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# Valproate-induced hyperammonemia in juvenile ceroid lipofuscinosis (Batten disease)

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ABSTRACT

*Purpose:* Valproate-induced hyperammonemia (VHA) and hyperammonemic encephalopathy (VHE) are well-known complications of valproate (VPA) treatment. Currently recognised risk factors for VHE include a high VPA dosage, the need for polytherapy and long duration of treatment. Despite the severe nature of the epilepsy, presence of concomitant psychiatric manifestations, and frequent need for polypharmacy associated with juvenile ceroid lipofuscinosis (JNCL, Batten disease) neither this disorder nor other subtypes of neuronal ceroid lipofuscinosis have previously been identified as risk factors for VHA/VHE. The aim of the present publication is to describe four cases with VHE in a well-defined Danish population of JNCL.

*Method:* An examination of medical records of all 35 patients with JNCL in Denmark was conducted and revealed fourteen patients treated with VPA.

*Results:* Four patients treated with VPA developed VHE. All patients were prescribed VPA in standard dosages, had normal plasma concentrations of VPA and received antiepileptic drug (AED) polytherapy. Symptoms occurred shortly after commencement or increase in dose of VPA, and were quickly reversible upon discontinuation of VPA. Carnitine supplement was administrated in two patients, which resulted in resolution of symptoms and normalized ammonium levels.

*Conclusion:* Patients with JNCL are in great risk of developing VHA and VHE due to a high rate of polytherapy. Furthermore, studies have shown that carnitine level can be depressed in JNCL, which may increase the risk of VHA and VHE. We recommend that increased attention should be given to these patients.



## 1. Introduction

Valproate (VPA) is a broad spectrum antiepileptic drug which, besides its use in epilepsy, also is used in treatment of psychiatric disorders and in migraine prophylaxis. VPA is commonly well-tolerated when serum-levels are maintained within the therapeutic range, but adverse effects like weight-gain, tremor, sedation, thrombocytopenia, and leucopenia may occur.[1] Serious side effects include teratogenicity, hepatotoxicity, pancreatitis, bone marrow suppression, polycystic ovary syndrome, and VPA-induced hyperammonemic encephalopathy (VHE).[1] VHE has been reported in both children and adults, and may untreated lead to life threatening coma and death. However VPA may also cause asymptomatic hyperammonemia (VHA).[2,3]

Neuronal ceroid lipofuscinoses (NCL) are a group of genetic diseases characterized by storage and accumulation of ceroid lipofuscin in the lysosomas and accompanying degeneration of especially the neuronal cells. The symptoms include retinopathy, epilepsy, psychiatric problems, dementia and motor dysfunction. At least ten different disorders are known.[4] Juvenile neuronal ceroid lipofuscinosis (JNCL), also known as Batten disease, is one of the most common types and is caused by a mutation in the CLN3 gene on chromosome 16.[5] In JNCL, loss of vision begins about the age of five to six years. Simultaneously, mental deterioration starts and, as well, a progressive loss of motor functions. Epilepsy normally initiates at the age of ten years and increases in frequency and severity with age. Furthermore, social, behavioral and attention problems emerge. Some patients develop regular psychosis. The disease usually leads to early death at a mean age of 22–28 years.[6] Major clinical symptoms are listed in Table 1.

Historically, diagnosis required characterization of storage material by electron microscopy of rectal, conjunctival or skin biopsies, electro-retinograms showing retinopathy and

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**Table 1**
Major clinical symptoms of JNCL.[4]

- Visual impairment
- Regression of motor milestones
- Seizures
- Cognitive decline
- Dyspraxia
- Bradykinesi
- Hallucinations

demonstration of vacuolated lymphocytes.[4] Currently, genetic techniques applied to DNA samples from blood or a buccal swab will allow the clinicians to make an accurate diagnosis. In addition, genetic tests are useful for prenatal diagnosis and genetic counseling of JNCL.[4]

A Finnish study reported that 70% of patients with JNCL had a satisfactory seizure control when treated with VPA.[6] However, patients with an unsatisfactory seizure control often need polytherapy in order to prevent life threatening seizures,[6] which increases the risk of side effects, including VHA and VHE.[2,3,7–22] Despite the severe nature of the epilepsy, occurrence of concomitant psychiatric manifestations, and need for polypharmacy, occurrence of VHA/VHE in Batten disease or other subtypes of NCL have not previously been reported in the literature. The aim of the present publication is to describe four cases with VHE in a well-defined Danish population of Batten patients and to provide a review of VHE.

