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Single low dose baclofen induced encephalopathy in patient with renal failure: Case report with literature review

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Abstract
Baclofen is a muscle relaxant widely administered, often used as a treatment for certain forms of spasticity and other diseases. It is excreted mainly through the kidneys; toxicity is a potentially serious adverse effect in patients with impaired kidney function. Here we report a case of 80-year-old female patient with renal failure presented with acute confusion within 24 hours of receiving one single low dose of baclofen. After negating all the causes of her current presentation, a diagnosis of baclofen toxicity was made and subsequently hemodialysis was done with improvement in her conscious level. We aim to highlight the potential risk of baclofen toxicity in patients with kidney impairment even with a low dose and recommend avoiding prescribing baclofen for such patients.

Keywords: baclofen, encephalopathy, renal failure, neurotoxicity

Introduction

Baclofen is a central agonist of GABA receptors, commonly used as a treatment of spasticity mostly associated with spinal cord injuries and multiple sclerosis [1]. Rarely, it might be used for managing other conditions such as trigeminal neuralgia, alcoholic liver disease, alcohol-related anxiety, gastroesophageal reflux disease and hiccups [2]. Baclofen has a bioavailability of 70% to 85% and is therefore rapidly absorbed through the gastrointestinal tract following oral administration. Peak plasma concentrations are generally observed 2 to 3 hours after ingestion. 69-85% of ingested baclofen is eliminated unchanged by the kidneys in patients with normal renal function, while only 15% is metabolized by the liver. While the half-life elimination of baclofen in healthy subjects is 2 to 6 hours [3]. This half-life increases in patients with renal insufficiency [4, 5], even at a lower dose of the drug. In addition, the drug is moderately lipophilic, approximately 30% of baclofen bound to protein and it can cross the blood-brain barrier [6, 7]. Accumulation of the drug in patients with renal insufficiency may cause neurological toxicity, resulting in acute changes in the mental state [8], including confusion affecting 1 to 11% of patients taking this drug [9]. Cases of baclofen-associated encephalopathy have been also reported in patients with renal failure or severely impaired renal function [10]. Baclofen clearance may be significantly enhanced by hemodialysis [HD] owing to its low volume of distribution and low protein binding. HD appeared to shorten the duration of toxic effects of baclofen in several patients with severely impaired renal function [9, 11]; however, consciousness usually improves only after a delay of several hours after the end of HD. While baclofen elimination mechanism during haemodialysis is not well understood, it removes up to 79% of serum baclofen in one hemodialysis session [12], therefore, it appears to be a suitable and effective treatment option according to its outcomes. In this case, we are reporting a patient with renal failure who developed encephalopathy from a single low dose of baclofen.

Case description

An 80-year-old female patient, known case of diabetes mellitus, hypertension, and chronic renal failure with baseline creatinine from 3 to 4mg/dl, on regular hemodialysis twice per week for the last 5 years. She has been suffering from progressive generalized rigidity of all 4 limbs affecting her ambulation and had become bed ridden for the last 6 months. For the above complaint she was prescribed baclofen 10 mg twice daily. Upon taking the first dose of baclofen 10 mg that night, next morning the patient was found drowsy upon awakening, and progressively deteriorated over the day to becoming deeply comatose by the evening with a few jerky movements in all 4 limbs. There were no other neurological symptoms nor fever. Her last session on hemodialysis was a day before. As such, she was brought to our emergency in a state of coma of 10 hours duration.

On examination, she was deeply comatose, only opening her eyes on deep pain, with a GCS of 7/15. There was no gaze preference and pupils were bilaterally equal reactive to light and of normal size. The fundus examination was normal. There were no lateralizing signs however there was generalized cogwheel rigidity in all 4 limbs, depressed deep tendon reflexes and flexor plantar responses. Frequent and florid myoclonic jerks and flapping tremors of the hands were seen in both upper limbs. Neck was supple with no signs of meningeal irritation. The systemic examination of cardiovascular, respiratory and gastrointestinal was all unremarkable. The above findings were suggestive of metabolic etiology. Vitals signs showed high blood pressure

of 160/90mm of Hg.

