Author’s response to reviews

Title: Tacrolimus-induced Parkinsonism in a patient after liver transplantation-case report

Authors:

Karin Gmitterova (gmitterova.karin@gmail.com)
Michal Minar (mmminar@gmail.com)
Miroslav Zigrai (m.zigrai@gmail.com)
Zuzana Kosutzka (zuzanakosutzka@gmail.com)
Alice Kusnirova (kusnirova.alice@gmail.com)
Peter Valkovic (peter.valkovic@gmail.com)

Version: 1 Date: 05 Apr 2018

Author’s response to reviews:

Comments to Reviewer 1:

We thank the reviewer for the helpful comments and constructive criticism.

Ad 1: The authors could comment on whether they feel that tacrolimus should be used first line, given issues around toxicity and if sirolimus should be used instead as first line treatment. What would be the pros and cons of doing this?

However, the immunosuppressant regimens vary between individual centres and new agents with promising results are enteric clinical practice, while the use of calcineurin inhibitors (CNIs) represents the first-line treatment option after liver transplantation (LT). CNIs are the principal choice for immunosuppression after LT and almost 97% of transplanted patients are discharged from the hospital on this treatment (PMID:21850697). Among CNIs, tacrolimus (Tac) is the drug of choice in the majority of patients. Results from a meta-analysis have confirmed that Tac treatment reduces post-transplant mortality, graft loss and reduced rejection (PMID:28362060, PMID:16827858). A newly developed once-daily dosage formulation of tacrolimus has also achieved a positive impact on adherence to immunosuppressive therapy (PMID: 26264233).

Sirolimus as the inhibitor of the mammalian target of rapamycin (mTOR) was first approved for renal transplantation and recently also in liver recipients with renal dysfunction and, in order to reduce or stop CNIs use in the event of adverse effects (e.g. renal impairment or neurotoxicity) (PMID: 26636736, PMID:24405697, PMID:15919502). Interestingly, sirolimus possesses an anticancer potential what favours the mTOR inhibitors as the treatment of choice in patients transplanted for hepatocellular carcinoma (PMID:23278125, PMID:12042641). Nevertheless,
sirolimus treatment was also associated with a range of adverse events leading to increase incidence of graft rejection and discontinuation of therapy (PMID:20815021, PMID:26597456, PMID:26636736, PMID:25088685). The known adverse effects of sirolimus include dose-dependent hyperlipidaemia, thrombocytopenia, anaemia, leukopenia and prolonged wound healing, but with the absence of neurotoxicity, nephrotoxicity and diabetogenesis (PMID:9808489, PMID:28182044, PMID:15919502). A multicenter study reported that the early use of sirolimus in de novo liver transplant recipients is associated with higher rates of sepsis compared to the use of conventional-dose tacrolimus alone (PMID:20815021).

In summary, despite a wide range of adverse events, CNIs-based immunosuppression is still the cornerstone of immunosuppressive regimens and Tac represents the first-line treatment option (Grade I levels of evidence) in patients after LT, resulting in better long-term graft and patient survival (revised in PMID:26597456). Hence, sirolimus represents an effective (but also more expensive) substitute for CNI-induced adverse side effects or to avoid further CNI nephrotoxicity (PMID:24935293, PMID:19765436, PMID:26608590). Moreover, it is an alternative option to CNIs therapy in preventing graft rejection in the case of adverse events and is of special interest for use in hepatic malignancies (PMID:23278125). Conversion to sirolimus can be done safely and provide adequate immunosuppression without increased incidence of infection in liver transplant recipients (Gr. I level of evidence) (PMID:26597456). However, some data point to a higher risk of graft rejection in sirolimus treated patients (PMID:26597456, PMID:26636736, PMID: 25088685). Further studies are needed to assess the value of sirolimus as the primary immunosuppressor after LT.

We thank the reviewer for this suggestion. We implemented this by inserting short comments in the section Discussion.

