Original article / *Araştırma*

Role of valproate in hyperammonemic encephalopathy in women in a tertiary psychiatric clinic

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ABSTRACT

Objective: *In patients with acute mental status change with elevated serum ammonia levels, when there is concomitant use of valproate, carbamazepine or any other susceptible agent, hyperammonemic encephalopathy is a possible phenomenon. Our aim was to describe this underreported phenomenon in detail and find possible risk factors associated with valproate induced hyperammonemic encephalopathy.* ***Methods:*** *We analyzed retrospective records of two years for female inpatients in the psychiatric ward for women in our hospital. Spearman's rho correlation analysis was used for assessing the relation between serum ammonia and valproate levels. During the two years' period, 961 patients were treated in the inpatient clinic. Because of a suspicion of hyperammonemic encephalopathy, serum ammonia levels of 37 patients were analyzed, revealing a total of 34 patients with high ammonia levels, warranting a diagnosis of hyperammonemic encephalopathy.* ***Results:*** *In 28 of these patients hyperammonemic encephalopathy was associated with valproate use. The time interval between initiation of valproate treatment and hyperammonemia was 11±7 days. For these patients, initiation dose of valproate was 883.93±249.83 mg/day (median: 1000 mg/day), daily valproate dose was 914.90±202.87 (median: 928.25) mg and during encephalopathy; valproate blood level was 82.36±25.80 ng/mL (median: 87.50 ng/mL). Serum ammonia level was positively correlated with initiation dose of valproate ($\rho_{(28)}$=0.472, p=0.011) and valproate blood levels during hyperammonemia ($\rho_{(28)}$=0.522, p=0.004). Polypharmacy and long-term intramuscular treatment were also prevalent in patients with hyperammonemic encephalopathy.* ***Discussion:*** *Early suspicion of hyperammonemic encephalopathy in patients taking valproate may improve the outcome of this under recognized problem.* ***(Anatolian Journal of Psychiatry 2019; 20(6):589-596)***

Keywords: *bipolar disorder, valproate, lithium, hyperammonemia*

Bir üçüncü basamak psikiyatri servisindeki kadınlarda hiperamonyemik ensefalopatide valproik asidin rolü

ÖZ

Amaç: *Akut mental durum değişikliği olan hastalarda yüksek serum amonyak değeri ve valproik asit, karbamazepin veya diğer etken ajanlardan birinin kullanımı varsa, hiperamonyemik ensefalopati olası bir durumdur. Literatürde nadir bildirilmiş olan bu durumu ayrıntılı olarak tanımlamayı ve valproik asite bağlı hiperamonyemik ensefalopati riskini artıran etkenleri araştırmayı amaçladık.* ***Yöntem:*** *Geriye dönük olarak, hastanemizdeki kadınlar için yataklı psikiyatri servisinde tedavi görmüş olan hastaların iki yıllık kayıtlarını inceledik. Serum amonyak düzeyleri ve valproik asit düzeyleri arasındaki ilişkiyi Spearman's rho korelasyon analizi ile inceledik. İki yıllık dönemde, yatan hasta servisinde 961 hasta tedavi edilmişti. Otuz yedi hastada hiperamonyemik ensefalopati şüphesi ile serum amonyak düzeyi tetkik edilmiş ve 34 hastada amonyak düzeyleri yüksek saptanarak hiperamonyemik ensefalopati tanısı*

