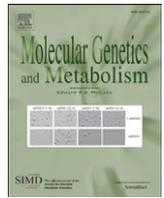




Contents lists available at SciVerse ScienceDirect

## Molecular Genetics and Metabolism

journal homepage: [www.elsevier.com/locate/ymgme](http://www.elsevier.com/locate/ymgme)

## Conference Proceedings

## Neurologic considerations in propionic acidemia

John Schreiber <sup>a</sup>, Kimberly A. Chapman <sup>b</sup>, Marshall L. Summar <sup>b</sup>, Nicholas Ah Mew <sup>b</sup>, V. Reid Sutton <sup>c</sup>, Erin MacLeod <sup>b</sup>, Kathy Stagni <sup>d</sup>, Keiko Ueda <sup>e</sup>, Jill Franks <sup>f</sup>, Eddie Island <sup>g</sup>, Dietrich Matern <sup>h</sup>, Loren Peña <sup>i</sup>, Brittany Smith <sup>f</sup>, Tiina Urv <sup>j</sup>, Charles Venditti <sup>j</sup>, Anupam Chakarapani <sup>k</sup>, Andrea L. Gropman <sup>a,\*</sup>

<sup>a</sup> Department of Neurology, Children's National Medical Center, Washington, DC, USA

<sup>b</sup> Section of Genetics and Metabolism, Children's National Medical Center, Washington, DC, USA

<sup>c</sup> Department of Molecular & Human Genetics, Baylor College of Medicine & Texas Children's Hospital, Houston, TX, USA

<sup>d</sup> Organic Acidemia Association, Pinole, CA, USA

<sup>e</sup> Tufts Medical Center, Boston, MA, USA

<sup>f</sup> Propionic Acidemia Foundation, Highland, IL, USA

<sup>g</sup> Transplant Program, Georgetown University, Washington, DC, USA

<sup>h</sup> Mayo Clinics, Rochester, MN, USA

<sup>i</sup> University of Illinois College of Medicine at Chicago, Chicago, IL, USA

<sup>j</sup> National Institute of Health, Bethesda, MD, USA

<sup>k</sup> Birmingham Children's Hospital, Birmingham, UK

## ARTICLE INFO

Available online xxxx

## Keywords:

Propionic acidemia

Neurological

Seizure

Neuroimaging

Spectroscopy

Inborn error of metabolism

## ABSTRACT

Propionic acidemia (PA) is an organic acidemia which has a broad range of neurological complications, including developmental delay, intellectual disability, structural abnormalities, metabolic stroke-like episodes, seizures, optic neuropathy, and cranial nerve abnormalities. As the PA consensus conference hosted by Children's National Medical Center progressed from January 28 to 30, 2011, it became evident that neurological complications were common and a major component of morbidity, but the role of imaging and the basis for brain pathophysiology were unclear. This paper reviews the hypothesized pathophysiology, presentation and uses the best available evidence to suggest programs for treatment, imaging, and monitoring the neurological complications of PA.

## 1. Introduction

Propionic acidemia (PA) is an organic acidemia which classically presents in the neonatal period with vomiting, lethargy, refusal to feed, hypotonia, and less frequently with dehydration and seizures [1,2]. Acute neurologic events such as metabolic stroke-like episodes and seizures may or may not be associated with systemic metabolic acidosis in patients with PA. Long term chronic neurological complications, even in the presence of optimal therapy include intellectual disability, spastic quadriplegia and athetosis all of which significantly impact a patient's quality of life [3,4]. Since its original description in 1961, patients with PA were identified to have a variety of neurologic signs and symptoms [5]. Neurological findings, characteristic and more unusual, are reviewed in Table 1 and include ataxia and basal

ganglia changes which historically were often the findings suggesting a PA workup (Table 1).