Section: Discussion, page 6; line (s) 31-34 new version: p. 15; line(s) 56-58, p.14; line (s) 1-3

The sentence: “….solid organ transplantation, but approximately 30% of patients experience some form of adverse neurological events [3]”

was modified to “...solid organ transplantation and despite a wide range of adverse effects tacrolimus still represents the cornerstone of immunosuppressive regimens and the first-line treatment option after liver transplantation [5]. However, approximately 30% of patients experience some form of adverse neurological event [6].

Section: Discussion, page 7; line (s) 27-28 new version: p. 15; line(s) 5-7

We inserted the following statement: Hence, sirolimus represents an alternative in the occurrence of tacrolimus-induced adverse events and is of special interest for use in hepatic malignancies [5].

Ad 2: It should be "biopsy proven" not "bioptically proven".

We apologize for the mistake.
The sentence: “…51-year old woman with bioptically verified primary biliary cirrhosis…” was changed to: “…51-year old woman with biopsy proven primary biliary cirrhosis…”

Comments to Reviewer 2:

We greatly appreciate the constructive comments of the reviewer. Our answers are given below:

Ad 1: a) One differential diagnosis that needs to be considered in this case will be osmotic demyelination syndrome (ODS).... Can the authors provide the range of serum sodium (lowest v.s highest recorded level) during the pre-operative and immediate post-operative period?

We thank the reviewer for raising this question. Central pontine myelinolysis is a rare and severe complication and also a devastating cause of morbidity and mortality after liver transplant (LT). It is defined as non-inflammatory, frequently symmetrical and predominantly central pontine demyelination. The demyelination also affects extra-pontine areas such as the basal ganglia, thalamus and lateral geniculate body hence the term osmotic demyelination syndrome (ODS) was proposed for this entity. The incidence of ODS after LT ranges from 1 to 10% in clinical studies (PMID:25427166, PMID:24233816, PMID:19797900). Nevertheless, the isolated affection of extrapontine structures without the involvement of pontine regions represents less than 10% of all ODS cases after LT (PMID:25427166). Although the exact cause of ODS is probably multifactorial, rapid correction of hyponatremia has been described as a major risk factor (PMID:28422408, PMID:24233816, PMID:15316041, PMID:19797900). However, ODS in the absence of hyponatremia or in hypernatremic state was also reported (PMID:21143100, PMID:7729094, PMID:19488548).

Of note, liver transplantation is a strong independent risk factor for ODS (PMID:11430268). A marked variation of perioperative serum Na+ remains the main risk factor even in patients without preexisting hyponatremia (PMID:25427166, PMID:28422408). To avoid the fluctuation of electrolytes during the LT care is crucial for the prevention of ODS. Other risk factors for developing ODS related to liver transplant aspects such as the duration of LT, massive intraoperative bleeding and/or high cyclosporine levels have been identified (PMID:27358774, PMID:8610399, PMID:28422408, PMID:19797900). The majority of cases (90%) occurs within the first week after LT but the clinical presentation of ODS can be delayed to 14 days post osmotic shift (PMID:10918744, PMID:19797900).

Clinical manifestation is also highly variable reflecting the location of the lesion. Typically, 2 to 7 days after treatment of the underlying disease or correction of osmotic imbalance, the following symptoms develop: lethargy, dysarthria, ophthalmoplegia, quadriplegia often with positive Babinski sign, ataxia, and changes in reflexes. When patients survive, most of them have significant neurologic deficits (PMID:16410743, PMID:25810613).

Based on this, ODS was considered as the main differential diagnosis in this case. Although the onset of the first clinical signs related to the LT procedure was delayed as in the majority of
reported movement disorders cases (2-7 days); this does not reliably exclude the diagnosis (PMID: 23660544). However, the clinical manifestation of ODS is commonly more complex and impairment of other neural pathways is frequently present (e.g. pyramidal, oculomotoric, speech problems). Mutism, parkinsonism, dystonia, and catatonia have all been described (PMID:15316041, PMID:23660544). Worth noting is that the majority of published cases of ODS manifested by parkinsonism was related to inappropriate correction of electrolyte disbalance or serum osmolality fluctuation (PMID: 19444382, PMID:10833626, PMID:21353739).

