Case Report

Status epilepticus and topiramate induced metabolic acidosis in a patient with multiple sclerosis under natalizumab therapy

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ABSTRACT

Status epilepticus and topiramate induced metabolic acidosis in a patient with multiple sclerosis under natalizumab therapy.

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Therapy armamentarium for multpile sclerosis include a variety of drugs. Natalizumab, a humanized antibody, is widely used in relapsing-remissing multiple sclerosis. Anticonvulsants, like topiramate, are also widely used for symptomatic relief. We hereby describe a case of Status epilepticus and topiramate induced metabolic acidosis in a female patient with multiple sclerosis under natalizumab therapy.

Key words: Natalizumab, topiramate, Multiple sclerosis, metabolic acidosis, Status epilepticus

INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating and neurodegenerative inflammatory disease in adults between 18 and 35 years of age and constitutes the second cause of neurological disability in young adults[1].

There is no definite cure for multiple sclerosis (MS). Treatments available aim at relieving symptoms of the disease, treating acute exacerbations, shortening the duration of an acute relapse, reducing frequency of relapses, and pre-

venting disease progression (disease-modifying drugs)[2].

Natalizumab is a monoclonal antibody that acts as an α4 integrin) antagonist to prevent leukocyte trafficking into central nervous system (CNS). Natalizumab's high efficacy has led to a broad use in MS both as first and second line treatment[3]. Topiramate, an anticonvulsant with several mechanisms of actions, is used in MS patients as symptomatic treatment for tremor, spasticity, dysaesthetic pain[2].

In this report, we describe a case of Status epilepticus and topiramate induced metabolic acidosis in a female patient with multiple sclerosis under natalizumab therapy.

CASE REPORT

A 44-years old female patient was transported to Emergency Department (ED) with Mobile Intensive Care Unit (MICU) due to Status Epilepticus. Her medical history included MS (ICD_{10}- G35) with Kurtzke Expanded Disability Status Scale (EDSS) ambulation score 6.0 and Functional System score (FSS) 5, under topirmate 50 mg p.os q.d., bromazepam 3mg p.os. q.h.s. and natalizumab 300 mg i.v. q 28d for the last 4years. A recent (4 months before) Magnetic Resonance Brain Imaging was also available. The last therapy with natalizumab was delivered 4 hours before the beginning of the seizures. Before infusion, the patient was examined for signs of infections or progressive multifocal leukoencephalopathy.

Initial treatment included diazepam 10 mg i.v. at home; yet due to continuous generalised tonic-clonic seizures, the patient received also levetiracetam 1000mg iv bolus and another 1000mg as c.i.v. infusion till arrival to the hospital. Upon arrival at hospital, seizures were controlled. Total duration of seizures was 35 min and recorded STESS (Status Epilepticus Severity) score:2.

Clinical examination at Emergency Department revealed hypotension (Blood Pressure - 140/85 mmHg), tachycardia (Heart Rate – 140 bpm), relative bradypnea (Respiratory rate of 9 bpm) with measured SpO_2 in air of 85% and body temperature of 38.9^o C. Neurological examination records consist of a Glasgow Coma Scale (GCS) of E1/V1/M4, normal pupils' size and reaction, yet with left upwards gaze and positive Babinski sign in both legs. Initial arterial blood gases (ABG) analysis revealed acidosis with pH: 7.23, $PaCO_2$:72.8 mmHg, PaO_2 :50.9 mmHg (at FiO_2:30%), Glu: 174 mg/dl, Lac: 1.3 mmol/l. Hb:11.5 gr/dl. Rapid Sequence Intubation (RSI) where performed, the patient was transported to computer scan (CT) imaging of chest and brain, where no serious abnormalities were noted; and then admitted at Intensive Care Unit. Calculated initial severity scores were: APACHE (Acute Physiology and Chronic Health Evaluation) II 21, SAPS II (Simplified Acute Physiology Score) 35 and SOFA (Sequential Organ Failure Assessment) score 5. Upon admission, Cerebral Spine Fluid (CSF)

was also performed with normal biochemical results, and negative microbiological panel (Table 1). Diagnostic test for SARS-Cov2 (bronchoalveolar lavage-BAL) was also negative. Microbiological cultures from blood, BAL and urine were also negative.

Table 1. Microbiological panel tested.