## 2. Methods

In Denmark all patients with JNCL are associated to the Centre for Rare Diseases, Department of Pediatrics, Aarhus University Hospital. In March 2012 a thorough examination of medical records of all 35 patients with JNCL was conducted.[5] The records contain a continuously maintained history of the clinical course, including seizure activity, medication used and hospital admissions. Fourteen patients received VPA. Consecutive measurements of ammonium during VPA treatment were at that time not part of the routine. However, four cases with suspected VHE were revealed. None of these four patients had any underlying metabolic disease besides their JNCL. All were homozygous for the common 1.02 kb deletion in the CLN3 gene.[5] Normal range of ammonium is 11–32 μmol/l and VPA 300–700 μmol/l. In addition, a literature search using the Pubmed database was conducted using the following terms: valproate, encephalopathy, hyperammonemia, valproate-induced hyperammonemic encephalopathy, Batten disease, juvenile ceroid lipofuscinosis. Publications without reports of VPA and ammonium levels were excluded.

## 3. Case reports

### 3.1. Case 1

Case 1, a 19-year old male was admitted to the acute medical unit due to increasing drowsiness, which had emerged close to coma. He was diagnosed with JNCL at the age of six. Three weeks prior to the admission, VPA (1000 mg/24 h; 13 mg/kg/24 h) was initiated. He still received oxcarbazepine (1500 mg/24 h) and quetiapin (200 mg/24 h). On admission, which was shortly after intake of VPA, plasma level of VPA was 756 μmol/l. As the symptoms occurred shortly after introduction of VPA, VHE was suspected. Accordingly, VPA was discontinued and ammonium level and liver parameters were measured. There was no impact on the liver parameters. Ammonium level was 110 μmol/l. Within 24 h after discontinuation of VPA he started to wake up, and after 48 h he had completely regained consciousness. The ammonium level was reduced to 48 mol/l.

### 3.2. Case 2

Case 2, a 17-year old female diagnosed with JNCL at the age of seven. She had showed a rapid progression and suffered severe epilepsy. In addition to phenobarbital (90 mg/24 h) and clonazepam (7 mg/24 h), VPA (300 mg/24 h; 6 mg/kg/24 h) was prescribed. Six weeks later she experienced increased drowsiness, but with rather unaffected consciousness. VPA level was 261 μmol/l, and ammonium level was 83 μmol/l. There was no impact on liver parameters. One week later, the ammonium level had increased to 132 μmol/l, and as she now was drowsy all the day, VPA was discontinued. Within the next two days, she gradually resolved to her habitual status, and one week later, the ammonium level was within the normal range, i.e. below 32 μmol/l.

### 3.3. Case 3

Case 3, a 22-year old female admitted to hospital due to increasing drowsiness. JNCL was diagnosed at the age of six years. Epilepsy initiated when she was 12 years old. Initially, the epilepsy was well controlled by clobazam (60 mg/24 h; 1 mg/kg/24 h), but due to an increase in seizure activity, VPA was added. Four months prior to admission, the dose was increased to 1600 mg/kg/24 h (26 mg/kg/24 h). At admission, the levels of VPA and ammonium were 596 μmol/l and 58 μmol/l, respectively. Liver parameters were normal. The VPA therapy was continued unchanged, and administration of carnitine 250 mg/day was initiated. Soon after, her drowsiness resolved, and the level of ammonium gradually decreased to 9 μmol/l.