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konmuştu. ***Sonuçlar:*** *Yirmi sekiz hastada hiperamonyemik ensefalopati valproik asit kullanımı ile ilişkiliydi. Valproik asitin başlanması ve hiperamonyemi arasındaki süre 11±7 gündü. Bu hastalarda valproik asit başlangıç dozu 883,93±249,83 mg/gün (medyan: 1000mg/gün), günlük valproik asit dozu 914.90±202.87 mg (medyan: 928.25 mg) ve ensefalopati sırasında valproik asit kan düzeyi 82.36±25.80 ng/mL (medyan: 87.50 ng/mL) saptandı. Serum amonyak düzeyleri, valproik asit başlangıç dozu ($\rho_{(28)}$=0.472, p=0.011) ve valproik asit kan düzeyleri ile ($\rho_{(28)}$=0.522, p=0.004) pozitif korelasyon göstermekteydi. Hiperamonyemik ensefalopatisi olan hastalarda çoklu ilaç kullanımı ve uzun süreli intramusküler antipsikotik kullanımının da sık olduğu görüldü.* ***Tartışma:*** *Valproik asit kullanan hastalarda hiperamonyemik ensefalopatiden erken akla gelmesi, farkındalığın az olduğu bu sorun ile ilgili klinik sonuçların daha olumlu olmasını sağlayabilir.* ***(Anadolu Psikiyatri Derg 2019; 20(6):589-596)***

Anahtar sözcükler: *Bipolar bozukluk, valproik asit, lityum, hiperamonyemi*

INTRODUCTION

Valproate's efficacy has been approved as a mood stabilizer in bipolar disorders and other psychotic disorders with affective features.[1] Mental status changes due to hyperammonemia is a rare but potentially serious side effect of valproate.[2,3] Other clinical features of hyperammonemia are lethargy, agitation, confusion and coma. Ataxia, vomiting, fever, focal neurological signs and seizures may accompany. In order to differentiate hyperammonemic encephalopathy in patients with mental status changes, detection of ammonia levels is advised.[4] The diagnosis of encephalopathy is a phenomenological one and when serum ammonia levels are abnormally high, valproate or any other susceptible agent can be responsible in the etiology.

Valproate and its metabolites causes hyperammonemia mainly by reducing the availability of N-acetyl glutamate (NAG) (Baddour et al).[5] NAG is a cofactor for carbomyl phosphate synthetase enzyme in the urea cycle. One of the mechanism which decreases NAG is direct stimulation of glutaminase in the kidney and indirect inhibition of the enzyme N-acetyl glutamate synthase. Acetyl-CoA is also necessary for NAG synthesis and valproate is associated with depletion of carnitine reserves which operates in the beta-oxidation of fatty acids, resulting decreased levels of acetyl-CoA (Colomer et al).[6]

High initiation dose, long term duration of treatment, concomitant use of topiramate were reported as the possible risk factors of hyperammonemic encephalopathy induced by valproate. Hepatic enzyme inducing agents and female gender were also reported as increase the risk.[7,8] Risperidone and olanzapine were the antipsychotics with a suspicion of increasing the risk.[9]

We aimed to uncover the features of the inpatients with valproat induced hyperammonemic encephalopathy (VHE) in our clinic for women, in order to show the occurrence of this phenomenon in daily clinical practice. Determining the possible factors associated with VHE was also one of our concerns. In our study, we investigated the retrospective records of our inpatients in order to find clues for the risk factors associated with hyperammonemic encephalopathy for this clinical sample. Valproate starting dose, valproate maximum dose, valproate cumulative dose, mean valproate dose, valproate serum level were the variables analyzed with an aim to find a correlation with serum ammonia level.

METHODS

Our study consisted of female psychiatric inpatients who were hospitalized between January 01th 2015 and January 01th 2017, in the tertiary treatment center for women with psychiatric disorders. Detection of ammonia levels was not a routine procedure and serum ammonia levels were detected only in patients who were suspected of hyperammonemic encephalopathy.

Inclusion criteria:
1. Being hospitalized in the psychiatric clinic for women in our hospital,
2. Detection of ammonia levels (with the suspicion of hyperammonemic encephalopathy)

Exclusion criteria:
1. Patients diagnosed with cirrhosis before admission

All the medical records which were available and associated with the cases were reviewed. Our study protocol was approved by the ethical review board of our research and training hospital in June 06th 2017 (application number: 12582-00042328859). The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or compatible ethical standards.

The inpatient treatment psychiatric ward in the study was a tertiary unit for patients with homicidal, suicidal or other prominent self-harm risks.