The laboratory work-up of the patient showed creatinine on arrival was 5.2 mg/dl. However, her complete blood count, electrolytes, liver function test, inflammatory markers, thyroid profile, ammonia level and urine analysis were all normal. Hepatitis B, C and HIV were all negative. Computerized Tomography [CT] scan of the brain was performed on the day of admission; it revealed bilateral fronto-parietal periventricular hypo densities, denoting chronic white matter ischemia [Figure 1]. Additionally, bilateral basal ganglia and right pontine small hypo dense areas were seen [Figure 2]. Magnetic Resonance Imaging [MRI] of the brain was conducted on the second day of admission which confirmed the CT scan findings with no additional significant pathology [Figure 3 and Figure 4]. However, EEG upon admission showed diffuse slow waves theta and delta activity along with triphasic waves more prominent over the bi-frontal area denoting a metabolic encephalopathy [Figure 5].

Patient was diagnosed with baclofen induced encephalopathy and therefore received 6 sessions of daily hemodialysis.

Her level of consciousness improved dramatically after the first hemodialysis session and she was able to communicate. Within 2-3 days she became fully conscious, flapping tremors and myoclonic jerks disappeared. A repeated EEG was performed on the third day of admission which showed normal alpha background activity at 8 to 10 Htz [Figure 6]. On the seventh day, she was fully conscious and oriented and was discharged home.

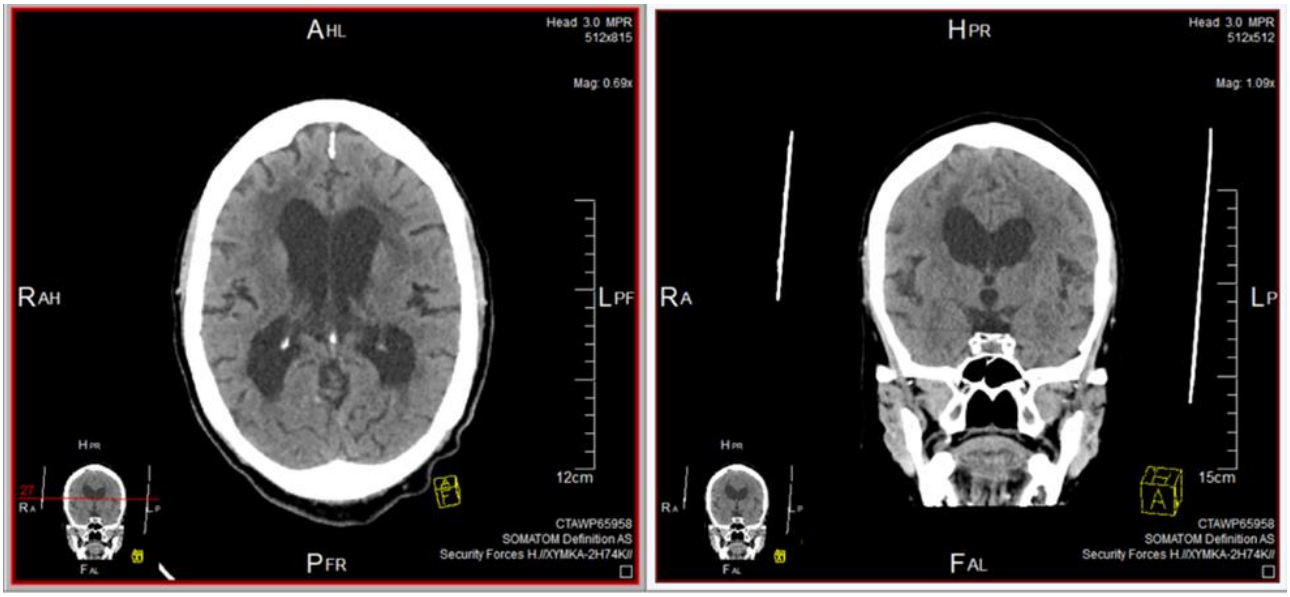

Fig 1: Non-contrast CT scan of the brain revealed bilateral fronto-parietal periventricular hypo densities, denoting chronic white matter ischemia.