Esherichia coli	Herpes simplex virus – 1 (HSV-1)	Chlamydia pneumonia	Streptococcus pneumoniae
Haemophilus influenzae	Herpes simplex virus – 2 (HSV-2)	Chlamydia psitaci	Neisseria meningitidis
Listeria monocytogenes	Human herpesvirus 6 (HHV-6)	Legionella spp.	Streptococcus spp.
Neisseria meningitidis	Human herpesvirus 7 (HHV-7)	Mycobacterium tuberculosis	Staphylococcus aureus
Streptococcus agalactiae	Varicella zoster virus (VZV)	Parvovirus B19	Pseudomonas aeruginosa
Streptococcus pneumoniae	Cryptococcus neoformans gattii	Κυτταρολογικός έλεγχος	Haemophilus influenzae
Cytomegalovirus (CMV)	Adenovirus	Haemophilus influenza	Listeria monocytogenes
Enterovirus	Human polyomavirus 2 (JCV)		

Initially ICU therapy included sedation and analgesia with midazolam, fentanyl infusion, with early (2nd day) change to propofol and remifentanil continuous venous infusion targeting a Richmond Agitation Sedation score (RASS) around 0 and Critical Care Pain Observation Tool (CPOT) tool of 0-1. Antiepileptic regiment included levetiracetam 1gr q 12h i.v. and topiramate 100 mg p.os q.d. Yet, during the first 8 days, right arm tremor was periodically spotted. The latter was initially treated with propofol boluses, yet it significantly reduced with increased levetiracetam dosing (1.5gr q12h). The rest of her drug regiment included empiric antibiotics treatment (clindamycin 600mg/8h iv, ampicillin/sulbactam 3gr/6h iv), gastric ulcer antithrombotic prophylaxis.

Daily temperature rises up to 38.4ºC with concominant tachycardia (treated with metoprolol 50mg t.i.d. p.os) despite negative repeated microbiological samples, no infection related laboratory results and addition of amikacn 10 mg/kg iv qd after the 4th day; along with a refractory covert metabolic acidosis despite mechanical ventilation raised the suspicion of a toxic effect (Table 2, Table 3).

Topiramate administration was stopped at the 8th day of her hospitalization and 2 days later both fever and metabolic acidosis reversed. At the morning of the 12th day, left arm tremor also seized.

A day later she was discharged from ICU without any sequels. neurological evaluation revealed impaired cognitive functions and memory and instability. Motor function gradually returned to baseline. A subsequent MRI of the brain did not reveal any new changes, comparing to the one before the incident (Supplemental file).

Table 2. Selected Laboratory exams during ICU hospitalization.

Day	Hct	Hb	PLT	WBC	CRP	PCT	Glu	Cr	Ur
1st	34.8	11.3	236	15.03	0.1	0.32	124	0.7	20
2nd	31	10.1	179	17.19			93	0.64	13
3rd	33.6	10.8	233	18.24	0.38	12.2	96	0.64	10
6th	30.3	9.8	254	7.16	0.15	4.3	158	0.61	16
7th	29.4	9.6	255	7.3	0.12	3.3	145	0.62	18
10th	29.5	10	359	14.4	0.11	3.5	74	0.58	22
11th	29.3	9	252	13.91	0.007	1.3	115	0.58	34

Day	Na^+	K^+	Ca^{+2}	Phos	Pr_{tot}	Alb	CPK
1st	137	4.3	7.3	2.7	5.8	3.7	138
2nd	139	4.2	6.8	1.9	4.7	3	258
3rd	137	3.9	6.9	2.7	4.9	3	494
6th	135	4.4	7.5	5.6	4.9	2.7	82
7th	138	4.3	7.3	4.5	5.4	3.2	100
10th	136	4.4	7.5	3.5	5.1	2.9	61
11th	137	4.5	8	3.6	5.9	3.1	34

Hct- haematocrit (%)
Hb- haemoglobin (g/dl)
PLT-platelets (k/μl)
WBC- white cells (k/μl)
CRP- c reactive protein (mg/dl)
PCT-procalcitonin (ng/ml)
Glu- glucose (mg/dl)
Cr – creatinine (mg/dl)
Ur -urea (mg/dl)
BUN- blood urea nitrogen (mg/dl)
Prtot- Protein total (g/dl)
Alb-albumin (g/dl)
CPK- creatine phosphatase (mg/dl)

Table 3. Time course of Arterial Blood Gases exams during ICU hospitalization.

Day	pH	PaO_2	FiO_2	$PaCO_2$	HCO_3^-	Lac	BE	AG
1st	7.31	93.8	50	35.4	17.1	0.8	-7.4	6
2nd	7.44	124	35	27.4	18.4	1	-5.0	6
3rd	7.38	138	35	33.9	19.7	0.7	-4.5	6.5
4th	7.42	157	40	33.2	21.8	0.4	-2.5	4.9
5th	7.4	149	35	32.7	20.1	0.4	-3.8	5.9
6th	7.39	122	35	34.5	20.7	0.7	-3.3	4.4
7th	7.4	141	40	28	17.1	0.5	-6.7	5.9
8th	7.41	121	35	28.9	18.3	0.7	-5.4	5
9th	7.42	155	35	29.7	19.3	0.6	-3.8	5.6
10th	7.35	131	35	33.2	17.7	0.4	-6.8	4.5
11th	7.43	81	35	32	20.6	1.1	-2.4	6

PaO_2 - arterial partial oxygen pressure (mmHg)
$PaCO_2$ - arterial partial carbon dioxide pressure (mmHg)
FiO_2 -fraction of inspired oxygen (%)
HCO_3 - bicarbonates (mEq/l), Lac - Lactate (mmol/l),
BE - base excess,
AGc - anion gap corrected.

