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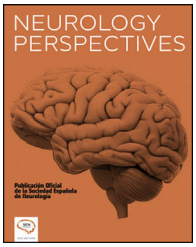

REVIEW

Neurological complications of liver transplantation in paediatric patients

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Liver transplantation;
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Abstract
Introduction: Liver transplantation is the only curative treatment for patients with end-stage liver disease. Neurological complications are one of the main causes of morbidity and mortality.
Objective: To study neurological complications after liver transplantation in paediatric patients.
Methods: We conducted a retrospective study, including all paediatric patients younger than 17 years undergoing liver transplantation over a 12-year period at our centre.
Results: Forty-six liver transplantations were performed in 38 patients. The most common indication was biliary atresia. Up to one-third of patients presented neurological complications, with psychomotor agitation being the most frequent. Incidence of neurological complications was significantly higher in the group of infants than in older age groups. Encephalopathy was more common in patients with acute liver failure than in those with chronic liver failure.
Conclusions: Neurological complications, and particularly psychomotor agitation, are common after liver transplantation in paediatric patients.

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PALABRAS CLAVE
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Encefalopatía;
Neurotoxicidad;
Tacrolimus

Complicaciones neurológicas del trasplante hepático en pacientes pediátricos

Resumen
Introducción: El trasplante hepático (TH) es el único tratamiento curativo para enfermos en situación de fallo hepático terminal. Las complicaciones eurológicas (CN) son una causa importante de morbimortalidad.
Objetivos: Estudiar la incidencia de CN en pacientes pediátricos sometidos a un TH.
Pacientes y métodos: Estudio retrospectivo en el que se incluyeron todos los pacientes menores de 17 años sometidos a TH durante un periodo de 12 años.
Resultados: Se realizaron 46 TH en 38 pacientes. La indicación más frecuente fue la atresia de vías biliares. En un tercio de los pacientes hubo alguna CN, siendo la más frecuente la agitación psicomotora. Se encontró una menor incidencia de CN en el grupo de lactantes con respecto a los pacientes de mayor edad, de forma estadísticamente significativa. El desarrollo de encefalopatía en casos de fallo hepático agudo fue más frecuente que en aquellos con insuficiencia hepática crónica.
Conclusiones: Las CN en los niños son frecuentes después de un TH, siendo la más frecuente la agitación psicomotora.

Introduction and objectives

Liver transplantation is the only curative treatment for patients with end-stage liver disease.[1,2] Despite advances in the fields of organ preservation, immunosuppressive therapy, surgery, and perioperative management, the incidence of complications following liver transplantation remains high.[2] More specifically, neurological complications are a major cause of morbidity and mortality in these patients.[3,4] Approximately one-third of all transplantations are performed in patients younger than 1-year old, and half are performed in patients younger than 2 years of age. Post-transplant survival in children has increased to 90%.[5] The main indication for liver transplantation in paediatric patients is primary biliary cirrhosis (65%), caused in most cases by biliary atresia, but also by familial cholestasis, Alagille syndrome, and alpha-1 antitrypsin deficiency. Other frequent indications include metabolic liver disease, unresectable benign or malignant liver tumours (hepatoblastoma, hepatocarcinoma), and acute liver failure (of toxic, infectious, or metabolic aetiology, etc).

Few studies have analysed the incidence of neurological complications in paediatric patients undergoing liver transplantation, with different series reporting rates between 8% and 46%.[1–10] One of the first series published on the topic concluded that adults were at higher risk of neurological complications than children (23% vs. 8%).[5] Subsequent studies have classified neurological complications as early or late, depending on the moment of onset.[6] Early neurological complications include acute encephalopathy, seizures, and cerebrovascular events, whereas the most frequent late neurological complications are headache, poor coordination, tremor, and cognitive alterations (executive and visuospatial dysfunction), in addition to neuropsychiatric disturbances.[6,7] Several authors have attempted to determine the risk factors for neurological complications,[8–10] finding an association with the following conditions: toxic levels of immunosuppressants (mainly calcineurin inhibitors), poor neurological status prior to the surgery, kidney failure, and transplant rejection.

The main objective of this study is to analyse the incidence of neurological complications in a population of paediatric patients undergoing liver transplantation and to describe the characteristics of these complications. As a secondary objective, we analyse possible risk factors for the development of neurological complications, both before and after transplantation, and compare them to those of the population undergoing liver transplantation and presenting no neurological complications.