Of note is that our patient has no evidence of chronic hyponatremia. One month before LT – Na serum level was 137.9 mmol/L (reference range 135-146 mmol/L); K serum level was 4.77 mmol/L (range 3.5-5.1 mmol/L), Ca 2.25 mmol/L (reference range 2.2-2.65 mmol/L), and serum osmolality 279 mmol/kg (range 275-295 mmol/kg).

Before the LT (26.1.2016), the serum sodium, potassium and calcium values were also normal (Na 138.9 mmol/L, K 4.62 mmol/L and Ca 2.33 mmol/L), serum osmolality - 284 mmol/kg and immediately post-transplant the patient had normal sodium levels (143.2 mmol/L).

One week after the LT (2.2.016), no relevant serum changes in Na (137.7 mmol/L), K (3.62 mmol/L) and Ca (2.24 mmol/L) were detected either.

At the time of clinical manifestation (10.2.2016) the values of Na, K and osmolality were also normal (Na 136.4 mmol/L, K 4.98 mmol/L, osmolality 292 mmol/kg).

The lowest recorded value of serum Na was 130.6 mmol/L (7.2.2016) corresponding to a mild hyponatremia, and the highest serum level of Na was 149.5 mmol/L (31.1.2016); however, in both conditions the serum osmolality showed reference values (277 v.s. 293 mmol/kg). These conditions were corrected according the recommended guidelines (PMID:24569125).

Despite the slight fluctuations in the sodium serum level, the rate of its variation did not exceed 7 mmol/L during any 24 hours and this fluctuation was not associated with pathological serum osmolality, as one of the risk factors for development of ODS (PMID:22922267, PMID:18583636, PMID:28422408). Therefore, we do not assume a relevant influence of these factors on our results.

Moreover, there was a chronological relationship between the course of clinical symptoms and immunosuppressive treatment supporting our diagnosis. Tacrolimus as a potent immunosuppressive agent causes a variety of adverse effects including neurotoxicity, which represents the most common indication for conversion to other treatment options (PMID:10743694). These adverse effects generally occur early after LT. Although the adverse events are usually dose-related, they may occur even within the normal therapeutic range. In addition, there was a slight increase of Tac above normal levels in our patient, increasing the probability of neurotoxicity. Nevertheless, difficulties remain in understanding its biological background. Dose dependent blood brain barrier damage, endothelin mediated vasospasm, alteration in mitochondrial and lysosomal function, are all hypothesized as a possible mechanism of neurotoxicity (PMID:25122673, PMID:11778669).
Calcineurin (CN) is involved in the regulation of Ca2+ homeostasis, which is suggested to be disrupted by α-synuclein, whose misfolding and accumulation is a pathological hallmark of Parkinson’s disease. As has been proven, α-syn accumulation leads to sustained highly elevated levels of cytoplasmic Ca2+ intake that results in toxicity. The enhanced sensitivity of the neurons in substantia nigra to Ca2+ stress increases the destructive potential of α-synuclein. Interestingly, whereas an intermediate concentration of Tac inhibits CN, thus acting as a protective against α-syn toxicity, a higher concentration of Tac eliminated this protection. Surprisingly, complete inhibition of CN also results in toxicity (PMID:25122673)

Hence, onset and progression as a consequence of tacrolimus administration and improvement of clinical state after stopping Tac supports the diagnosis of drug-induced Parkinsonism. At the time of writing this case report, we had found only one more similar case report available in research databases (PMID:23080517). All these aspects point to the conclusion that tacrolimus induced Parkinsonism appears to be a unique and extremely rare clinical presentation, especially in the setting of orthotopic liver transplant.

Ad 1: b) Were there any hemorrhagic complications during the operation, which require massive transfusion of blood products?