In literature of neurological findings reported in PA, we found a number of common presentations (Table 2). Some patients have been described with typical neurologic findings but without the expected metabolic acidosis [3]. Atypical acute neurologic findings described in at least one patient include developmental regression, aphasia, hemiplegia, and dyskinesias. Chronically, individuals may develop spastic quadriplegia and athetosis [3]. Given these common and atypical findings, the neurologic presentation of PA is a key element in diagnosis and assessment. More recently, newborn metabolic screening and targeted genetic analysis of relatives with PA allows for initiation of treatment in asymptomatic individuals. Nevertheless, even with optimal treatment, there is still some degree of neurologic impairment [6].

Understanding the pathophysiology of neurologic symptoms has improved in recent years and is starting to provide neuro-biochemical explanations for some of the more common complications of the disease including developmental delay, intellectual disability, seizure, cranial nerve abnormalities, and metabolic strokes. In addition, there is a growing knowledge from imaging that further inform understanding of neuro-pathophysiology and provide data concerning clinical

Abbreviations: PA, propionic acidemia; EEG, electroencephalogram; <sup>18</sup>FDG, <sup>18</sup>Fluoro-2-deoxyglucose; CSF, cerebrospinal fluid.

\* Corresponding author at: Department of Neurology, Children's National Medical Center, 111 Michigan Avenue, N.W., Washington, DC 20010, USA. Fax: +1 202 476 5226.

E-mail address: [agropman@childrensnational.org](mailto:agropman@childrensnational.org) (A.L. Gropman).

1096-7192/\$ – see front matter  
doi:10.1016/j.ymgme.2011.10.003

Please cite this article as: J. Schreiber, et al., Neurologic considerations in propionic acidemia, Mol. Genet. Metab. (2011), doi:10.1016/j.ymgme.2011.10.003

**Table 1**  
Selected cases of propionic acidemia with unusual neurologic findings.

Reference	Age	Gender	Prior history	Laboratory evidence of ketoacidosis	Signs/symptoms
[27] Delgado et al.	9 months	M	None	Yes	Hypotonia, neurologic regression
[37] Shigematsu et al.	10 months	F	Mild developmental delay	Yes	Hemiplegia which persisted for 3 months
[38] Lücke et al.	4½ years	F	None	Yes	Coma
[3] Nyhan et al.	7 years	M	PA diagnosed at 7 months, hypotonia	No	Wheelchair bound, hypotonia, athetosis (chronic)
[39] Haas et al.	8 years	F	PA diagnosed in neonatal period	No	Acute aphasia and generalized hypotonia, necrosis of basal ganglia
[28] Scholl-Burgi et al.	11 years	F	PA diagnosed at 5 days	No	3 stroke-like episodes over 13 months with acute reversible hemiplegia and vegetative symptoms
[20] Johnson et al.	12 years	M	Chronic pancreatitis and abd. Pain	Yes	Acute encephalopathy, cerebral edema
[3] Nyhan et al.	20 years	M	Hypotonia, multiple episodes of increased ammonia	No	Spastic quadriplegia, athetosis (chronic)
[40] Sethi et al.	31 years	M	Developmental delay, episodes of vomiting/lethargy in infancy	No	Acute encephalopathy, involuntary movements

condition. This review covers these topics as well as provides recommendations to minimize neurologic complications in individuals with PA.

### 1.1. Pathophysiology of neurological symptoms

While there is not a complete understanding of the neuro-pathophysiology in PA, several metabolites and physiologic stressors are thought to account for many of the acute and chronic disease manifestations. These affect specific cellular metabolism, general intermediary metabolism, and physical brain structure. Cerebral edema and the resultant hypoperfusion occur in PA and are known to cause brain damage similar to that seen in urea cycle disorders [3]. In addition to these physical effects one must also consider the effects of PA related hypoglycemia, lactic acidosis, increased anion gap, elevate propionate, elevated glycine, ketosis, and hyperammonemia observed in acute PA. The mechanism for propionate-induced amino acid intolerance is a reduction in the concentration of N-acetylglutamate, which is required for activation of mitochondrial carbamoyl phosphate synthetase. This in turn leads to selective astrocytic vulnerability and brain edema (see below and Fig. 1). In addition to these known toxic effects, PA also appears to have insidious effects on the central nervous system (CNS) even in patients during the chronic state. Animal model studies, and neuroimaging, will elucidate the causes of neuropathology in PA.