Patients and methods

We conducted a retrospective study including all paediatric patients (younger than 17 years) undergoing liver transplantation at a tertiary hospital between 2004 and 2016, and analysed those patients presenting neurological complications. We gathered the following information: demographic data, initial diagnosis and reason for liver transplantation, previous neurological alterations, baseline status before the surgery (including need for mechanical ventilation and/or inotropic support, use of extracorporeal blood purification therapy with Molecular Adsorbent Recirculating System [MARS] before transplantation, immunossuppressant treatment received, etc), type of neurological complication, timing of onset, complementary tests, and treatment. We also analysed survival and presence of sequelae. In the statistical analysis, continuous variables are expressed as medians and quartiles 1 and 3, and categorical variables are expressed as absolute frequencies and percentages. We compared the groups of patients with and without neurological complications. Continuous variables in both groups were compared with the Mann–Whitney U test. Contingency tables analysis used the chi-square test and the Fisher exact test. P values < .05 were considered statistically significant. Statistical analysis was conducted with the SPSS software (version 21).

Definition of neurological complications

1. Psychomotor agitation: patients presenting excessive motor activity, with periods of disorientation, with EEG showing normal background activity and no epileptiform activity. Excessive motor activity may also be accompanied by autonomic alterations (tachycardia, hypertension, hyperhidrosis). We excluded patients who had received high doses of sedatives, whose neurological manifestations were classified as neurological alterations secondary to withdrawal syndrome.
2. Encephalopathy: patients presenting any type of alteration in the level of consciousness, including agitation, personality changes, lethargy, stupor, or coma, with EEG showing abnormal background activity (diffuse slowing and/or triphasic waves). Altered level of consciousness may be accompanied by tremor.

a. The degree of encephalopathy is classified clinically, as follows (modified from Ghosh et al.[1]):

- Grade I: alterations in the sleep–wake cycle, bradyphrenia, concentration problems (at least 2).
- Grade II: excessive sleepiness, temporal disorientation, tremor (at least 2).
- Grade III: stupor (the patient needs intense stimulation to open their eyes or follow a command), temporal and spatial disorientation.
- Grade IV: coma.

b. Patients with encephalopathy are further classified into two groups according to the presence or absence of epileptic seizures.

3. Focal neurological signs and/or other findings: patients who present focal neurological signs, including oculomotor alterations, facial palsy or alterations in other cranial nerves, limb weakness, sensory alterations, dysmetria, or ataxia.

Immunosuppressive therapy

Patients with neurological complications were classified into three groups according to the treatment i, with most patients being classified into groups A and B. These groups were as follows:

- Group A: tacrolimus and corticosteroids.
- Group B: tacrolimus, corticosteroids, and basiliximab.
- Group C: tacrolimus, corticosteroids, and mycophenolate mofetil.

Results

Patient characteristics, clinical status prior to transplantation, type of neurological complications, and complementary tests performed are summarised in Table 1. Fig. 1 shows the most representative cranial CT and brain MR images Table 2 compares the characteristics of patients with and without neurological complications after liver transplantation.

Patient characteristics

We analysed data from 46 liver transplantations, performed in 38 patients, 29 [63%] were performed in boys and 17 [37%] in girls. Median age at the time of surgery was 1.9 years (Q_1–Q_3: 0.7–8.5) and one-third were younger than 1-year old. The most frequent indication for liver transplantation was biliary atresia (n = 20; 53%). Eight patients undergoing liver transplantation required retransplantation due to hepatic artery thrombosis (n = 6) and acute rejection and vascular dysfunction (n = 2).

Sixteen procedures were associated with neurological complications during the post-operative period at the intensive care unit; with no significant difference based on gender (56% male vs. 44% female), with a median age of 6.7 years (Q_1–Q_3: 1–12.5). A quarter of all neurological complications occurred in children younger than 1-year old. The most frequent indication for liver transplantation in the group of patients with neurological complications also was biliary atresia (n = 6; 37.5%). Most of the liver grafts were from deceased donors (n = 12; 75%). Neurological complications most frequently manifested within a week of the procedure, with 85% of complications occurring in the first 10 days.

Clinical status prior to liver transplantation

Most patients presenting neurological complications had chronic liver disease before the procedure (n = 11; 69%); less frequently, they presented acute liver failure (n = 3) and primary graft failure requiring emergency retransplantation (n = 2). Before the transplantation, 18% of patients (n = 3) required vasoactive drugs and mechanical ventilation. Furthermore, 12% (n = 2) required extracorporeal blood purification therapy with MARS.