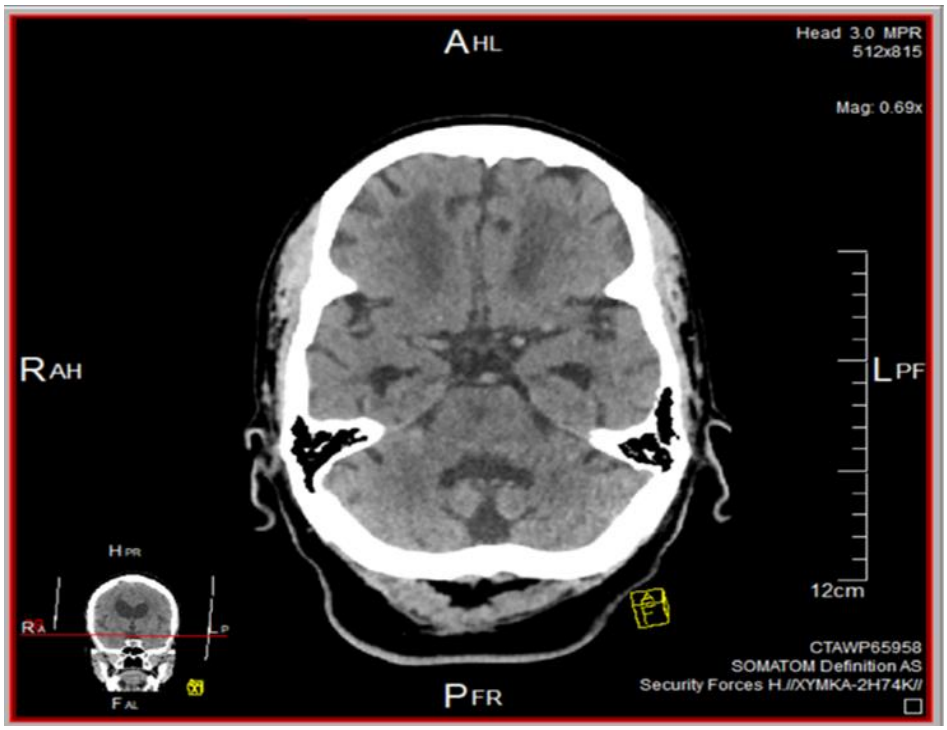

Fig 2: Non-contrast CT scan of the brain shows right pontine small hypodense area with no surrounding mass effect.

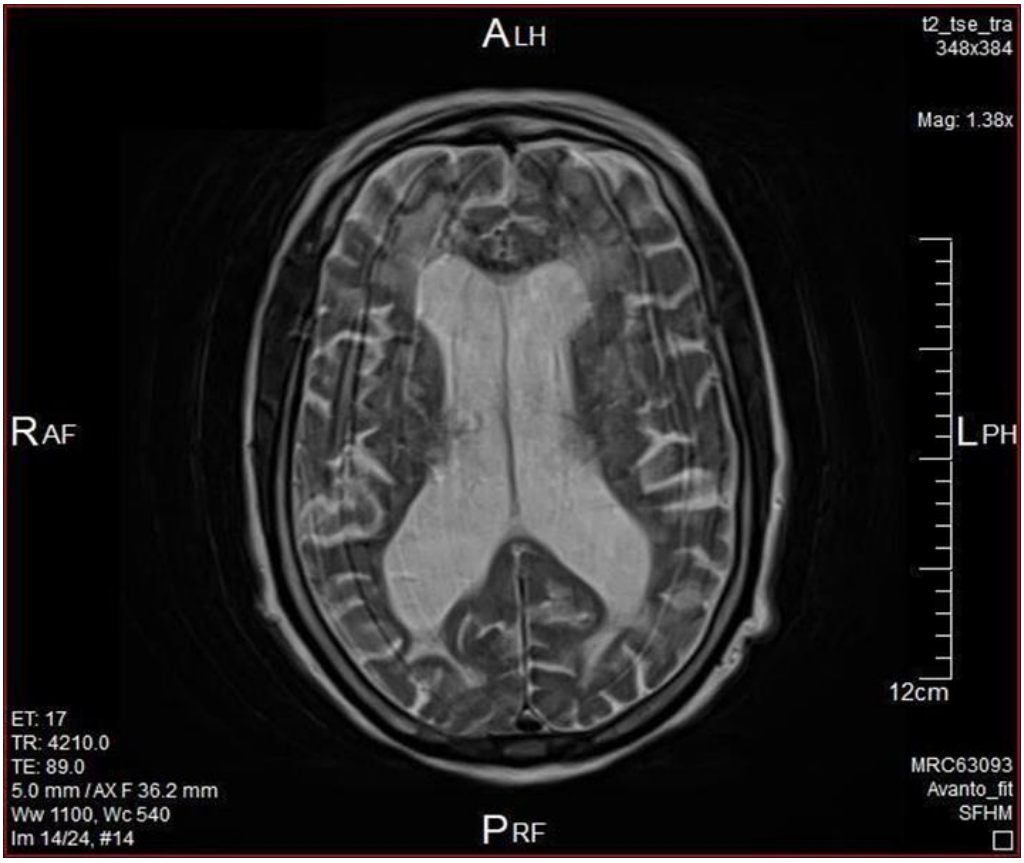

Fig 3: MRI image shows brain involutional changes with pri-ventricular sheets of abnormal T2 bright signal.