DISCUSSION

Natalizumab is a humanized antibody that acts mainly towards $\alpha_4\beta_1$ integrin (also known as very late antigen, VLA-4) a molecule that mediates migration of immune cells to the inflamed brain. Dosing includes 300mg infusion every 4 weeks achieving a mean plasma concentration of 110 ± 52 μg/m, while its half-life is 11 ± 4 days[3-4]. Several studies have proven its utility in MS, as it reduces disease activity and progression; and it has positive effects on cognition, depression, fatigue, and quality of life[4]. Today it is used mainly in relapsing-remitting MS (RRMS)[4-5].

Natalizumab side effects vary from allergic reactions, pharyngitis, urinary tract infections, utricaria, arthralgia, fever to more serious drug induced liver injury (DILI), drug-induced immune thrombocytopenia, erythroblasts abnormalities, recurrent vaginitis, HSV infections, primary central nervous system lymphoma[3-6]. Serious problem is also emergence of a potentially fatal progressive multifocal leukoencephalopathy (PML), an opportunistic infection by JCV with reported incidence of 3.4/1000 (95% CI 3.08–3.74) in Natalizumab treated MS patients, with higher risk in those with history of therapy duration over 2 years.[3-5]. In big series, up to 9% of patients reported unexpected side effect (in 62.5% of which severe) such as tachycardia, blurred vision with anxiety crisis, pneumonia, and increased γ-glutaryl transferase; while other reports mention cyclical suicidal ideation, myocardial infarction, retinal necrosis and cutaneous sarcoidosis-like reactions [7-9].

Topiramate is a sulphamate anticonvulsant used apart from treatment of epilepsy, for a numerous other conditions, such as migraine, bipolar disorder, post-traumatic stress disorder, alchohol dependence, bulimic nervosa, tobacco dependence, obsessive –compulsive spasm, idiopathic intracranial hypertension, infantile spasms and neuropathic pain[10]. Due to a molecular structure like acetazolamide and to inhibiting carbonic anhydrase enzyme activity, it can lead to renal tubular acidosis (type 3), as result of ultrafiltration and reabsorption of bicarbonate in both proximal and distal tubules. Clinical presentation varies from mild to severe, often accompanied with nephrolithiasis, hyperventilation, and osteopenia. Other acidosis producing diseases such as chronic renal failure or infection may aggravate patient's condition, though genetic polymorphism of carbonic anhydrase isoenzymes may also play a role[10-11]. Hiperidrosis and hyperthermia (to the point of heatstroke with maximum temperature of 41.1^{o}C) have also been reported both in children and in adults[12]. Suspension of drug use is the only reported efficient strategy to reverse the above conditions.

In our case, we believe that metabolic acidosis and daily temperature rise is caused by topiramate administration. Increased dosing regiment (compared to patient's baseline) may contribute to aggravation of the condition, as we cannot exclude the absence of mild symptomatology before hospital admission (while on lower daily regiment). Discontinuation of topiramate reversed both conditions. Another interesting fact is time connection with natalizumab administration and onset of status epilepticus. Microbiological and imaging evaluation for PML was negative. Though there is scarce data (one report) that natlizumab therapy may reduce seizure activity in MS[14], we cannot exclude drug-triggered epilepsy. Right arm tremor, which initially treated as inadequate sedation, reduced with increased anticonvulsant therapy, and eventually ceased at a timetable in accordance with natalizumab's half-time; reinforces our hypothesis. Other hypotheses could for emergence of epilepsy could be a new small cortical or juxtacortical MS lesion or an immune reconstitution inflammatory response syndrome; yet these are more distant probabilities[15]. Available data from long term use of natalizumab do not report any drug - induced seizures[16], yet the overall relative literature is limited.

CONCLUSION

The above patient seems to have suffered from unexpected complications of 2 drugs arisen at the same time. Though clinicians are always in alert for therapy side effects; situations where side effects are emerging simultaneously from two (or more) drugs can be extremely challenging to handle; especially when clinical manifestation is out of the expected range. Thorough daily analysis of the available data and testing unconventional hypotheses may be helpful in this condition.

Addittional materials:

Supplement File 1.

Acknowledgements

Not applicable.

Authors' contributions

Conceptualisation: T.A.; Case Management: E.S, T.A, F.D; Literature Review: T.A, K.M. Draft preparation: T.A., K.M.

Funding

Not applicable.

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

No IRB approval required.

Acknowledgements:

The authors would like to thank Dr. Ourania Agalliadou-Dioritou, head of the Intensive Care Unit for her support to the management of the case

Consent for publication

Patient consent obtained

Competing interests

The authors declare that they have no competing interests.

Received: December 2020, Accepted: December 2021 Published: March 2021.

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Citation: Aslanidis Th, Drampa F, Mytkani K, Syrmou E. Status epilepticus and topiramate induced metabolic acidosis in a patient with multiple sclerosis under natalizumab therapy. Greek e j Perioper Med. 2021;20(b):42-49.