (28); [3] (75); [4] (54); [5] (56); [6] (34); [7] (68); [8] (63)

*AIP and VP. † Cases early treated with heme arginate. ‡ Totally of attacks/of patients. § Only psychosis is included; n.a., not applicable

(68). Asymmetrical weakness in the arms can precede severe symmetrical polyneuropathy.

Another outstanding feature of PNP in acute porphyria is the preservation of the ankle jerks in about half of patients while otherwise there is global areflexia (68). Respiratory failure, the most severe complication of muscle weakness because of diaphragm paresis, has been common in the earlier series (10%-64%) (28,54,68,75) but uncommon in patients treated at the early phase of an acute attack (56).

The sensory symptoms of PNP are usually due to irritation (painful paresthesia, hyperesthesia) (79) which may be misdiagnosed as conversion. Sensory loss is less common. Both "glove-and-stocking" distribution of sensory loss typical for length-dependant polyneuropathies (eg, in diabetic PNP) or patchy proximal have been described (68). Cranial neuropathy affecting mainly III, VI, IX and X cranial nerves is present in 35-55% of acute attacks with PNP (68,75).

Focal CNS involvement has been observed in 7 to 50% of the patients with porphyric PNP (63,68) (Table 1). Acute PNP without abdominal pain is a rare phenomenon (3,30). However, when progressive muscle weakness manifests, the intensity of abdominal pain may decline (28,34,75), which may lead to misdiagnosis.

In the majority cases with AIP a predominantly motor type of PNP accompanied by abdominal pain has been described. Single cases of mononeuritis multiplex (41,68), focal motor polyneuropathy (68), "pseudo myasthenia" (28) during an acute attack have been published. This suggests that patients with AIP may have variable neurological manifestations during an acute attack. In some of the cases, however, the diagnosis of acute porphyria was based on inadequate biochemical diagnostics or their interpretation, and thus, acute porphyria might not be the cause of the symptoms (30,65,78).

The routine examination of cerebro-spinal fluid (CSF) in patients with AIP and PNP is usually normal (28,57,68) indicating the absence of neuroinflammatory process in the CNS and the proximal nerves.

Myalgic or dysesthetic pain in the extremities was common in our patients and lasted usually for 1-2 weeks following muscle weakness (63). This temporal association has not been described previously and could suggest that this type of pain is related to muscle weakness similar to myalgias described in Guillain-Barré syndrome (53).

Three cases of rhabdomyolysis during an acute attack have been published (20,48,88) but it is probably much commoner since no systematic analysis of creatinine kinase have been done during attacks.

Neurophysiological and neuropathological studies

Porphyric neuropathy has been considered to be axonal (38). Surprisingly, this view is based on a scarce evidence of 39 patients with PNP studied neurophysiologically during an acute attack (2,6,17,24,41,50,57,67,68,75,84,89). In only half of them quantitative measurement of porphyrin precursors has been done (2,6,24,41,84) to confirm the diagnosis.

In addition to diffuse axonopathy of the motor nerves occasional cases of mononeuritis multiplex (41) have been reported. In several studies, in which axonal motor neuropathy has been suggested, the values of velocities have been significantly decreased (range 25-50 m/s, mean 40 m/s based on numerically available data (2,6,24,41,50,57,67) in combination to prolonged distal latency, minimal F-wave latency (6,41,50) temporal dispersion and conduction block (6) . These results indicate that the patients have had also features of demyelinating neuropathy. In our series four severely affected patients, who were studied during an acute phase of PNP, had similar features of demyelination and axonopathy. The most dramatic (>60 %) decrease of motor conduction velocities was prominent already after a week of the onset of PNP and resulted a patient's death within a month. Two additional patients with acute PNP had axonopathy but no features of demyelination indicating that demyelination can be a sign of a more severe attack.