As previously mentioned, intraoperative bleeding remains a serious problem affecting the outcome of transplanted patients (PMID:23383361, PMID:15934985). Since there is minimal consensus on transfusion guidelines during LT, various studies have shown a large variability in the use of various blood products among transplant centres (PMID:21514137). The impact of blood transfusion has been shown to be an important and independent predictor of post-transplant outcome, such as recovery of graft function. Several studies showed an inverse relationship between a transfused amount of blood products and the patients’ outcome (PMID:14625833, PMID:15934985, PMID:18165548). The relationship between blood requirement and an increased risk of postoperative complications and increased mortality has also been demonstrated (PMID:21603030, PMID:9756002, PMID:23383361). Based on these facts, a variety of transfusion strategies, advances in surgical technique and anaesthesiology management have been adopted over the past decade to limit the transfusion requirements during the peri-operative period.

Only limited data have been published concerning risk factors for ODS in respect of transfusion approaches in LT (PMID:28422408, PMID:4233816). In patients developing ODS, the number of platelet units and fresh frozen plasma given during surgery was higher, hemorrhagic complications were more frequent, and variations of Na before and after LT were higher. The association of >2 of these conditions were strongly associated with the occurrence of ODS (PMID:24233816). Consistently, a recently published meta-analysis reported that major risk factors for the development of ODS include severe pretransplant hyponatremia (serum Na <125 mmol/L), the magnitude of its change in the pre versus post-transplant state, higher positive intraoperative fluid balance, and the presence of postoperative hemorrhagic complications (PMID:28422408, PMID:25347235).
According the anaesthesiology records, our patients required multiple blood transfusions during LT (2 RBC units, 1 fresh frozen plasma). Based on the aforementioned data this corresponds to Low Blood Loss group (<6 RBC units transfused) in LT associated with better post-procedural and long-term prognosis compared to High Blood Loss (≥6 RBC units transfused) group (PMID:15934985). No post surgery-related hemorrhagic complications or other clinically relevant events predisposing the patient to development of ODS were observed. Thus, even in this case, we do not assume a significant influence of these aspects to our results.

In conclusion, ODS after LT may (although extremely rarely) manifest also with isolated extrapontine lesions. The rapid fluctuations of serum sodium concentration, also in the absence of pre-existing hyponatremia, and osmotic imbalances and/or their inappropriate correction, higher intraoperative fluid intake and the presence of surgery-related postoperative hemorrhagic complications represent the main risk factors for myelinolysis in patients undergoing LT.

Forasmuch as none of these conditions were present during the pre- and/or postoperative state, we do not assume significant interference with our results. We discussed these facts in the manuscript.

Section: Case presentation, page 4; line 56 new version: p. 11; line 58, p. 12; line(s) 1-12

We inserted the paragraph: “Osmotic demyelination syndrome (ODS) as a consequence of liver transplantation was also considered in the differential diagnosis; however, the onset of clinical presentation after LT was delayed as in typical cases. Nevertheless, no supportive signs for this diagnosis were found (e.g. hypo/hypernatremia before LT, relevant peri/post operative fluctuation of serum sodium/potassium and/or osmotic imbalances) [2]. No surgery related risk factors supportive for ODS (e.g. massive bleeding or higher intraoperative fluid intake) were noted either [3]." Thus, metabolic as well as endocrine dysfunctions were ruled out as the major cause of this condition.

Ad 2: The temporal relationship between the onset of parkinsonian signs and the clinical history of liver transplant and immunosuppression is not clear....

The surgery (LT) was performed on 26.01.16 with immediate initiation of the treatment with mycophenolate mofetil and methylprednison.

Eight days after LT (03.02.2016) early graft rejection signs appeared and the patient was admitted to emergency unit care in the Dpt of Anaesthesiology). Laboratory signs of a dynamic increase of AST, ALT, GMT, ALP and total bilirubin were detected. Approximately 15–30% of LT recipients develop one or more episodes of acute cellular rejection representing an early post-transplant complication. Acute (cellular) rejection most commonly manifests within 1 month after LT and 60% of all episodes occur within the first 6 weeks (PMID:26597456). This can be successfully treated with increased immunosuppression in almost all patients. This was also the reason for switching treatment to Tac (PMID:26597456).
On 10.02.2016 (2 weeks after the LT and on the 7-th day of Tac treatment), the first clinical presentation occurred in terms of developing symptoms of disorientation and confusion. The results of routine blood and electrolytes parameters (Ad 1 a) were normal.