Trigger factors

The most frequent trigger factor was tacrolimus levels above the therapeutic range (20 ng/mL) (n = 7; 43.8%). Other alterations detected in blood analyses and linked to the neurological complications were uraemia (>40 mg/dL, or 6.7 mmol/L) (n = 3), hyperammonaemia (>150 μg/dL in neonates, >70 μg/dL in infants, and >45 μg/dL in children older than 2 years) (n = 6), and severe hyponatraemia (<125 mEq/L) (n = 2).

Progression

Nine patients died during the post-operative period, with a median of 8 months (Q_1–Q_3: 1–25) after the procedure; this represents a mortality rate of 19.6%. Two patients died due to severe diffuse cerebral oedema. The group presenting neurological complications had a mortality rate of 40%, with a median survival time of 24 months after surgery (Q_1–Q_3: 0.7–31). The mean follow-up period was 6 years (Q_1–Q_3: 1.5–11); most patients with neurological complications achieved favourable outcomes. In the last follow-up, 70% of patients showed no signs of encephalopathy or neurological sequelae. Two patients with history of encephalopathy

Table 1 Characteristics of the patients presenting neurological complications after liver transplantation.

Patient/ episode	Age (years)/ sex	Indication for LT/ liver failure pre-LT	Retransplantation	MARS/ VAD/ OTI	Immuno suppressive therapy[a]	Type of NC	Non-contrast cranial CT	Brain MRI	EEG	Other factors	Outcome/post-LT survival time (months)
1/1	12/♀	Hepatocarcinoma/ chronic	No	No	A	Grade II encephalopathy	Normal	NP	GS	-	Death/26
2/2	15/♂	Hepatocarcinoma/ acute	Yes	No	A	Psychomotor agitation	Normal	Normal	Normal	-	
2/3		Vascular dysfunction/graft failure								-	Death/24
3/4	6/♀	Unknown cause/ acute	No	Yes	B	Grade I encephalopathy	Normal	Normal	GS	Tacrolimus toxicity	Death/36
4/5	6/♀	Biliary atresia/ chronic	No	No	A	Psychomotor agitation	Normal	NP	Normal	Tacrolimus toxicity	Alive
5/6	8/♂	Biliary atresia/ chronic	No	No	A	Psychomotor agitation	Normal	NP	Normal	Tacrolimus toxicity	Alive
6/7	0.8/♂	Biliary atresia/ chronic	No	No	B	Grade III encephalopathy	Global atrophy	Atrophy and non-specific white matter hyperintensity	GS and triphasic waves	Tacrolimus toxicity	Alive
7/8	1/♂	Retransplantation due to HAT	Yes	No	C	Grade II encephalopathy with seizures	Global atrophy	Global atrophy, otherwise normal	GS and epileptiform activity	Tacrolimus toxicity	Alive
8/9	0.6/♂	Biliary atresia/ chronic	No	No	B	Psychomotor agitation	Normal	NP	Normal	Tacrolimus toxicity	Alive
9/10	5/♀	HAV/acute (FHF)	No	Yes	B	Encephalopathy/ coma	Cerebral oedema, tonsillar herniation[b]	NP	GS, arreactive		Death/0.3
10/11	3/♀	Biliary atresia/ chronic	No	No	B	Psychomotor agitation	Normal	NP	Normal	-	Alive
11/12	14/♂	Copper deposition/ chronic	No	Yes	B	Grade III encephalopathy	Atrophy, right cerebellar haematoma	Atrophy, haematoma, and signs of CPM[c]	GS with epileptiform activity	Tacrolimus toxicity	Alive
12/13	10/♀	Unknown cause/ chronic	No	No	B	Grade II encephalopathy with seizures	Posterior white matter hypodensity	Hyperintensity suggestive of PRES[d]	GS	Arterial hypertension	Alive
13/14	16/♂	Cirrhosis due to HCV/chronic	No	No	A	Grade III encephalopathy with seizures	Diffuse cerebral oedema	Diffuse cerebral oedema	GS with epileptiform activity	Bacterial peritonitis	Death/1
14/15	0.7/♀	Biliary atresia/ chronic	No	No	A	Psychomotor agitation	Non-specific white matter changes	Normal	Normal	-	Alive