Neuropathological studies which have been done from sural biopsies or autopsy material have supported both demyelination (19,27,33) and axonal changes (5,76) usually co-existing in the same nerve . Some authors have suggested independent mechanisms of axonal and myelin damage during an acute attack (5,6), while the others have proposed either primarily axonal (76) or myelin involvement (19,27,33) and secondary involvement of the other part of the nerve.
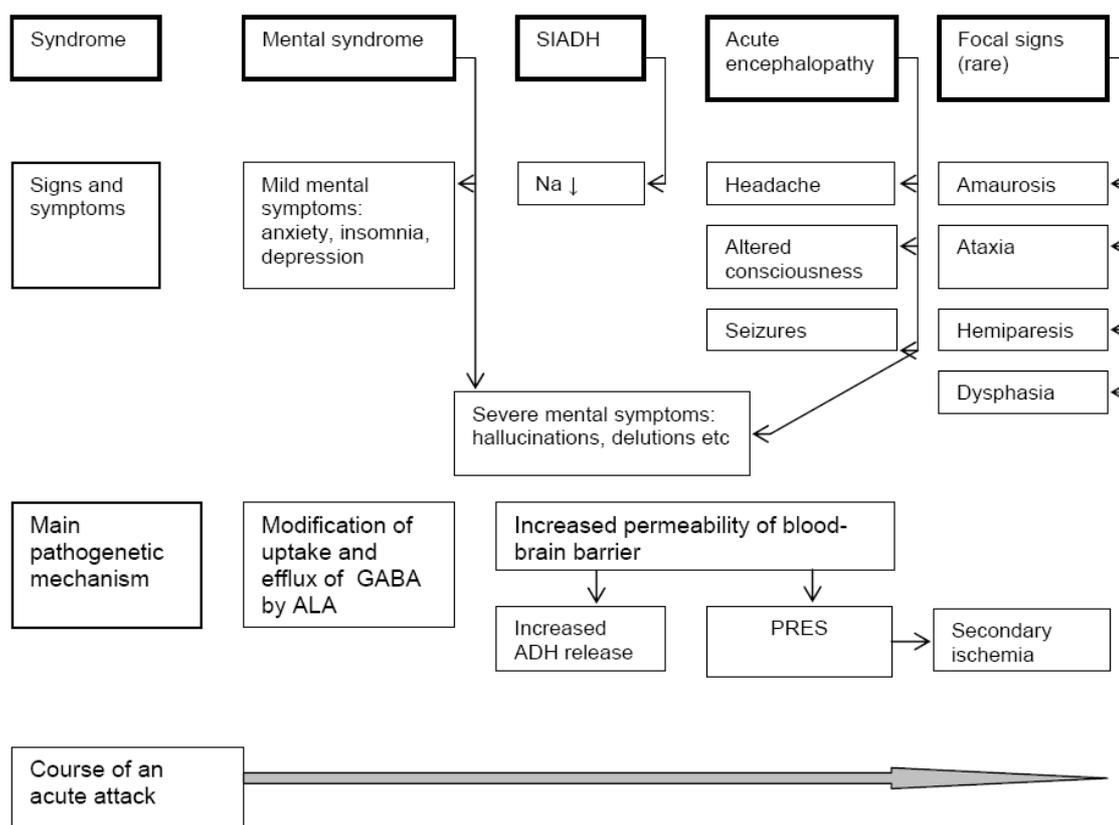
SIADH, syndrome of inappropriate secretion of antidiuretic hormone
PRES, posterior reversible encephalopathy syndrome

Figure 3. Clinical manifestations and potential mechanisms of CNS involvement in AIP

ACUTE ENCEPHALOPATHY

Acute encephalopathy manifesting in a combination of headache, altered consciousness and behaviour or seizures can be a sign of an acute attack (Figure 3) (63). Of note, other causes of acute encephalopathy such as encephalitis or sinus thrombosis must always be exluded even in patients with AIP, before symptoms can be classified as porphyrinogenic. CSF in patients with encephalopathy during an acute attack has been normal (1, 12, 21, 42, 47, 80,82).

Acute encepaholopathy in AIP can be visualized as posterior reversible encephalopathy syndrome (PRES) in neuroimaging (1, 7, 12, 21, 26, 40, 42,47,77,80,82,87) (Table 2) if the timing is correct and diffusion-weighted (DW) MRI is used. Clinical symptoms of acute porphyria resemble those of other acute encephalopathies related to PRES which could explain both

encephalopathy and seizures in AIP. PRES suggests breakage of blood-brain barrier (58) also in AIP patients, which permits access of neurotoxins such as ALA to neurons. The exact mechanism of permeability impairment in AIP has not been studied. Blood pressure increases commonly during an acute attack, but not to the level of malignant hypertension (>180/100 mm) (Table 2). This favours the theory of endothelial toxicity being the main cause of vasogenic oedema in AIP and hypertension acts more likely as a co-factor for PRES as described in eclampsia (58) and uremia.

Generalised or focal epileptic seizures accompany 2% to 20% of acute attacks (11,56,75). According to our experience, epileptic seizures occur in combination with other signs of severe encephalopathy even without hyponatremia. Of 236 patients, 25-61 % had mild to moderate hyponatraemia during an acute attack (28,34,56,63,68,75) (Table 1), which

in the absence of loss of sodium due to diarrhea, vomiting or polyuria, is usually a manifestation of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (76). The reduced bright signal of posterior pituitary lobe detected in a patient's MRI (T1-weighted) after severe hyponatraemia favours inappropriate release due to breakage of blood-brain barrier rather than inappropriate synthesis of ADH as a mechanism of SIADH (88).