The next day (11.02. 2016) the consultation of a psychiatrist and neurologist was requested due to the prevailing disorientation and occurrence of parkinsonian signs. The serum level of Tac was above the limit, and so the next day (12.02.16) the dose of Tac was reduced. Despite this treatment adjustment, the clinical signs of extrapyramidal symptomatology persisted (as has been confirmed repeatedly by neurological assessment).

According to the recommendation, when patients develop severe tacrolimus-related side effects, the drug is held for 3-5 days and then either the treatment is restarted at a low dose or the dose is reduced (as in the case of our patient); if side effects persist or worsen, patients are converted to other treatment options. Hence, the next day (16.02.2016) treatment was switched to sirolimus.

From 23.02.16 a clinically detectable improvement was achieved (13 days after first symptoms started and 7 days after treatment modification) with relief of rigidity, hypokinesia and tremor.

We addressed this criticism by incorporating the following statements:

Section: Case presentation, Page 4; line 41 new version: p. 11; line 41

The sentence: „She successfully underwent orthotopic liver transplantation“..

was changed to „She successfully underwent orthotopic liver transplantation (LT)“

Section: Case presentation, Page 4; line 49 new version: p. 11; line (s) 49-51

The paragraph „Due to laboratory signs of early graft rejection, she was admitted to hospital. After modification of her previous therapy ....“

was changed to „Due to laboratory signs of early graft rejection (8 days after LT) she was admitted to emergency unit care. After subsequent modification of her previous therapy....

Section: Case presentation, Page 4; line 53 new version: p. 11; line 56

The sentence: „Two weeks after the transplant, she developed symptoms of disorientation...

was changed to: Two weeks after the transplant and 7 days of tacrolimus treatment, she developed symptoms of disorientation and confusion.

Section: Case presentation, Page 5; line 41 new version: p. 13; line 1
The original sentence: „...the dose was therefore reduced (8 mg/day) and later, tacrolimus...” was changed to „...the dose was therefore reduced (8 mg/day) and 3 days later, tacrolimus...”

Section: Case presentation, Page 5; line (s) 44-48 new version: p. 13; line (s) 5-7

The previous statement „One week after the intervention, the patient’s tremor and brady/hypokinesia markedly improved (MDS-UPDRS III- 1 and MDS-UPDRS III- 1)” was changed to „One week after the treatment modification and 2 weeks after the first onset of parkinsonian signs, the patient’s tremor and brady/hypokinesia markedly improved.

Ad 3: During the period of confusion, was the patient still able to obey command and reliably complete assessments for bradykinesia? Were there signs of pyramidal tract involvement in this patient? What was the degree of disability - was she still ambulant?....

The neurologic assessment in the reported patient was performed as part of conciliar examination during hospitalisation in internal medicine due to deterioration in the quality of consciousness and the presence of tremor. No objective signs of the involvement of pyramidal tract or other systems (oculomotoric, bulbar, cerebellar) was revealed by neurologic assessment. Extrapyramidal symptoms (tremor and rigidity) were in the foreground of clinical picture, which was the main reason for further neurologic evaluation (MDS-UPDRS assessment according to the recommended instructions). Despite the state of confusion, this did not substantially influence the ability of the patient to follow instruction and after demonstration of tasks by the examining neurologist (movement disorders expert with MDS-UPDRS Certificate), she was able to perform the basic action focused on examination of bradykinesia (MDS-UPDRS items 3.4, 3.5, 3.6). Moreover, the examination was performed repeatedly over 3 consecutive days by the same neurologist, with similar results in all tested domains (tremor, brady/ hypokinesia and rigidity). The full UPDRS is generally not used in routine clinical practice because of the time demands. As previously reported, a shortened version (UPDRS-8) capturing the most critical elements of the wide spectrum of motor domains (bradykinesia, tremor, gait) exhibited a good correlation with the UPDRS total scores and were significantly sensitive to change as full UPDRS motor scores in assessing change (PMID:22329569). All these clinically important motor domains were repeatedly examined and assessed also in our patient.