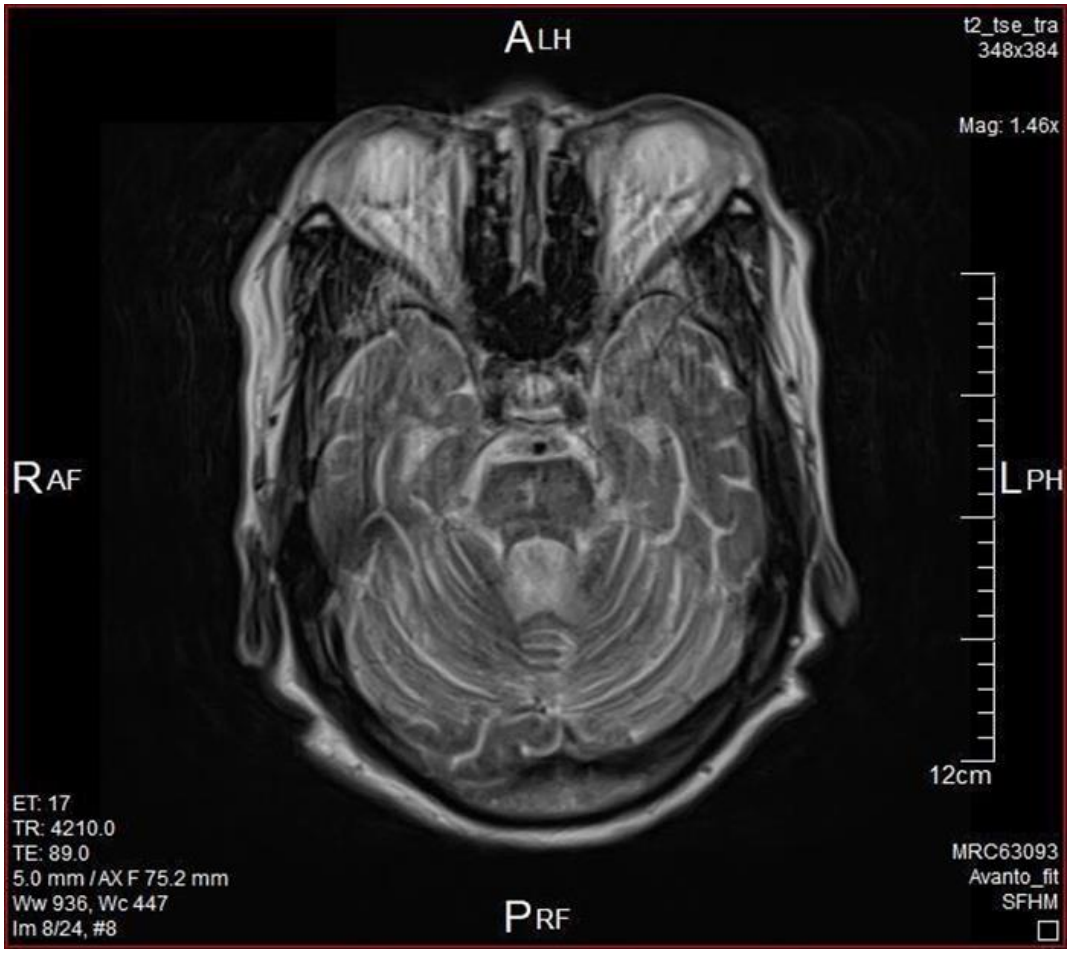

Fig 4: MRI image of the brain shows small old right Paramedian pontine infarction.