Transient cortical blindness (42,82,87), hemianospia (49), cerebellar ataxia (13,27), parkinsonism (13,68), finger tremor (68), dysphasia (1) and central pontine myelinolysis (77) have been published in single cases during an acute attack, but in general focal CNS involvement as a potential sign of PRES with secondary ischaemia is rare during an acute attack.

Acute mental symptoms

Mild mental symptoms such as anxiety and insomnia are usually present at the beginning of an acute attack even before abdominal pain developes (34,68). Aberrant behavior and various psychiatric manifestations (so-called mental syndrome of acute porphyria) (83) occurs transiently during an acute attack. Frequency of these manifestations has varied from series to series (19% - 56%, Table 1) which may be due to underestimation of mild mental symptoms.

In remission, no segregation of acute porphyria and schizophrenia or bipolar disorder has been found in a large series of 344 AIP patients studied (60). Anxiety has been reported to be commoner among AIP patients than in the general population (52, 60) even in remission.

PATHOGENESIS OF NEUROLOGICAL SYMPTOMS DURING AN ACUTE ATTACK

Haem is synthesized in every human aerobic cell, but mainly in erythroid cells and in the liver, and it is used as a prosthetic group of haemoproteins (39). Each of seven porphyrias results from a partial deficiency of one of the enzymes in the haem biosynthetic pathway, but only acute hepatic porphyrias (AIP, variegate porphyria, hereditary coproporphyria and porphyria due to deficiency of ALA dehydratase) manifest similarly with acute neuropsychiatric attacks, which are clinically indistinguishable from each other (39).

Accumulation of porphyrins and their precursors is initialized via activation of ALA synthase (ALAS1) in the liver, which is the second and rate-limiting enzyme in the haem biosynthesis. This induction results in symptoms only if an additional enzyme causing acute porphyria such as HMBS, is deficient (Figure 1). ALAS1 can be induced directly at transcriptional and translational level by many drugs, chemicals and alcohol (25) or indirectly by low glucose concentration (32) and stress (70). These factors may provoke accumulation of porphyrin precursors and on the other hand, ALAS1 can be inhibited via negative feedback mechanism using haem, the end-product of the biosynthesis (25). Glucose inhibits ALAS1 indirectly via peroxisome-proliferator-activated receptor γ coactivator 1α (PCG-1α) *in vitro* conditions (32). Therefore, both haem preparations and glucose infusions have been used to treat acute attacks (34, 56).

In the brain, haem is also synthesised locally (16,36) but the role of intra-neural synthesis of porphyrins and their precursors in neurological manifestations of an acute attack, is unclear. Since the studies of brain ALAS activation have presented controversial results (59, 71), it is unknown whether regulation of the haem pathway in the neural tissues resembles that of hepatic (25) or erythroid (73) or none of them.

Neurological manifestations of acute porphyria could be precipitated either by direct neurotoxicity of porphyrin precursors, which has been demonstrated *in vitro*, or by deficiency of neural haem-containing enzymes or both (51) (Figure 1). A blood-nerve barrier lowers ALA concentration in the perineural fluid, which is around 30% of that measured in serum (51) (Figure 2) but it is high enough to be neurotoxic (46,51,61) and cause axonal degeneration and polyneuropathy. In contrast, only 1% of ALA crosses the unaffected blood-brain barrier (29, 51, 62), and thus, additional factors are needed to cause PRES. Lower protection of the blood-brain barrier in the limbic area and high affinity of ALA even in very low concentration to GABA and glutamate receptors due to their structural similarity (10) could explain mental symptoms at the early phase of an attack.

Free radicals originating from ALA, although demonstrated only in supraphysiological concentrations *in vitro* conditions (18) (Figure 2), could explain demyelination in severe PNP. Schwann cells

Table 2. Clinical manifestations of 11 published cases with acute porphyria and PRES during an acute attack