In a differential diagnosis, considering the medical history, the development of a qualitative consciousness disorder after LT was, inter alia, the diagnosis of ODS was considered (discussed in Ad 1). Regarding the temporal relationship of clinical symptoms onset and subsequent commencement of Tac treatment, as well as their improvement after a change of therapy, and while considering the results of the other examinations, the diagnosis of “tacrolimus-related parkinsonism” was not determined until some time after the initial neurologic examination. That was also the main reason why the video recording unfortunately has not been taken in a „parkinsonian“state.
One week after sirolimus treatment, the patient’s tremor and brady/hypokinesia markedly improved (MDS-UPDRS III-1 and MDS-UPDRS III-1) and only a mild degree of tremor (MDS-UPDRS III-1) was present at the time of discharge from hospital. The first year after being discharged, the state was controlled in a 3-month follow-up period with a gradual reduction of treatment (levetiracetam and clonazepam). The patient is currently in outpatient neurological care in a 6-month follow-up period. A slight degree of rest tremor without interference with daily activities is present; not requiring medicament treatment (regarding hepatic conditions).

Section: Case presentation, page 5; line: 19 new version: p. 12; line (s) 36-39

We inserted the following sentences: No pyramidal signs or impairment of other systems (oculomotoric, bulbar, cerebellar) were revealed by neurologic assessment. A brain MRI.

Section: Case presentation, page 5; line: 51 new version: p. 13; line (s) 12-17

We put the sentence according the reviewer’s suggestion: Only a mild degree of rest tremor (MDS-UPDRS III-1) was present in this patient at the time of discharge from the hospital. Due to further improvement….

Ad 4: The described basal ganglia changes are quite subtle on the MRI Image. Can the authors upload a better resolution of the MRI image and insert arrows to indicate the areas of abnormalities....

Based upon a question raised by reviewer we have re-evaluated the MRI scan findings (independently assessed by two radiologists). Whereas both of them consistently revealed no signal changes in pons or brain stem suggestive of central pontine myelinolysis, the assessment of basal ganglia regions was discrepant (in the evaluation of signal intensity in FLAIR sequences). Moreover, the T2-hyperintensities in basal ganglia were interpreted by both as subtle and less evident. Even though, the signal changes were detected in the region of basal ganglia, these do not display the signal intensity as observed in the cases of extrapontine myelinolysis (typically hyperintensities in T2-, FLAIR and DWI sequences). In addition, this finding also strongly supports our diagnostic intention. Since no reported case with tacrolimus-induced Parkinsonism with MRI scan results is available in the literature, there is a lack of data which would allow us to solve the aforementioned issues. The participation of other pathological mechanism as those suggested for ODS (or a combination of various pathologies) might count as possible explanation.

We apologize for these inaccuracies. We uploaded the figure at a higher resolution and inserted arrows to indicate the abnormalities.

Section: Abstract (Case presentation), page 3; line: 31 new version: p. 10; line (s) 29-31

The original sentence: “A brain MRI was performed with the presence of T2 and FLAIR hyperintensities in basal ganglia bilaterally“...
was modified to: „A brain MRI was performed with the presence of T2-hyperintensities in basal ganglia bilaterally“

Section: Case presentation, page 5; line: 21 new version: p. 12; line 41

We revised the sentence: A brain MRI was performed that revealed hyperintensities in T2 and FLAIR- sequences in basal ganglia bilaterally.....

To: A brain MRI was performed that revealed subtle hyperintensities in T2- sequences in basal ganglia bilaterally...