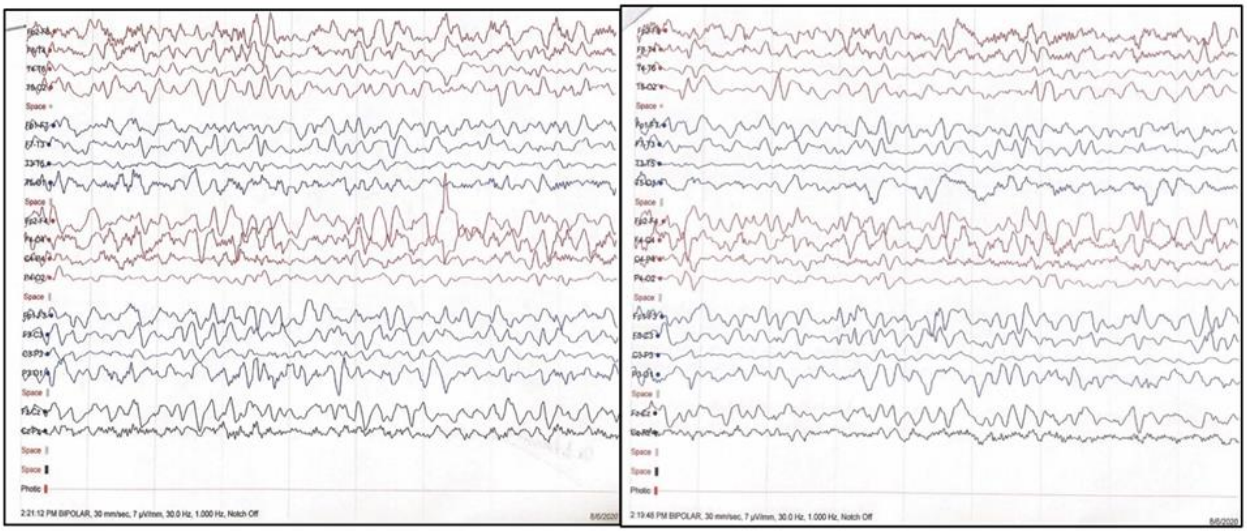

Fig 5: EEG result showed diffuse slow waves theta and delta activity along with triphasic waves more prominent over the bi-frontal area.

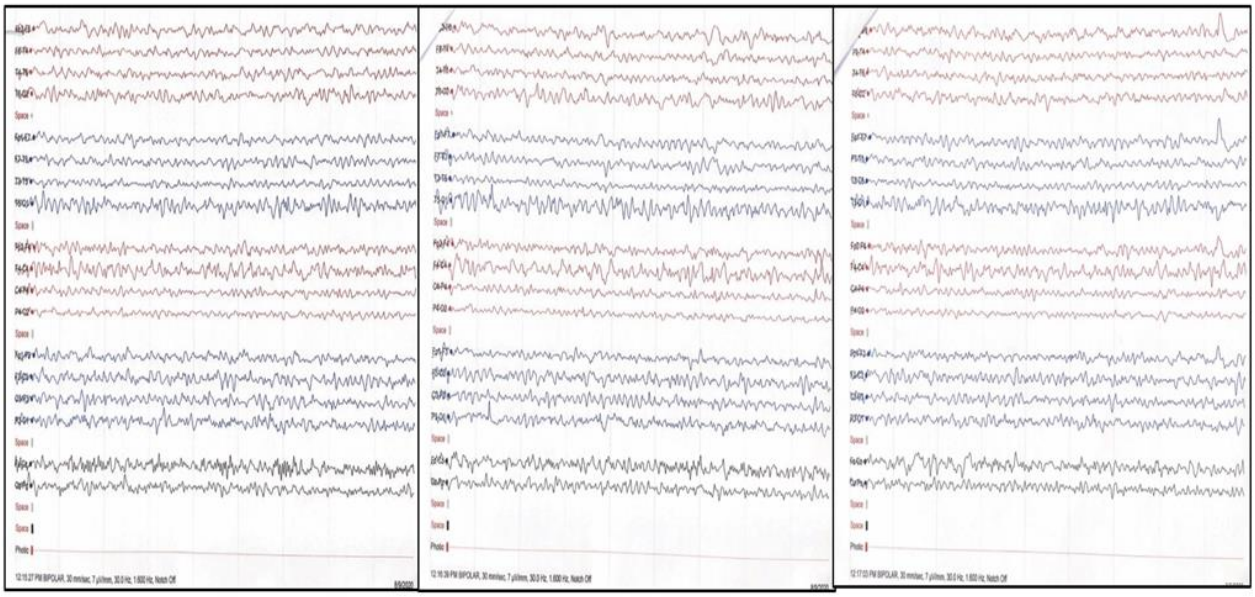

Fig 6: EEG result showed normal alpha background activity at 8 to 10 Htz.