### 3.4. Case 4

Case 4, an 18-year old female diagnosed with JNCL at the age of eight years. Initially, she was treated with a combination of topiramate (TPM) (350 mg/kg/24 h) and oxcarbazepine (2100 mg/kg/24 h). Due to increase in seizure frequency, VPA (1000 mg/24 h; 16 mg/kg/24 h) was initiated eight months earlier, and at admission she had been seizure free for several months. However, a severe drowsiness close to lethargy had gradually emerged despite low plasma levels of VPA (267 μmol/l). VHE was suspected and she was admitted to hospital. Ammonium level was however only slightly increased (63 μmol/l). Liver parameters and carnitine levels were within normal range (free carnitine: 39 μmol/l (24–64 μmol/l); acetylcarnitine: 3.55 μmol/l (1–13.62 μmol/l)). Despite normal ranges of carnitive levels, administration of carnitine 250 mg was initiated. In addition, VPA dose was reduced to 500 mg/24 h. Subsequently, the level of ammonium decreased to 38 μmol/l, and drowsiness resolved. Few weeks later, seizures again increased in frequency and severity, and the dose of VPA was gradually increased to 1500 mg/24 h (25 mg/kg/24 h) under the guise of carnitine treatment. She then became lethargic. The plasma concentration of VPA and ammonium level had increased to 495 μmol/l and 61 μmol/l, respectively. The dose of carnitine was increased to 500 mg/24 h, and within few days, despite an unchanged VPA dose, the lethargy disappeared and the level of ammonium decreased to 12 μmol/l.

## 4. Discussion

VHA is a condition characterized by elevation of plasma level of ammonium above 40 μmol/l. It may be asymptomatic or presents as VHE.[1] Mild and transient hyperammonemia (HA) occurs frequently during VPA therapy.[23] VHE is without clinical or laboratory evidence of hepatotoxicity and can occur at normal therapeutic VPA blood levels. The four patients were prescribed

**Table 2**
A review of VHE in children.

| Author | Sex/age | Diagnosis | VHE symptoms | Daily dose of VPA (mg) | Associated medications | Ammonia level (μmol/l) | VPA level (μmol/l) | Duration of therapy |
|---|---|---|---|---|---|---|---|---|
| Carlson et al. (2007)[7] | M – 11 | Aspergers syndrome<br>ADHD<br>Mania and psychosis | Agitation<br>Disrobing<br>Vomiting | 750 | Lithium<br>Ariprazole<br>Dextroamphetamine | 213 | 603–624 | NA |
| Cheung et al. (2004)[8] | M – 15 | Mental retardation and inverted duplication for chromosome 15. Epilepsy | Irritability<br>Drowsiness, Decreased appetite<br>Increased minor seizures. | 42 mg/kg | Topiramate<br>Phenytoin | 61 | 774 | NA |
| Chou et al. (2008)[25] | F – 14 | Absence seizures | Dizziness<br>Malaise<br>Vomiting<br>Lethargy | 1000 | None | 184 | 1261 | 3 weeks |
| Young et al. (2010)[36] | M – 15 | Bipolar disorder<br>MODY | Sleepiness | 1750 | Lithium<br>Haloperidol<br>Herbal medicine | 96 | 693 | NA |

*Abbreviations*: NA, not available; M, male; F, female; MODY, Mature onset diabetes of the young.

VPA in standard dosages and all had plasma concentrations of VPA within the therapeutic recommended levels. All received VPA in poly-therapy, and in case 1 an anti-psychotic drug was administered as well. In children, poly-therapy has been reported to be a risk factor of VHA and VHE.[2,7,8,23] Yamamoto et al.[22] reported concomitant use of phenytoin, phenobarbital and topiramate as a risk factor of VHE in children. Adults receiving phenytoin, phenobarbital and carbamazepine in combination with VPA also experienced increased ammonium levels.[9,10,23] Topiramate was prescribed in combination with phenobarbital and VPA in one patient.[10] Furthermore, poly-therapy has been described as a risk factor of VHE in the psychiatric setting,[11–14] among mentally impaired individuals,[15,16] and among elderly.[17] Tables 2 and 3 summarize the existing case reports of VHE in children and adults.