While most autopsies conducted on patients with PA reveal no gross central nervous system abnormalities [7], some neuropathological cases demonstrate specific patterns of injury. Observations of damaged or Alzheimer type II astroglia (also termed metabolic glia) have been made [7,8,9,10]. This is thought to be the result of propionate accumulation and its metabolism in glial cells. This would result in selective astrocytic vulnerability [10]. In patients expiring during an acute metabolic crisis, hypoxic-ischemic changes are also evident on autopsy [8,9] suggesting disrupted energy metabolism and oxidant response capability. Beyond this simple explanation, it is thought that the neurological and neuropathological changes observed in PA are also due to a combination of accumulation of toxic metabolites

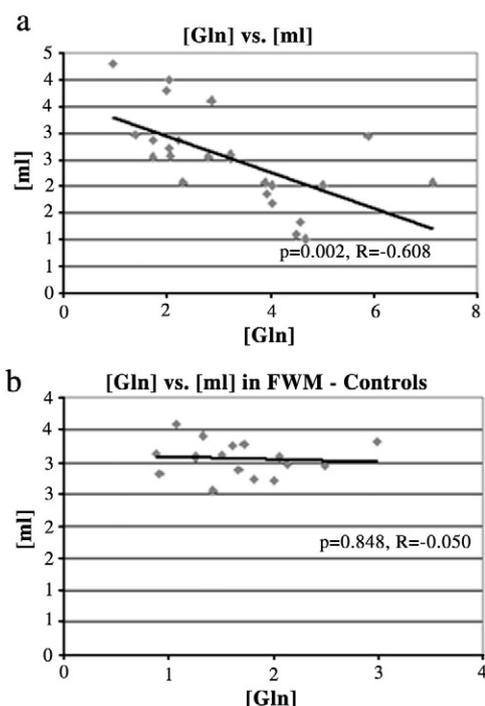
**Table 2**  
Common neurological manifestations seen in patient with PA [1].

Neurologic finding	Initial presentation	Any time
Hypotonia	48%	54–90%
Lethargy	51%	63–67%
Seizures	23%	43–47%
Myoclonus	12%	20%
Coma	15%	28–30%

(methylcitrate, propionate, and ammonia), reduction of cellular energy stores, cytoskeletal alterations, deregulation of histone acetylation, oxidative injury, and epileptogenesis. Additionally, locally synthesized dicarboxylic and tricarboxylic acids such as methylcitrate cannot escape the blood brain barrier passively and may be neurotoxic at high concentrations [11,12]. PA metabolites may inhibit and deplete enzymes vital to the Krebs cycle including pyruvate dehydrogenase, oxoglutarate dehydrogenase complex, and succinate:CoA ligase, and deplete intermediates including acetyl CoA, oxaloacetate, succinyl CoA, and glutamate [11].

Moreover, oxidative stress may be important in mediating PA's detrimental effects on cognition. A decline in performance on the water maze (a learning task) observed after injection of PA in rats was prevented by ascorbic acid, an anti-oxidant [13]. Propionate may also alter neuronal gene expression by increasing neuronal histone acetylation [10].

Although biochemical toxicity is known, propionate alters *in vitro* intermediate filament phosphorylation through its action on protein



**Fig. 1.** Inverse relationship between glutamine and myoinositol in hyperammonia but not in controls.

phosphatases and kinases, resulting in morphological alterations in cerebral cortex astrocytes [14,15]. This phosphorylation appears at least partially dependent on *N*-methyl-D-aspartate (NMDA) glutamate receptors [16]. Thus, NMDA receptors represent a potential therapeutic target in PA. Intrastratial injection of PA caused the appearance of seizures and increased protein carbonyl content (a marker of protein oxidative damage) which was prevented by an NMDA-receptor antagonist [17]. The high glycine seen in PA may actually exert an excitatory action through NMDA glutamate receptors [11]. In addition, many patients with PA have hyperammonemia and this also has acute and chronic effects on neurotransmitter systems, energy metabolism, and astrocyte protein expression [18]. The neuropathology on a gross and microscopic level provides targets for new therapies which, in turn, will theoretically improve outcomes such as developmental delay, intellectual disability, metabolic stroke-like episodes and seizures.