Discussion

Baclofen is one of the widely used drugs in neurological disorders. The standard baclofen dose in neurological disorders is ranging between 5 to 60 mg/daily [13, 14] and doses higher than this can be associated with adverse neurological events, even with normal renal function for instance; muscle weakness, dizziness, confusion, lightheadedness and impaired consciousness [15]. The neurological toxicity of baclofen is dose related, as drug in its therapeutic dose acts on spinal GABA receptors but in higher doses this differentiation is lost, and GABA receptors of brain are stimulated resulting in sedation and coma. However, baclofen toxicity becomes more serious and complicated among patients with impaired kidney function as approximately 85-90% of the drug is excreted via the kidneys [16]. So, in patients with impaired renal function and on baclofen who developed abnormal mental state, a strong suspicion of baclofen-induced encephalopathy should be considered. Indeed, testing of creatinine and urea should be done for any patients intended to receive baclofen.

Table 1 represents our literature review of 33 cases with impaired renal function who developed baclofen toxicity, in which the majority of cases were prescribed 15 mg/day to 30 mg/day of baclofen [1, 5, 19, 28, 8, 10, 12, 14, 16, 18], only 4 cases were prescribed 5 mg/day [4, 13, 29, 30], while 3 cases were prescribed 10 mg/day [16, 31, 32].

In regard to the onset of symptoms, as shown in Table 1, most of the cases have developed neurological symptoms after 2 to 3 days with maximum presentation within 7 days of receiving the drug [4, 8, 23, 25, 27, 29, 32, 9, 10, 12, 13, 16, 18, 20] while only 6 cases developed symptoms in the first 24 hours [1, 14, 16, 17, 21, 26] and only 1 case presented with neurological symptoms within 12 hours with a dose of 15 mg [28]. The reported clinical manifestations mostly include disorientation and decreased consciousness. Only 2 cases presented with rhythmic movements suspicious of a myoclonus [8, 16].

EEG was only performed in 10 of these 33 cases [4, 8, 10, 18, 20, 22, 31], out of which 3 cases had normal EEG [18, 22] and 7 cases showed triphasic waves representing metabolic encephalopathy [4, 8, 10, 20, 21, 31]. CT brain in majority of cases was normal [1, 5, 23, 24, 27, 8, 10, 14, 16, 18, 21, 22], and only one case had non-specific changes [20].

In our case, as compared to the above case published by Su

W, *et al*. [28], the presentation was more acute at 10 hours, and the starting dose of baclofen was even lower (10 mg). The main neurological symptoms in our case was coma with frequent and florid myoclonic jerks along with flapping tremors of the hands which dominated the clinical picture, a recognized feature of metabolic encephalopathy.

EEG of our patient has confirmed the features of metaoblic encephalopathy including triphasic waves which improved to normal alpha background activity within 48 hours following HD. All other workup of metaoblic encephalopathy was normal in particular ammonia levels.

The presence of generalized rigidity before starting baclofen and its dramatic improvement following dialysis needs further explanation. Uremic encephlaopathy per se can also contribute to rigidity as evidenced by improvement in rigidity following hemodialysis for baclofen toxicity.

Table 1: Summary of our literature review of 33 cases with impaired kidney function who developed baclofen toxicity

First author/ citation	Age	gender	baclofen dose	Reasons for giving baclofen	onset of symptoms	clinical manifestation	GCS	creatinine	EEG	Brain imaging (CT scan)	outcome
E.Khazneh, et al. (1)	47	Female	25 mg/ day	lower back pain and bilateral knee pain	1 day	Decrease level of consciousness	9	5.5 mg/dL	Not done	Normal	After a total of 5 hemodialysis sessions, she was fully awake
S. S. Beladi Mousavi, et al. (5)	1- 48 2- 79	1- Male 2- Male	1- 20 mg/day 2- 30 mg/day	1- lower back pain 2- lower back pain	NA	confusion	1- 13 2- 11	1- 7.6 mg/dL 2- 6.8 mg/dL	Not done	1- Normal 2- Cortical atrophy	After supportive care including mechanical ventilation and intensive hemodialysis, their neurologic symptoms gradually disappeared
Radhakrishnan H. (17)	58	Male	20 mg/day	NA	1 day	Confusion followed by drowsiness followed by unresponsiveness	8	6.1 mg/dL	Not done	Normal	Altered sensorium improved significantly after two dialysis sessions. He was discharged after five days with normal sensorium
Diana H Dang, et al. (10)	81	Female	30 mg/day	NA	2 days	unsteady gait, confusion, incoherent speech, ataxia and dysarthria	NA	0.73	nonspecific encephalopathy	Normal	The following day after drug discontinuation, a significant improvement was noticed in the patient's status. At discharge, her mental status had returned to baseline.
Amr El-Husseini, et al. (8)	75	Female	30 mg/day	ant. cruciate ligament tears and the meniscus of the right knee	2 days	Lethargic with decrease level of consciousness myoclonus.	NA	4.3	Slowing of EEG suspected metabolic encephalopathy	Normal	Altered Mental status began to resolve after the first hemodialysis session, EEG normalized. Patient discharged without and residual neurological deficits
Mohsin Ijaz, et al. (14)	57	Female	20 mg/day	muscular spasm	1 day	progressive confusion and a generalized decrease in muscular tone	11	9.1	Not done	Normal	After 3 sessions of hemodialysis, a complete return to baseline mental status were seen (GCS 15).
N. Bassilios, et al. (13)	65	Male	5 mg/day	hiccups	4 days	acute confusion and agitation.	NA	510 µmol/l	Not done	old infarcts in caudate nucleus	After the first 4h haemodialysis session, there was a complete recovery of the neurological status
John K. Roberts, et al. (16)	1- 48 2- 72 3- 47 4- 65	1- male 2- female	1- 30 mg/day 2- 15 mg/day	1- NA 2- leg cramp 3-myoclonus 4postoperative	1- NA 2- 2 days 3- 10 days 4- NA	1- decrease level of consciousness followed by unresponsiveness	1- 3 5- 4	NA	Not done	5- Normal	1- Daily hemodialysis was undertaken and mental status