A systematic review concluded that measurement of ammonium in asymptomatic patients treated with VPA is unnecessary,[21] and that VPA should not be discontinued solely on the basis of HA. Other studies emphasize the need for measurements of ammonium level in patients with multiple risk factors such as being under 2 years of age, VPA level higher than the therapeutic range, poly-therapy, concomitant use of other anti-epileptic drugs, and in those with known carnitine deficiency or congenital abnormalities of the urea cycle.[2,9,22,24]

The clinical manifestations of VHE include an acute or sub-acute decrease in consciousness level with progression from drowsiness to lethargy and coma. Symptoms like confusion, personality change, irritability, ataxia, visual disturbance, lethargy, focal neurological deficits, nausea, vomiting and increased seizure frequency occur. These findings may even lead to an increase in VPA dose before diagnosis, with the consequent worsening.[1,11,24] VHE can occur with normal dose and plasma levels of VPA,[25] and liver parameters are most often quite normal. The four cases all showed signs of VHE. Symptoms occurred shortly after commencement or increase in dose of VPA. Electro-encephalograms (EEGs) were not performed in any of our cases. However, the symptoms disappeared immediately after discontinuation of VPA (cases 1 and 2) or administration of carnitine (cases 3 and 4), which strongly argues against a non-convulsive status epilepticus as the cause of the drowsiness and lethargy reported in the cases.

### 4.1. Pathophysiology of VHE

VPA can lead to VHE because of several mechanisms. An increased uptake of glutamine and the release of ammonium in the kidneys favors HA mediated by a VPA metabolite, sodium 2-propyl-4-pentenoate. Furthermore, the VPA metabolites propionate and 4-en-VPA reduces levels of hepatic N-acetylglutamate (NAG) and a decrease in acetyl-CoA which inhibits the urea cycle and diminishes the removal of ammonia. Drugs like phenytoin, phenobarbital and carbamazapine leads to an increase in 4-en-VPA resulting in HA, which may explain why polytherapy favors development of HA and VHE.[24]

VHE occurs as a course of reduced glutamine synthesis in the brain by VPA. Furthermore, intracellular concentrations of glutamate and ammonium in astrocytes increase, and cerebral edema, raised intracranial pressure and neuronal damage develops.[26] VPA is a short chain fatty acid which requires carnitine for oxidation. VPA combines with carnitine within the mitochondria resulting in valproylcarnitine ester, which then is transported out of the mitochondria and eliminated in the urine, thus depleting carnitine stores.[27] Overall, ammonia concentrations are directly correlated with the dosage and serum concentrations of valproic acid and inversely correlated with serum concentrations of carnitine.[28]

### 4.2. Carnitine deficiency and hyperammonemia

Carnitine deficiency (CD) can be an isolated autosomal recessive disorder, or can arise from secondary causes, such as inborn errors of metabolism, renal failure, hepatic disease, malnutrition, or the use of medications, such as VPA.[29] In a prospective study, Hamed et al.[3] described that plasma ammonium concentration was significantly elevated in VPA mono-therapy and poly-therapy after one year of treatment. Among 60 patients treated with VPA, 38 developed low levels of carnitine and received treatment with carnitine. In addition, a significant decrease in total or free blood carnitine concentrations or both has been reported in patients receiving antiepileptic polypharmacy.[30] Carnitine has been found to be beneficial in treatment of VHE following either a VPA overdose or usual dosages of VPA.[28] Supplementation with carnitine has been recommended in children on VPA therapy, who receive more than one anticonvulsant, have a poor nutritional status, or are following a ketogenic diet. In adults, carnitine treatment may be considered if there are impairment of hepatic parameters, presence of HA, a significant decrease in serum free carnitine levels, or symptoms suggestive of CD.[31] Administration of exogenous carnitine reduces level of ammonium by binding to VPA and relieving the inhibition of urea synthesis. Several studies suggest that supplementation with carnitine reduces the ammonium level.[27,28,31,32] In the present case series, treatment with carnitine was not tried in case 1 or 2, but significantly reduced ammonium levels were seen concomitant to carnitine administration in cases 3 and 4, despite unchanged administration of VPA.