### 1.2. Developmental delay and intellectual disability

Patients with PA, even under good metabolic control, have developmental delay and intellectual disability. There may be correlation between degree of impairment and brain and blood levels of propionic acid or propionyl CoA. North et al. conducted a 15 month prospective study on six PA patients (aged 22 to 166 months) supplemented with carnitine and who followed a strict dietary regimen which included provisions for periods of illness [6]. Developmental progress slowed in all children as a product of age, including two patients with no significant episodes of hyperammonemia or ketoacidosis and normal growth [6]. Cognitive impairment became more pronounced during the second year of life. Motor function was generally more impaired than cognitive function at all ages. In the oldest child, development reached a plateau at 8 years old. This child also exhibited symptoms of attention deficit which was unresponsive to methylphenidate. Similarly, several children displayed easy distractibility. Despite the developmental and attention impairments, none had evidence of focal neurologic deficits, movement disorder, or epilepsy, suggesting that strict management may limit these focal neurologic sequelae.

Another study in 17 patients, ages 1 to 22 years, Sass et al. found that (intelligence quotient (IQ) was reduced in three, borderline in two and normal in five patients with PA [2]. Another seven were classified as having "delayed cognitive functions" [2]. Moreover, Surtees et al. reported that 10/11 with early-onset disease had IQ of 60 or below compared to 1/9 with late-onset [4]. These data suggest that age of onset correlates with outcome but that chronic changes in development may be independent of initial management success. Further research may determine the process that continues neurologic damage in these patients. However, as in most intoxicating errors of metabolism, one needs to assess the severity and duration of the initial insult as a predictor of neurologic outcome. It is not clear if duration of insult defines the outcome as may be the case in other inborn errors of metabolism.

### 1.3. Seizures

Seizures may represent an acute or chronic manifestation of PA [1]. Seizures are common in patients with PA and in infancy and early childhood, they tend to be generalized or myoclonic in nature, whereas during later childhood they become mild generalized or absence in type. Focal seizures are less common, but when focal seizure activity is present, it is usually localized in the temporal region and may reflect underlying structural damage. Infantile spasms with hypsarhythmia as the initial presentation of PA have been reported in a 6 month old boy [19]. Treatment with vigabatrin resulted in resolution of spasms and complete normalization of EEG. EEG during acute metabolic decompensation in PA may simply show severe, diffuse slowing [20], but will return to normal when metabolically stable [2].

The most extensive study of epilepsy in PA patients was done by Haberlandt et al. [21]. EEG findings and seizure types are summarized in Table 3. Epileptiform discharges were generalized with frontal preponderance in seven and focal or multifocal in two [21]. Interestingly, 11 out of 17 patients with PA had less than three episodes of metabolic decompensation, but still had seizures or epileptiform discharges. Seizure frequency ranged from two per month to six per day. In five, seizures were mainly induced by infections [21].

Therapy for seizures in this cohort corresponded to seizure type so that seven patients required an antiepileptic medication [21]. Four were treated with valproic acid, four with benzodiazepines, three with phenobarbital, two with levetiracetam, one each with oxcarbazepine, and ethosuximide (the patient with exclusively absence seizures and an otherwise normal EEG background). These medications were tolerated without side effects and one patient each taking valproic acid and ethosuximide remain seizure free at last follow up. Ozand found that two patients given phenobarbital for seizures during infancy had an inadequate response [22]. Much of the reported experience regarding epilepsy treatment in PA pre-dates the development of many of the newer antiepileptics, which often have fewer side effects. Many of these agents would be reasonable options in the proper clinical context.

Due to the effects of valproate on urea cycle metabolism, the benefit of seizure control must be weighed with a PA patient's risk for hyperammonemia due to secondary urea cycle dysfunction. In addition to the patients treated above, Wolf has also used valproic acid titrated up to 18 mg/kg per day in one 11-year-old boy with a mixed multifocal and generalized epilepsy, reporting that it reduced the number of absence seizures [23]. Valproic acid does not inhibit propionyl CoA carboxylase (PCC) activity *in vivo* or *in vitro* [23].