Table 1 (*continuación*)

Patient/ episode	Age (years)/ sex	Indication for LT/ liver failure pre-LT	Retransplantation	MARS/ VAD/ OTI	Immuno suppressive therapy[a]	Type of NC	Non-contrast cranial CT	Brain MRI	EEG	Other factors	Outcome/post-LT survival time (months)
15/16	10/♂	PSC/chronic	Yes	No	A	Grade II encephalopathy	Subdural haematoma	Subdural haematoma	GS	Primary graft failure	Retransplantation

CPM: central pontine myelinolysis; CT: computed tomography; GS: generalised slowing; EEG: electroencephalography; FHF: fulminant hepatic failure; HAT: hepatic artery thrombosis; HAV: hepatitis A virus; HCV: hepatitis C virus; LT: liver transplantation; MARS: molecular adsorbent recirculating system; MRI: magnetic resonance imaging; NC: neurological complications; NP: not performed; OTI: orotracheal intubation; PRES: posterior reversible encephalopathy syndrome; PSC: primary sclerosing cholangitis; VAD: vasoactive drugs.

[a] Immunosuppressive therapy: A) tacrolimus + corticosteroids; B) tacrolimus + corticosteroids + basiliximab; C) tacrolimus + corticosteroids + mycophenolate mofetil.

[b] Fig. 1A.

[c] Fig. 1B and 1C.

[d] Fig. 1D.

presented significant disability due to severe cognitive impairment.

Inter-group comparison

Table 2 presents the variables compared in patients with and without neurological complications.

Apart from age, no statistically significant differences were found. with older patients suffering more neurological complications than younger. The remaining variables showed no significant differences, although we did observe a trend towards higher risk of neurological complications among patients requiring MARS therapy those with toxic levels of tacrolimus. Moreover,the mortality rate was higher among patients with neurological complications. We did not observe a higher incidence of neurological complications among patients requiring retransplantation. Subgroup analysis revealed that patients with acute liver failure presented a higher risk of encephalopathy comparte to those with chronic liver failure (P = .003).

Discussion

Paediatric patients undergoing liver transplantation frequently develop neurological complications. Previous studies have analysed the incidence of neurological complications, reporting rates ranging from 8% to 46%.[1–10] In our series, 16 patients (34.8% of all transplantations) presented neurological complications. These patients showed a significantly higher median age than patients presenting no neurological complications and this finding is consistent with those reported by other researchers.[1–4] Previous studies have reported a higher incidence of neurological complications in patients receiving liver grafts from deceased donors than in those receiving the organ from a living donor.[4,5] In our series, few patients received grafts from living donors; therefore we were unable to analyse the potential association between the type of donor and the risk of neurological complications.

Encephalopathy is one of the most frequent neurological complications in the context of hepatocellular dysfunction and liver transplantation. Incidence ranges from 15% to 33% in paediatric patients, and these rates are higher than those reported in some series of adult patients (11%–15%).[5] In our series, encephalopathy was more frequent among patients with acute liver failure; similar to previous published studies.[6–10]

Seizures are another of the most frequently reported neurological complications of liver transplantation, usually classified as acute symptomatic seizures.[1–3,5] In the context of liver transplantation, seizures can be secondary to structural causes (e.g., cerebrovascular events, hypoxic–ischaemic encephalopathy), central nervous system infection, and toxic-metabolic causes (e.g., ion imbalance, immunosuppressive therapy).[1–3,7–11] In our series, seizures were associated with cerebral oedema, posterior reversible encephalopathy (see below), and toxic levels of tacrolimus.

Regarding the potential association between calcineurin inhibitors (tacrolimus and cyclosporine) and neurological complications, previous studies suggest that these drugs may be neurotoxic.[11–15] On the one hand, they inhibit