Pt	Diagnosis of acute porphyria confirmed	Seizures	Severe mental symtoms	Focal CNS signs	Head ache	Abdo-minal pain	Auto-nomic features	PNP	Blood pressure mm Hg	S-Na, 135-145 mmol/L	Vaso-spasm*	Follow-up
1	+	+	Hallucinations	Babinski	No	+	n.a.	+	170/120	128	n.a.	10 d: Normal MRI
2	+	+	Confusion	Dysphasia	No	+	n.a.	+	n.a.	n.a.	n.a.	7 w: Normal MRI
3	+	+	n.a.	Amaurosis	n.a.	n.a.	n.a.	+	Normal	n.a.	n.a.	14 d: CT normal 6 mo: Mild residual MRI lesions;
4	+	+	n.a.	Amaurosis, Anosognosia	n.a.	+	+	+	170/100	n.a	n.a.	4 w: MRI minimal improvement, no clinical sequels
5	+	+	Confusion	Apraxia	n.a.	+	n.a.	n.a.	n.d.	121	+++	4 d: MRI parietal foci (contrast enhancement), normal MRA
6	No	+	Lethargy, Hallucinations	Amaurosis	n.a.	+	n.a.	n.a.	180/100	130	n.a.	26 d: Normal MRI
7	No	No	Cognitive dysfunction?	Amaurosis	+	+	+	n.a.	180/100	n.d	n.a.	
2nd attack	No	+	n.a.	Amaurosis	n.a.	+	+	n.a.	170/110	n.d	No	Died, brain autopsy normal
8	+	+	Stupor	n.a.	n.a.	No	+	+	210/140	121	n.a.	3 mo: Normal MRI
9	No	+++	Hallucinations	no	n.a.		n.a.	n.a.	n.a.	n.a.	No	6 w: Residual MRI lesions, no clinical sequels
10	+	+	Confusion, hallucinations	no	+	+	+	n.a.	160/115	Low	+	1 w: Residual MRI lesions
11	+	+	Lethargy	Amaurosis	n.a.	+	+	+	170/110	n.a.	No	10 d: Residual MRI lesions, clinical sequels (PNP)

[1] (40), [2] (1), [3-4] (42), [5] (7), [6] (80), [7] (87) [8] (12), [9] (21), [10] (47), [11] (82).
*Based on conventional or MRI/angiography or doplerography. PNP, peripheral neuropathy; n.a. not applicable

have been shown to be more vulnerable to oxidative damage caused by ALA than neurons (23).

Of porphyrin precursors, only ALA was shown to be neurotoxic *in vitro* (51), and the recombinant human HMBS preparation, which decreased the level of plasma porphobilinogen but not that of ALA (72), has been inefficient in the treatment of an acute attack (4). This provides additional support to the main role of ALA in neurotoxicity.

Currently there is no evidence for abnormal activity of the haem-containing enzymes in the neural tissues measured in the brain homogenates of a mouse model (compound heterozygous HMBS (-/-) (37) or AIP patients. In contrast, the activity of many haem proteins in the liver such as cytochromes and tryptophan pyrrolase are decreased when measured both in mice and patients with AIP, respectively (37,45,55). Eg., deficiency of hepatic tryptophan pyrrolase has been responsible for 2-fold increase in serotonin and tryptophan levels in patients during an acute attack (66) and in remission (9) suggesting alteration of tryptophan metabolism in them. The role of peripheral 5-HT_3, 5-HT_4 and 5-HT_7 and 5-HT_{1A} receptors in gut (31) and bladder motility (15) has been reported, and thus, the abnormal tryptophan metabolism could partly contribute to the autonomic symptoms of AIP (51). The growing knowledge of diverse signaling molecules and their receptors in autonomic nervous system (31) suggests that the mechanism underlying autonomic dysfunction is multifactoral.

The reversible nature of the symptoms during an acute attack favours neurotoxicity of porphyrin precursors to haem deficiency (39). A full clinical remission in a severely affected patients after liver transplantation (74) supports the role of porphyrin metabolites, and the liver as the main source of porphyrin production plays a crucial role also in the pathogenesis of neurological symptoms. The course of an acute attack is probably directly related to the permeability of blood-brain and blood-nerve barriers to porphyrin precursors, which are small size molecules (39). Absence of a barrier for autonomic nerves and a sparse blood-brain barrier in hypothalamus and limbic areas may explain initial manifestations such as dysautonomia and mild mental changes in an acute attack. When the excess of ALA proceeds and the barrier function is disrupted, PNP and severe encephalopathy will develop.

Vulnerability of neuronal and vascular structures to toxic effects of porphyrins and their precursors vary inter-individually (85), and this may be affected by other genes related to neuronal resistance (35) or to efflux systems of porphyrin metabolism (86).

Not all patients have clinical symptoms despite high plasma concentration and increased excretion of porphyrin precursors (39). The penetrance of AIP has varied from 10 to 40 % based on different patient data (85). Thus, the phenotype must be modified by other often polymorphic genes especially by those in metabolic pathways and survilance of the neurons and resistance of vascular structures. In addition, many exogenous factors such as infections and drugs have a crucial role in the pathogenesis of an acute attack and genetic counselling of the patients has decreased the incidence of acute attacks substantially during the last decades (85).

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