	5- 66	3- female 4- male 5- male	3-15 mg/day 4- 30 mg/day 5- 10 mg/day	neck pain 5- muscle spasm	5- 1 day	2- confusion 3-confusion 4- drowsy 5- less responsive hyperreflixia and flaccid					improved back to baseline. 2- underwent daily hemodialysis and improved after her second session 3- stop baclofen 4- urgent HD 5- urgent hemodialysis ,on consecutive day improved conscious level.
Nader Bassilios, et al. (29)	65	male	5 mg/day	hiccups	4 days	acute confusion and agitation.	NA	510 µmol/l	Not done	Old infarcts in caudate nucleus	After the first 4h hemodialysis session, there was a complete recovery of the neurological status.
Chu-Lin Chou, et al. (30)	68	male	5 mg/day	intractable hiccups.	NA	Altered consciousness, blurred vision and muscle weakness	11	3.4mg/dl	Not done	Not done	NA
Vin-Cent Wu, et al. (12)	70	female	15 mg/day	left leg soreness	3 days	confusion	NA	8.26 mg/dl	Not done	cortical atrophy	There was a complete recovery of consciousness 8 h after hemodialysis. She received another hemodialysis session 30 h after admission. The patient was discharged from the hospital 72 h later in good condition.
Junseop Lee, et al. (18)	1- 71 2- 35	1- male 2- Female	1- 30 mg/day 2- 20 mg/day	1- NA 2- right rib fracture	3 days for both patients	confusion	NA	1- 7.6 mg/dL 2- 13.6 mg/dL	Normal in both patients	Normal in both patients	1- Patient's consciousness returned completely after 2 sessions of hemodialysis was completed. 2- Baclofen was discontinued and 3 session of hemodialysis done. The patient's mentality began to recover during the second hemodialysis session.
Lauren M. Porter, et al. (19)	69	female	20 mg/day then increased to 40 mg/day	back pain	1 week	encephalopathy, ataxia and dystonia	NA	NA	Not done	Not done	Signs and symptoms resolved with hemodialysis.
Joseph T. Hormes, et al. (20)	58	female	30 mg/day	painful flexor spasms.	2 days	Disorientation with agitation	NA	97.2 µ mol/L.	Periodic sharp waves	Nonspecific changes.	baclofen was discontinued, the patient improved in 24 hours, and her mental status returned to baseline.
S. Ovu, et al. (21)	66	female	30 mg/day	acute on chronic neck pain	1 day	acute encephalopathy myoclonic jerk	NA	NA	generalized periodic discharge with triphasic morphology	Normal	received hemodialysis and improved.
Kuo-Su Chen, et al.	1- 72 2- 65	1- female	20 mg/day	1- pain relief 2- low back	1- 2 days 2- NA	1- twitching, upward gaze,	1- 7 2-	1- 3.4 mg/dL	1- Triphasic wave with	Not done	1- HD was performed on the