Table 1. Clinical features

n=37	Range	Mean±SD (Median)
Age	19-69	45.03±11.35 (48)
Duration of hospitalization	6-103	40.43±23.53 (37)
Duration of psychiatric disorder (Year)	1-50	15.64±11.39 (13)
Number of mood episodes	1-27	5.78±5.87 (4)
Duration of intramuscular treatment (n=35)	1-34	11.00±6.91 (9)
Number of electroconvulsive therapy (n=4)	6-10	9.00±2.00 (10)
Highest ammonia level	8-839	170.14±138.27 (141)
Duration of hospitalization after hyperammonemia	3-91(days)	20.62±18.52 (14)
Duration between first valproate	3-37(days)	11.85±7.91 (11)
Valproate initiation dose (n=28)	500-1500	883.93±249.83 (1000)
Valproate maximum dose (n=28)	500-1500	1035.72±232.87 (1000)
Valproate mean daily dose (n=28)	500-1500	914.90±202.97 (928.25)
Valproate cumulative dose (n=28)	2000-72500	12732.14±14095.89 (9500)
Valproate level during hyperammonemia (n=28)	27.6-125	82.36±25.80 (87.50)
Lithium level during hyperammonemia (n=5)	0.64-0.89	0.81±0.10 (0.84)
Alanine amino transferase (n=36)	6-73	19.72±14.58 (16.50)
Aspartate amino transferase (n=36)	11-155	27.27±26.47 (18)
Gamma glutamyl transferase (n=30)	7-72	23.46±17.92 (17)

Table 2. Psychiatric diagnostic features

n=37	n	%
Manic episode with psychotic features	23	62.2
Manic episode without psychotic features	1	2.7
Schizophrenia	4	10.8
Schizoaffective disorder	4	10.8
Dissociative disorder	1	2.7
Borderline personality disorder	1	2.7
Psychotic disorder, other specified	2	5.4
Bipolar depression with psychotic features	1	2.7

Table 3. Psychopharmacological treatment

n=37	n	%
Haloperidol	34	91.9
Risperidone	10	27.0
Quetiapine	34	91.9
Clozapine	3	8.1
Chlorpromazine	12	32.4
Olanzapine	3	8.1
Diazepam	17	45.9
Lorazepam	23	72.9
Amisulpride	3	8.1
Aripiprazole	3	8.1
Zuclopenthixol	3	8.1
Carbamazepine	1	2.1
Fluoxetine	2	5.4
Venlafaxine	1	2.7

For patients suspected of hyperammonemic encephalopathy, in order to avoid false positive results for hyperammonemia, precautions such as prohibition of smoking of the medical personnel before taking blood samples or avoidance of delays in the transfer of the samples to the laboratory were some of the strictly proceeded routines of our clinic.

IBM SPSS statistical package (version 19.00) was used in the analysis of the data. Descriptive statistics such as minimum and maximum values, frequencies, percentages, means, medians and standard deviations were determined. The correlation of highest ammonia level with valproate starting dose, valproate maximum dose, valproate cumulative dose, mean valproate dose, valproate serum levels were analyzed.

Our clinical personal in the psychiatric ward were

Table 4. Doses of the psychopharmacological agents of patients with encephalopathy