### 1.4. Cranial nerve abnormalities: optic neuropathy

Optic nerve abnormalities are chronic changes which are associated with PA [22]. Ianchulev et al. examined six patients between the ages of 2 and 10 years diagnosed with PA at birth [24]. All three girls were normal, but all three boys had optic nerve atrophy with age-dependent severity which did not appear to correlate with amino acid levels. At least one case report has documented optic nerve atrophy in a woman with PA [25]. The extent to which optic neuropathy is present in the general PA population is not well known due to lack of reporting [22]. This again may reflect effects of PA not accounted for by known pathophysiology. Patients with PA should be evaluated with at least an annual ophthalmologic dilated exam (see "Chronic Management and Health Supervision of Individuals with Propionic Acidemia" in this issue).

### 1.5. Metabolic stroke-like episodes

Patients with PA can have metabolic stroke-like events, especially involving the basal ganglia resulting in movement disorders. In a study of 17 patients with PA, four patients had "moderate invalidity" with an extrapyramidal movement disorder and nine had "mild

**Table 3**

Seizure type and EEG findings in 17 patients with PA and seizures followed for 1–22 years (median 6 ½ years) [21].

Clinical seizure and/or EEG finding	Number of patients
EEG epileptiform with change in background	8
EEG epileptiform alone	2
Photosensitivity	4
Seizures (with epileptiform changes on EEG)	9
Tonic-clonic seizures	5
Absence	5
Focal	4
Myoclonic	2

invalidity" but were able to be "ambulatory without problems" [19]. Hamilton described the case of a 9-year old girl with PA who developed an acute encephalopathy after resolution of pancreatitis and improvement in organic acids [26]. Neuroimaging revealed edema and contrast enhancement in bilateral basal ganglia with subsequent hemorrhage. Neuropathological examination of this patient demonstrated vascular proliferation and swollen endothelial cells in the basal ganglia, thalamus, and substantia nigra, suggesting a breakdown of the blood-brain barrier in these areas with vasogenic edema and hemorrhage. On neuroimaging, edema, sometimes with restricted diffusion suggests a cytotoxic insult [20,27] and is a well-documented phenomenon in PA acutely, most frequently found in the basal ganglia, but also in the cerebral cortex.

As with many other metabolic conditions, the deep gray structures, particularly the basal ganglia (caudate, putamen, and globus pallidus) appear uniquely susceptible and vulnerable to the effects of PA, both during [1,4,20,11,28] and in between [26,11,29] periods of metabolic compromise, with edema evident on neuroimaging. The reason for this susceptibility is unknown, but can explain findings of the movement disorders observed in PA.

### 1.6. Role of neuroimaging in PA

The role for neuroimaging in PA management has not been well delineated. Advanced neuroimaging is not available in all centers, and one has to weigh the risk (sedation) with potential benefits. In PA, generalized atrophy, which develops during the first year of life, is the chronic change most commonly noted on neuroimaging [1,4,6,30]. There may also be a mild-moderate delay in myelination, which normalizes in most patients after 2 years of age [30]. This correlates with spongiform change on neuropathological studies which reflects a defect in myelin. The delayed myelination is typically found in infants, but largely disappears with age [7,9]. The severity of radiologic abnormalities seems to correlate with the degree of compliance to therapy [31,30], but not with the number of hospital or intensive care unit admissions [30]. Cerebellar hemorrhage is also an infrequent finding in neonates with PA and may be incidental [9,32].

One study performed serial magnetic resonance imaging (MRI) and positron-emission tomography (PET) on five PA patients diagnosed in the neonatal period [29]. Scans were initially normal, and then showed bilateral basal ganglia T2 hyperintensity with increased <sup>18</sup>Fluoro-2-deoxyglucose (<sup>18</sup>FDG, a tracer of glucose metabolism) uptake in the basal ganglia and thalami, and finally basal ganglia atrophy with

decreased uptake, suggesting that the basal ganglia may eventually "burn out". This may explain the clinical appearance of dyskinesias or movement disorders in the patients. Bergman et al. found T2 hyperintensity in the putamen and caudate of a PA patient with choreoathetosis, but not in two patients without extrapyramidal signs or symptoms [33].