**Table 3**
A review of VHE in adults.

| Author | Sex/age | Diagnosis | VHE symptoms | Daily dose of VPA (mg) | Associated medications | Ammonia level (μmol/l) | VPA level (μmol/l) | Duration of therapy |
|---|---|---|---|---|---|---|---|---|
| Gomez-Ibañez et al. (2011)[10] | F – 49 | Epilepsy with tonic-clonic seizures and partial complex seizures | Behavioral change<br>Involuntary movements<br>Disorientation<br>Aphasia<br>Unsteady gait | 1500 | Phenobarbital<br>Topiramate | 115 | 416 | 5 years |
| Shan et al. (2010)[13] | M – 41 | Schizophrenia | Drowsiness<br>Sleepiness<br>Unsteady gait<br>Unconsciousness | 1500 | Zotepine | 182 | 866 | 18 days |
| McCall et al. (2004)[14] | F – 62 | Brain aneurism repair with seizure disorder<br>Previously traumatic brain injury.<br>Anxiety<br>Hypertension<br>Hypothyroidism<br>Fibromyalgia<br>Chronic pain | Decreased level of consciousness<br>Confusion<br>Dizziness<br>Lethargy<br>Several falls | 250 | Estradiol<br>Levothyroxine<br>Diazepam<br>Cyclobenzaprine<br>Trazodone<br>Acetaminophen<br>Codeine<br>Sulindac | 99 | 520 | NA |
| Khoo et al. (2010)[16] | F – 38 | Mental retardation, Episodes of agitation, irritability and aggression | Fluctuations of agitation and sedation.<br>Unsteady gait. | 1500 | Quetiapine<br>Fluoxetine<br>Fluphenanzine Decanoate | 130 | 631 | 18 years |
| Wadzinski et al. (2007)[37] | F – 51 | PTSD<br>Migraine Depression | Unresponsiveness | 1000 | Topiramate<br>Quetiapine | 232 (10–47) | 1005 | 7 days |
| Wadzinski et al. (2007)[37] | F – 29 | OCD<br>Bipolar disorder | Short-term memory<br>Confusion Disorientation<br>Hypersomnia Blurred vision Slurred speech<br>Ataxia | 1500 | Fluvoxamine<br>Clonazepam | 182 (10–47) | 783 | 5 months |
| Eubanks et al. (2008)[38] | F – 33 | Bipolar disorder<br>PTSD<br>Borderline personality | Unresponsiveness | 1500 | Clonazepam<br>Venlafaxine<br>Mirtazapine<br>Buprionon<br>Hydroxyzine | 283 (2–30) | 832 | 3 days |
| Cuturic et al. (2005)[39] | F – 56 | Idiopathic complex partial epilepsy with secondary generalization | Confusion<br>Drowsiness<br>Unresponsiveness | 2500–3000 | Carbamazepine, Gabapentin | 479 (12–46) | 568 | NA |
| Deutsch S et al. (2009)[40] | F – 31 | Bipolar disorder with psychotic features, borderline personality, and migraine | Somnolence<br>Irritability<br>Dysarthry<br>Ataxia<br>Hearing voices | 1000 | Citalopram<br>Topiramata | 41 (9–35) | 721 | 2 weeks |
| Velioglu et al. (2007)[41] | M – 19 | 2 seizures 1 year before | Dizziness<br>Ataxia<br>Drowsiness, Nausea<br>Reduced level of consciousness | 500 | NA | 70 (9–33) | 277 | 4 days |
| Feil et al. (2012)[42] | M – 88 | Seizure disorder of unknown etiology | Confusion | 250 | NA | 490 (19–60) | 333 | 2 months |
| Hung et al. (2011)[43] | F – 21 | Hallucinations and aggressive behavior | Nausea<br>Vomiting Drowsiness<br>Disorientation Ataxia | 500–750 | NA | 133 | 742 | 4 days |
| Soares-Fernandes et al. (2006)[44] | F – 45 | Epilepsy | Somnolence<br>Coma | 1600 | Phenytoin<br>Phenobarbital | 479 | 305 | 1 day |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ziyeh et al. (2002)[45] | NA – 32 | Epilepsy caused by traumatic brain injury 6 years before | Vertigo<br>Disturbance of concentration<br>Ataxia<br>Asterixis | 1500 | None | 152 | 471 | 6 years |
| Fan et al. (2008)[46] | F – 72 | Bipolar disorder | Hand tremor Asterixis<br>Lethargy | 900 | Lamotrigine<br>Clozapin | 59 | 596 | 3 weeks |
| Lokrants et al. (2004)[47] | F – 72 | Partial epilepsy<br>Vascular dementia<br>Urinary tract infection | Slurred speech<br>Stupor<br>Tremor | 1500 | Pivmecillinam | 113 | 755 | 1 year |
| Stewart (2008)[48] | M – 76 | Bipolar disorder<br>Familial essential tremor<br>Recurrent SVT<br>Hypertension<br>Hyperlipidemia | Confusion<br>Lethargy | 3000 | Quetiapine<br>Primidone<br>Metoprolol<br>Atorvastatin<br>Lisinopril<br>Levothyroxine<br>Aspirin | 214 | 506 | 11 years |
| Tarafdar et al. (2011)[49] | M – 36 | Partial epilepsy<br>ITP | Confusion | 3500 | Phenytoin<br>Levetiracetam | 284 | 367 | NA |
| Sonik et al. (2011)[50] | M – 25 | Undifferentiated schizophrenia and antisocial personality disorder | Thought blocking<br>Uncooperative behavior<br>Disorganization<br>Psychosis | 1000 | Risperidone<br>Quetiapine | 101 | 550 (346–866) | 2 weeks |