n=37	Min-Max	Mean±SD (Median)
Haloperidol maximum daily dose	10-40	22.94±7.18 (20)
Haloperidol cumulative dose	10-1315	315.59±308.86 (225)
Risperidone max. daily dose	3-6	4.40±1.42 (4)
Risperidone cum. dose	3-101	33.70±31.93 (27)
Quetiapine max. daily dose	50-800	433.82±231.93 (400)
Quetiapine cum. dose	100-25900	6114.12±5993.23 (4313)
Clozapine max. daily dose	200-600	333.33±230.94 (200)
Clozapine cum. dose	1525-7200	3458.33±3420.98 (3240.98)
Chlorpromazine max. daily dose	25-600	260.41±227.50 (200)
Chlorpromazine cum. dose	25-6600	1939.00±2124.04 (1650)
Olanzapine max. daily dose	20	20±0.00 (20)
Olanzapine cum. dose	150-180	206.66±66.58 (190)
Amisulpride max. daily dose	800-1200	933.33±230.94 (800)
Amisulpride cum. dose	6400-80000	33466.66±40477.81 (14000)
Aripiprazole max. daily dose	10-20	15.00±5.00 (15)
Aripiprazole cum. dose	50-300	161.66±127.12 (135)
Zuclopenthixol max. daily dose	50-200	150.00±86.60 (200)
Zuclopenthixol cum. dose	150-400	316.66±144.33 (400)
Carbamazepine max. daily dose	600	600.00±0.00 (600)
Carbamazepine cum. dose	1400	1400.00±0.00 (1400)
Clonazepam max. daily dose	2	2±0.00 (2)
Clonazepam cum. dose	2	2±0.00 (2)
Diazepam max. daily dose	10-95	15.00±20.61 (10)
Diazepam cum. dose	10-255	100.58±68.78 (95)
Lorazepam max. daily dose	1-7.50	3.00±1.91 (2.5)
Lorazepam cum. dose	1-119.50	15.61±25.52 (8)

Table 5. Correlation analysis of highest ammonia serum levels with valproate doses and valproate serum levels

n=28	Highest serum ammonia level
Valproat starting dose	r=0.472 p=0.011*
Valproate maximum dose	r=0.052 p=0.791
Valproate cumulative dose	r=-0.003 p=0.989
Valproate mean dose	r=0.246 p=0.207
Valproate serum level	r=0.522 p=0.004**

**: p<0.05; **: p<0.01*

informed about the signs of encephalopathy for the clinical guidance of our patients and when if there had been the suspicion of encephalopathy, this was recorded and ammonia levels were detected. In all the patients with the suspicion of hyperammonemic encephalopathy, hyperammonemia levels were detected and continuous evaluation of the patient for the signs of ongoing encephalopathy were conducted. This was a retrospectively designed study and we were not able to apply clinical examination scales to these patients since this was not part of our routine clinical practice. We collected the information from the medical records.

RESULTS

During the period of two years that the study focuses, 961 inpatients were treated in our clinic. The diagnosis of hyperammonemic encephalopathy was suspected in 37 patients and serum ammonia levels were checked for these patients. Medical records of these patients were investigated in detail with an effort to find risk factors for hyperammonemic encephalopathy. In 34 of these patients, the diagnosis of hyperammonemic encephalopathy was confirmed with the detection of high serum ammonia levels. Regarding 37 patients in whom hyperammonemic encephalopathy was suspected; there were three patients who had clinical signs of encepha-

lopathy although serum ammonia levels were in the normal range. These three patients were diagnosed as encephalopathy with undefined etiology and we included these patients in our analysis since encephalopathy with normal ammonia levels was also a defined clinical phenomenon.

In our clinical sample of 37 patients with the clinical signs of encephalopathy; there were 28 patients who were given valproate. There was one patient with concomitant use of valproate and carbamazepine, one patient with valproate and lithium and four patients with only lithium as a mood stabilizer. There were four patients who had not been prescribed any mood stabilizer; for one of those patients, hyperammonemia was associated with antipsychotic polypharmacy (including chlorpromazine) and long term (34 days) use of intramuscular antipsychotics. For two of those patients without mood stabilizer; renal dysfunction, diabetes mellitus and long term intramuscular antipsychotic use (up to 17 days) were present. Polypharmacy was present for all of four patients who were not given mood stabilizer.

Time interval between initiation of valproate and detection of hyperammonemia was 11±7 days. In 22 of these VHE cases, initiation of valproate was during inpatient treatment, and it was before the hospitalization in 6 cases. Clinical characteristics of the cases with details of valproate treatment are shown in Table 1 and psychiatric diagnostic features are shown in Table 2. Additional medical comorbidity was present in 14 patients. These comorbidities were hypertension (n=6), hypothyroidism (n=3), diabetes mellitus (n=2), bronchial asthma (n=2), epilepsy (n=2), renal dysfunction (n=1) and malign neuroleptic syndrome (n=1).