(9)		2- Male	for both patients	pain		urine incontinence, and disturbance of consciousness 2- disorientation and agitation	11 then 8	2- NA	periodic discharge. 2- Not done		second day following the discontinuation of baclofen. Her level of consciousness slightly improved over the 6-hour period after the first HD treatment, second hemodialysis treatment was undertaken the next night and was fully awake by hospital day 5. A follow-up EEG after the second hemodialysis session revealed elimination of the triphasic wave. 2- HD was undertaken. No improvement in his level of consciousness was observed until 10-12 hours after the end of hemodialysis. He became progressively more alert, regaining full consciousness
Choi, Moon-Young, et al. (31)	57	NA	10 mg/day	right arm muscle spasm	NA	Confusion with no specific focal neurologic signs	NA	NA	Triphasic wave and frontal lobe syndrome with delta wave	NA	daily hemodialysis for 3 days, there was a complete recovery of an altered mentality. After one month later, the follow-up EEG showed normal finding with the resolution of abnormal waves
Abdul S. Mohammed, et al. (22)	73	female	20mg/day	low back pain	NA	speaking incoherently, confusion and unable to concentrate.	NA	4.9 mg/dL	Normal	Normal	received hemodialysis for two sessions with significant improvement in mental status without any residual symptoms.
Haque, W, et al. (23)	40	female	20mg/day	low back pain	4 days	Decrease level of consciousness	NA	5mg/dl	Not done	Normal	Patient refused HD. Her consciousness level gradually improved on conservative management. She was discharged with full consciousness on day 5.
Mahalingam N and Cader R (24)	51	Male	30mg/day	clonus of his left lower limb	2 days	delirious, drowsy and restless	11	1035 umol/L	Not done	Normal	improved gradually and after 3 consecutive sessions of hemodialysis
Meillier A,	54	Male	10	paraspinal	3 days	confusion	NA	10.98	Not done	NA	significant

et al. (32)			mg/day	muscle spasm				mg/dL			improvement in mental status without any residual symptoms
Kroczak M and Rakus A (25)	29	Female	20mg/day	/	2 days	weakness, nausea, vomiting and fears	/	/	Not done	/	patient's state of health improved after approximately two hours since the hemodialysis had been performed
Anwar Alam, et al. (26)	70	Male	30mg/day	recurrent hiccups	1 day	restlessness.	NA	2.31 mg/dl	Not done	diffuse cerebral atrophy along with periventricular ischemic changes	NA
Abdi M and KaramiZadeh K (27)	67	Female	50mg/day	spasm of the neck and shoulder muscles	36 hours	sudden decrease in the level of consciousness and confusion	8	2/5mg/dl	Not done	Normal	GCS change to 14, and the patient's recovery condition was stabilized.
W Su, et al. (28)	61	Female	15 mg/day	back pain and muscle spasms	12 hours	disorientation	8	NA	Not done	NA	Mental status improved, and after a second four-hour treatment on the next day, she was her usual self.
Fernande Lois, et al. (4)	79	Male	5 mg/day.	ingested the medication by mistake.	1 week	altered consciousness.	9	11.5 mg/dl	Tiphasic waves	cortical atrophy was shown	On day 5, a complete awakening was noted with a complete neurological recovery on the following day.
Our case	80	Female	10 mg/day	Generalized rigidity	10 hours	Decreased level of consciousness followed by coma. Myoclonic jerks and flapping tremors in both upper limbs	7	5.2 mg/dl	Diffuse slow wave theta and delta activity along with Triphasic waves	Chronic white matter ischemia	She was on 7 days of continues HD session. On the first day she was able to communicate. After 3 days she became fully consciousness and her jerky movement disappears. On 7th day she discharged home.

Conclusion

Baclofen toxicity is well recognized at higher and cumulative doses in patients with normal renal function. However, low dose baclofen toxicity with serious neurological events can readily occur in impaired renal function. Its features are consisting with a metabolic encephalopathy including flapping tremors, myoclonic jerks and triphasic waves in EEG in comatose paitents. As such, this clinical picture is easily overlooked as commonest cause of hepatic metaoblic encephalopathy and others..

We recommend checking renal function before starting even a low dose of baclofen and to keep a close follow up of patients for development of toxicity. Baclofen should not be considered for treatment if an eGFR is less than 30ml/min and even to use with caution in an eGFR 0f 30ml/min to 60ml/min especially if the patient is elderly,history of seizure,use of other CNS depressing drugs or alcohol use. HD should always be instituted urgently for treatment of baclofen toxicity and its neurological complications.

Statements

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Author Contributions

Rabia Muddassir: Study design, Manuscript writing, literature review, editing

Abdelrahman Idris: Manuscript reviewing and editing

Bashaer Alharbi: Literature review, Manuscript writing

Murouj Almaghrabi: Literature review, Manuscript writing

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