Magnetic resonance spectroscopy (MRS) showed decreased N-acetyl aspartate (NAA) and myo-inositol peaks and elevated glutamine/glutamate in the basal ganglia of all patients during stable metabolic conditions. These MRS changes reflect the impact of hyperammonemia on cerebral brain water with elevations of glutamine being osmotically active and leading to decrease of myo-inositol, which is also osmotically active. The decrease in NAA, is accounted for by neuronal cell loss, as NAA is a marker of neuronal integrity. Elevated lactate was also present in four out of five clinically and metabolically stable PA patients properly treated with protein restriction and carnitine supplementation [31]. The presence of spectroscopic abnormalities in a stable patient indicates that intraparenchymal metabolic balance may be disrupted even without significant perturbations in typical laboratory evaluations which may be partly explained by limited efflux of metabolites across the blood-brain barrier [12]. Hoffmann found that even "good" metabolic control may be associated with elevations of organic acids in the cerebrospinal fluid (CSF) [34].

The array of neuroimaging findings encountered in PA is summarized in Table 4.

Neuroimaging in the subacute stage can be used for baseline determination of damage, and in follow up to assess ongoing injury. Advanced neuroimaging (such as MRS or PET) can identify the earliest biomarkers markers of injury which can be followed throughout the disease course and potentially used to monitor therapies, although research in this area is needed. Previous experience with 1H MRS, for example, has shown that brain biochemical anomalies may persist, despite adequate metabolism as assessed by blood and urine measures (author experience). This is important, given the disconnection between treatment and neurologic damage previously described. In a study by Al-Ess et al. [35], PET studies demonstrated increased uptake in the basal ganglia and thalami, followed by decreased uptake in the basal ganglia at later stages of the disease. The structural (MRI) and the functional (PET) studies of the brain were found to be complementary in the evaluation of PA, and were in good correlation with the clinical findings. One, however, must consider the cost of these procedures (i.e. MRS often not covered by commercial insurance) and sedation risk. Imaging at 1.5 Tesla is

**Table 4**  
Neuroimaging reports and findings from the literature in patients with PA.

Reference	Patients	Technique	Findings
[30]	20	CT or MRI	Initially normal or white matter (WM) attenuation; 15/16 at > 1 month had volume loss; WM attenuation disappeared in nearly all after 2 years
[21]	11	MRI	9/11 generalized atrophy, 2 delayed myelination, 6 abnormal basal ganglia (BG) (3 with cystic defects)
[4]	8	CT	3/4 in early-onset group had cerebral atrophy; 3/4 in late-onset group had BG hypodensities which sometimes resolved and one had evidence of volume loss
[29]	5	Serial MRI and PET	Initially normal, followed by BG and thalami swelling and ↑ BG <sup>18</sup> FDG uptake, then BG atrophy and ↓ uptake
[31]	5	MRI and MRS	Elevated lactate peaks in 4/5; cerebral atrophy in the two with the longest delay to onset of therapy
[6]	4	MRI	Slight prominence of CSF spaces and thinning of corpus callosum; myelination appeared normal
[33]	3	MRI and MRS	MRI—delayed myelination and cerebral atrophy with BG T2 hyperintensity in one patient with choreoathetosis; MRS—elevation of glutamine/ glutamate
[3]	2	MRI	Volume loss, basal ganglia T2 hyperintensity; 20-year-old man had cerebral cortex and caudate atrophy
[9]	1	CT	Cerebellar hemorrhage
[27]	1	MRI	T2 hyperintensity with restricted diffusion in bilateral putamen
[20]	1	MRI	T2 hyperintensity with restricted diffusion in bilateral putamen, globus pallidi, caudate, and cortex
[28]	1	Serial MRI	Reversible hyperintensities in cortical gray matter and basal ganglia
[32]	1	MRI	Cerebellar hemorrhage
[11]	1	Serial MRI	Bilateral basal ganglia, cortical and subcortical WM T2 hyperintensity which resolved within 3 weeks with new volume loss

Abbreviations: CT = computerized tomography, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, BG = basal ganglia, CSF = cerebrospinal fluid, WM = white matter, <sup>18</sup>FDG = <sup>18</sup>fluoro-deoxyglucose.