Psychopharmacological medications of the patients with encephalopathy were shown in Table 3. There was polypharmacy (the use of three or more medications) in 32 of these patients. Twenty-five patients were given four or more medications. The daily doses and cumulative doses are shown in Table 4.

In the patients with VHE (n=28), valproate was stopped immediately in 13 cases and improvement was observed with hydration and close observation of the general medical condition. In three cases valproate dose was only decreased and clinical improvement was observed. In five cases, valproate dose was decreased first, but when no improvement was observed, valproate was needed to be withdrawn for clinical improvement. In seven cases, no change was made in valproate dose after the diagnosis of encephalopathy; improvement was observed after avoiding abundant polypharmacy. All the patients diagnosed with encephalopathy were discharged from the hospital with clinical improvement.

For the treatment of hyperammonemic encephalopathy, none of the patients in our study were given alternative agents such as levocarnitine, lactulose, charcoal, neomycin or rifamixin and hemodialysis was not needed for any patient. There were no cases of mortality.

Because the highest serum ammonia level was not normally distributed, Spearman's Rho correlation was used. There was moderate, positive statistically significant relationship between the highest serum ammonia level and valproate starting dose ($\rho_{(28)}$=0.472, p=0.011). Higher valproate starting doses were related to higher ammonia levels. There was also moderate, positive statistically significant relationship between the highest serum ammonia levels and valproate serum levels ($\rho_{(28)}$=0.522, p=0.004). Higher valproate serum levels were related to higher ammonia levels. There was no significant relationship between serum ammonia levels and maximum dose of valproate, cumulative dose of valproate or mean valproate dose (p>0.05) (Table 5).

DISCUSSION

Of the 37 patients with the suspicion of hyperammonemic encephalopathy and 34 patients with confirmed hyperammonemia, 28 of the cases were associated with valproate use. The duration between the initiation of valproate and detection of hyperammonemia was 11±7 days. Median valproate initiation dose was 1000 mg/day and median valproate blood level was 87.50 ng/mL for the patients with VHE. There was positive correlation between serum ammonia levels with valproate initiation dose ($\rho_{(28)}$=0.472, p=0.011), we suspect that the risk of VHE may be increased for the patients with high valproate initiation dose. There was also positive correlation between serum ammonia levels and valproate blood levels during hyperammonemia ($\rho_{(28)}$=0.522, p=0.004).

In a retrospective study of Lewis and collegues; there were 20 cases of hyperammonemic encephalopathy in 793 psychiatric patients treated with valproate.[10] In a recent study, the number VHE cases was 54 among 347 patients treated

with valproate.[5] In a meta-analysis comprised of patients with epilepsy, in a duration of 10 years, there were reported to be 51 cases with valproate induced hyperammonemic encephalopathy.[11] In our study comprised of 961 psychiatric inpatients in a period of two years, 28 of the 37 cases of hyperammonemic encephalopathy were associated with valproate. Although methodological differences make comparisons difficult, we suggest that incidence of VHE in women treated as psychiatric inpatients could be higher than patients with a psychiatric diagnosis in general hospital setting or patients diagnosed with epilepsy.

Our study was comprised of female inpatients. There were reports of increased risk of valproate induced hyperammonemic encephalopathy in women.[7,8] One possible explanation was that female patients had lower mean body weight, this causes differences in hepatic blood flow and valproate clearence.[8] In addition to this, male patients had higher uridine diphosphate transferase activity than females, valproate was metabolized mainly through this enzyme so this was another reason for differences in valproate metabolism.[8] Use of intramuscular antipsychotic medication for a longer period of time was reported as another risk factor for VHE and intramuscular medication use was prevalent in our study sample, but our study design prevents us from drawing firm conclusions.