Section: Discussion, page 7; line: 17

We omitted the sentence: „In our case, we observed intensity changes in the brain MRI congruent with vasogenic edema in basal ganglia“

Ad 5: a) The discussion on the 30 cases of parkinsonism complicating systemic lupus erythematosus [reference 7] does not seem to have a direct relevance to this case report.

The aim was to focus on the autoimmune-mediated mechanism in systemic disorders responsible for the neurological presentation as has been also described in other movement disorders (PMID:29406902, PMID:21577108). Moreover, the benefit of immunosuppression on relief of clinical symptoms provides a hint to the involvement of various immunological mechanisms in the pathological process. However, we realized that this information is confusing and omitted the following sentences from the manuscript:

Section: Discussion, Page(s): 6-7, Line(s): 59, 1,3,5

“There are 30 documented cases of Parkinsonism as a complication of lupus reported in literature...... A marked improvement of parkinsonian symptoms accompanying the effective treatment of initial disease was described in the majority of cases [7] “.

Ad 5: b) Suggest modifying the discussion to include common neurological complications seen in liver transplant.Interestingly, tacrolimus has been associated with central pontine myelinolysis post liver transplant....

Neurological impairment after liver transplantation is common and represents a major source of morbidity and mortality. Neurologic manifestations vary from minor complaints (headache, insomnia) to highly relevant syndromes such as central pontine/extrapontinne myelinolysis, speech disorders or neuromuscular complications (polyneuropathy, myopathy, Guillain-Barré
Osmotic demyelination syndrome represents a severe complication in LT, usually attributed to a rapid correction of hyponatremia and/or surgery related complications (PMID:28422408). Symptoms occur early after surgery and clinical manifestations may manifest various and not rarely atypical clinical presentations (PMID:16420387, PMID:25088893). To date, few cases reporting the tacrolimus-associated cases of central pontine myelinolysis have been reported in literature (PMID:21959523, PMID:25088893, PMID:12819864, PMID:22023701). Consistently, the prompt switching to a non-calcineurin inhibitor (e.g. sirolimus) is indicated.

Forasmuch as central pontine myelinolysis represents one of the most serious neurologic complications after liver transplantation and cases of tacrolimus induced central pontine myelinolysis were reported, we agree that this fact should not be omitted in the differential diagnosis.

We are very grateful for these suggestions. We included this information into the manuscript according to the suggestions of the reviewer.

Section: Discussion, page 6; line 36 new version: p. 14; line (s) 5-19

We added the following paragraph: „Manifestations vary from minor complaints (e.g. headache) to serious syndromes such as central pontine/extrapontine myelinolysis, speech disorders or neuromuscular complications [7, 8]. Osmotic demyelination syndrome (ODS) represents a severe complication usually attributed to a rapid correction of hyponatremia and/or surgery related complications [3]. Symptoms of ODS occur early after surgery and may manifest with various and not rarely atypical presentation [7, 9]. To date, only few cases reporting the tacrolimus-associated central pontine myelinolysis have been reported in literature [9-12].“ Tacrolimus-induced toxicity....

Section: Discussion, page 6; line: 39:

We omitted the sentence: „Symptoms may vary from mild tremor to severe encephalopathy, rarely leading to coma [3, 4]”.

Section: Discussion, page 7; line (s) 1-3   new version: p. 14; line (s) 41-46

We added this sentence: “To date, only one case report of new onset Parkinson Syndrome after LT supporting the diagnosis of tacrolimus-induced Parkinsonism was found in research databases [16].“

We thank for the extremely helpful comments and constructive criticism. We hope that we have sufficiently addressed the points of criticism raised by the reviewers and that our findings might be of interest to the readers of BMC Neurology. We would greatly appreciate a swift response as to whether this manuscript is of general suitability for publication.
Yours sincerely,

Karin Gmitterová, MD, PhD; Corresponding author
Second Department of Neurology, Comenius University
Limbova 5, 833 05 Bratislava, Slovakia
Phone: +421 (0) 2 5954 2241, Fax: +421 (0) 2 5954 2698
E-mail: gmitterova.karin@gmail.com