FDA approved, however, some sequences on 3 T magnets are not yet FDA approved, and may be considered research applications. This is an area where more information is needed.

### 1.7. Recommendations to maximize neurological outcomes

Maximization of neurological outcomes can be divided into two sections. The first focuses on acute interventions and the second on long term interventions. Prompt recognition and treatment (as described in "Acute Management of Propionic Acidemia" article also in this issue [35]), is essential to decrease acute brain injury from a metabolic decompensated milieu.

To improve outcomes in a PA patient who is acutely decompensated and seizing, it may be necessary to consider pentobarbital coma with 24-hour EEG to decrease metabolic demand, if more routine anticonvulsants, singly and in combination fail to control seizures. This is a last resort option. This option can only be undertaken in centers with capability for bedside monitoring and experience in pentobarbital coma. This type of intervention has been used for years in the treatment of neonatal epileptic encephalopathy. However, the use of head or total body cooling may prove advantageous, but there is currently no data and risks that include coagulopathy and thus it cannot be recommended at this time. In addition, most metabolically unstable PA patients will show slowing of normal EEG background rhythms, with or without epileptiform discharges. In particular, in deep coma, sleep-wake cycles will be disrupted and metabolic improvement often correlates with improvement of sleep-wake cycles (i.e. emergence of sleep architecture: spindles, vertex waves, etc.) on EEG allowing for assessment of the condition.

Because of the risk of seizures (even subclinical) which may promptly respond to therapies, every individual with PA should have an EEG at diagnosis and in follow up as clinical condition dictates. If epileptiform activity is identified a referral to neurology is indicated for consideration of possible therapeutic intervention.

In terms of the usefulness of neuroimaging in PA, while the early changes may lag radiographically, an MRI after clinical stabilization can be useful for assessment of areas of brain injury following severe acute decompensations or in PA patients who present with neurological abnormalities. Newer modalities such as diffusion tensor imaging (DTI) and MRS can identify alterations prior to changes on T1/T2 weighted images and, if available, may be helpful in this regard, especially as more individuals with PA undergo these studies [31]. Basal ganglia changes may be appreciated earlier on MRI using these techniques than evident on clinical evaluation.

In patients with PA who have abnormal screening MRI in the acute phase or have neurological changes, a follow up MRI several months later will help determine permanent changes and may further advise prognosis and burden of injury.

As discussed in "Chronic Management and Health Supervision of Individuals with Propionic Acidemia" also published in this volume [36], developmental and intellectual ability can be maximized with early initiation of physical, occupational and speech therapy services, optimal nutrition therapy, and aggressive treatment of metabolic decompensations.

## 2. Conclusions

PA may produce an array of neurologic abnormalities including encephalopathy, hypotonia, seizures, extapyramidal symptoms, optic nerve atrophy, stroke-like episodes, and attention deficits through several different mechanisms. Currently, optimal management and compliance may limit epilepsy, chronic extrapyramidal symptoms, and focal neurologic deficits, but probably cannot prevent all of the delay in cognitive and motor development. Regarding the treatment of epilepsy, multiple antiepileptics including valproic acid have been employed with some success. More experience, particularly with

newer agents, is needed to determine the best options to treat seizures and limit adverse effects. PA model systems, experimental neuroimaging, and cellular studies examining PA's effects on NMDA receptors, oxidative injury, energy generation, intermediate filament phosphorylation, histone acetylation, and epileptogenesis suggest potential targets for future therapeutic strategies. Finally routine imaging may more accurately track the course of PA associated neurologic disease than routine blood work.

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