For three of the patients with encephalopathy in our study, the serum levels of ammonia were within normal range. In the literature, there were cases with encephalopathy with normal ammonia levels.[11,12] Besides, there could be an etiology other than valproate for the cases of encephalopathy with normal ammonia levels. There were also cases with asymptomatic hyperammonemic encephalopathy in the literature.[13]

The time interval between initiation of valproate and detection of VHE changes in the previous reports range between a period shorter than a month and up to 10 years.[10] All of the VHE cases in our study were detected within 11.85±7.91 days with a range of three days and 37 days after initiation of valproate. We suggest the first month of valproate treatment could be a risky period for idiosyncratic side effects.

Valproate initiation dose was 883.93±249.83 mg/day and it was positively correlated with serum ammonia levels ($p<0.05$). Besides, valproate levels during hyperammonemia was also positively correlated with ammonia serum levels ($p<0.01$). These findings are in line with the previous reports that find correlation between valproate treatment and ammonia levels.[14,15] On the other hand, there are other studies that find no correlation between valproate levels and presence or severity of encephalopaty.[10,16,17] Since our study was comprised of inpatients in a psychiatry clinic, we could be able to monitor the levels of valproate more closely and this may be the reason for our finding a positive correlation unlike some of the researchers whose studies were comprised of patients in heterogeneous treatment settings.

In our study, there was one patient with a possible carbamazepine induced hyperammonemic encephalopathy and this was accepted as an idiosyncratic phenomenon in the literature.[18,19] There were also reported cases with simultaneous lithium use and hyperammonemia, but for these cases, it was not possible to assert a cause and effect relationship.[20] In our sample, there were three cases with lithium use, and one with combination of lithium and valproate. It is usually not possible to point a causal relationship for a specific pharmacological agent in the presence of polypharmacy.[21] Regarding our study, there was polypharmacy (three or more medications) in 86.4% of the patients. Moreover, 67.5% of the patients were using four or more medications. This finding underlines the abundant polypharmacy as a possible risk factor in patients with hyperammonemic encephalopathy.[14,15] Lewis and colleagues reported polypharmacy (three or more medications) in half of their patients.[10]

Clinical improvement in VHE after reducing or stopping valproate treatment was frequently reported in previous studies.[3,10,15] In many of the reports about VHE, the strategy was to stop valproate treatment in most cases.[12,22-23] In a retrospectively designed study, valproate was stopped in 40% of the patients but it was reported that valproate dose was even increased in one of the patients.[10] In our study, in 64% (n=18) of the patients, valproate was stopped. For seven patients, no changes were made in valproate dose. Although there was improvement without a change in the dose of valproate, the optimum strategy would be decreasing the dose or stopping any agent that could be associated with the etiology of hyper-ammonemic encephalopathy. Underestimation of the clinical significance of VHE could be the reason for making no change in the dose of valproate.[10]

Limitations of the study

Because of the study design, we could only focus on the patients that the serum levels of ammonia were detected because of the suspicion of hyperammonemic encephalopathy and for this reason, it was not possible to come to a conclusion about the precise incidence of VHE. The retrospective study design limits our data with patient files and online medical documents. There could be undiagnosed cases of VHE, since the mental status change in VHE could be attributed to worsening of the current psychiatric disorder or undiagnosed epileptic seizures. Detection of serum ammonia levels was not a routine procedure in our clinic and it was only used when there was suspicion of hyperammonemia. Absence of comparison of the patients with the signs of encephalopathy with the other group of patients who did not show the signs of encephalopathy and who had normal hyperammonemia levels were another limitation of our study. This would lead to more generalizable results with the addition of male patients and random sampling of these groups. Use of abundant polypharmacy in real-world clinical practice for inpatients also operates as a confounder that weakens the link between valproate and hyperammonemic encephalopathy.

A prospective study with detection of ammonia levels for all the patients on valproate treatment will provide more increased precision about the incidence or risk factors of VHE. Besides, scales or instruments for objectively recording the presence and severity of hyperammonemic encephalopathy will improve our knowledge about this under recognized clinical phenomenon.

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