*Abbreviations*: NA, not available; M, male; F, female; SVT, supraventricular tachycardia; ITP, idiopathic thrombocytopenic purpura.

### 4.3. Pathophysiology of VHE in Batten disease

Batten disease is caused by accumulation of lysosomal storage bodies. A significant constituent of this storage is the protein subunit c of ATP synthetase, which contains a trimethyl lysine (TML) residue. Presence of TML in the stored protein leads to degradation of the protein, thus releasing free TML. Free TML is the first intermediate in the carnitine pathway. Thus, accumulation of TML containing subunit c leads to CD.[33] Katz[33] examined 80 people who either were patients with Batten disease, carriers of the disease, or controls. Mean total and free carnitine concentration in patients with Batten disease were 63% respectively 61% of the levels observed in normal controls. In a dog model of JNCL, half of the attended had improvement in symptoms when treated with carnitine as a dietary supplement, compared to non-treated[34] and in a mouse study,[35] carnitine supplementation significantly increased life expectancy. In addition, following 25 weeks of carnitine treatment the mice had significantly less storage material in the cortical neurons than mice without carnitine treatment. The authors suggested, that carnitine may act via a feedback mechanism which slows the synthesis of TML containing subunit c. So far, no study of carnitine treatment in JNCL patients has been published, but these observations suggest, that patients with JNCL may have an increased risk of developing HA or even VHE when treated with VPA. In the present case series, four of 14 patients treated with VPA in poly-therapy had VHE, but as measurements of ammonium were not performed on routine, further patients may have had an asymptomatic increase in ammonium that could ultimately result in development of VHE.

## 5. Conclusion

Patients with JNCL are in great risk of developing VHE due to a high rate of poly-pharmacy. In addition, carnitine levels may be depressed in Batten disease, which might be a second reason for an increased risk of VHE. We therefore recommend that increased attention to VHA/VHE should be given to these patients.

## Conflict of interest statement

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal' position on issues involved in ethical publication, and affirm that this report is consistent with those guidelines.

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