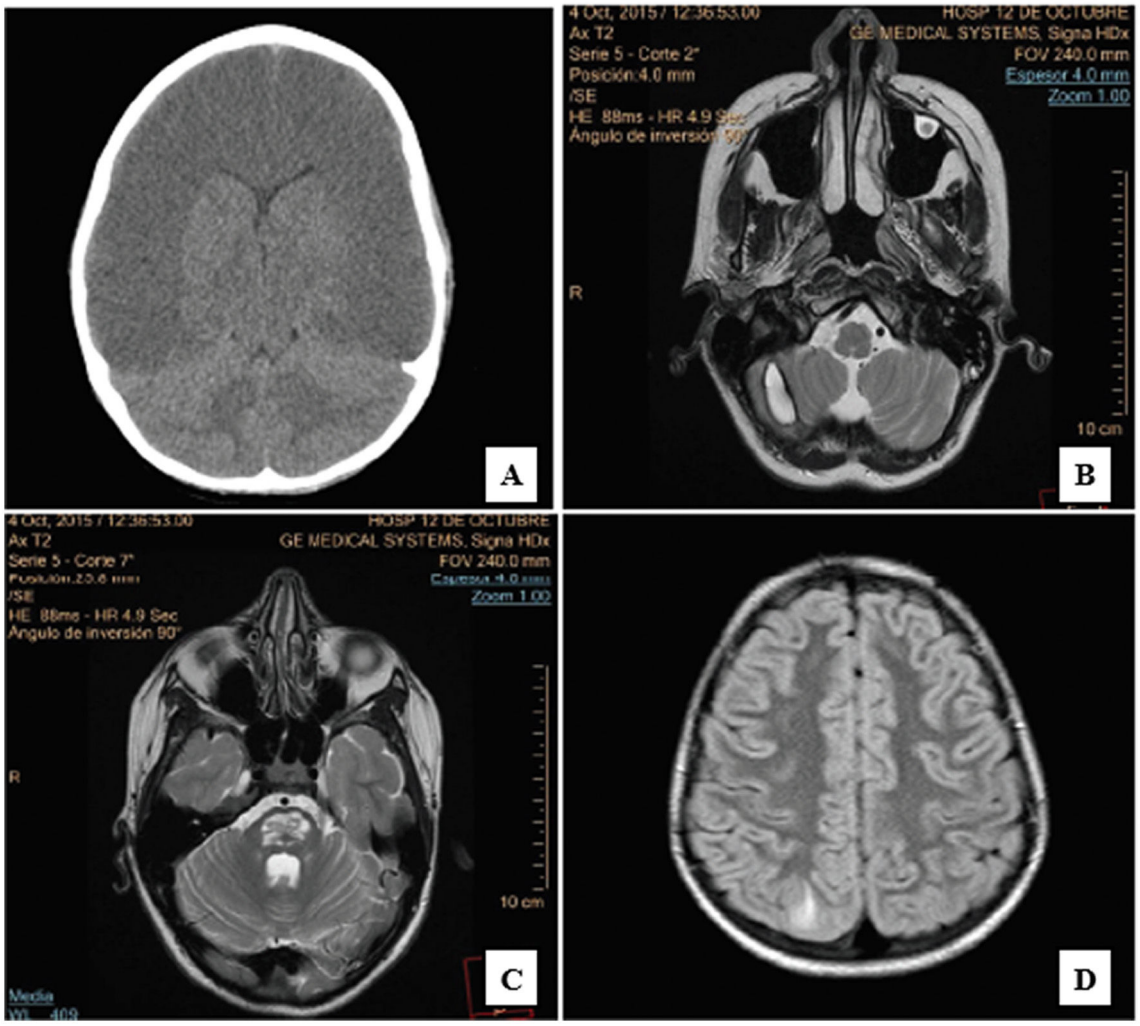

Fig. 1 A) Non-contrast cranial CT: diffuse parenchymal hypoattenuation, loss of cortico-subcortical differentiation, and collapse of the ventricular system, compatible with diffuse cerebral oedema. B) Brain MRI (T2-weighted, axial plane): oval hyperintensity with a hypointense halo in the right cerebellar hemisphere, compatible with haematoma. C) Brain MRI (T2-weighted, axial plane): hyperintensity affecting nearly the entire central region of the pons, suggestive of central pontine myelinolysis. D) Brain MRI (FLAIR, axial plane): patchy hyperintensities in the juxtacortical and subcortical white matter of the parieto-occipital region of the right hemisphere.

calcineurin in cells, leading to apoptosis of oligodendrocytes and glial cells, which are rich in calcineurin. On the other, these drugs modify the activity of excitatory amino acid receptors (NMDA) and inhibitory amino acid receptors, such as (GABA). However, the neurotoxicity of calcineurin inhibitors does not always occur in the context of toxic levels.[14,15]

Posterior reversible encephalopathy syndrome (PRES), observed in one of our patients, is a clinico-radiological entity characterised by headache, visual alterations, and seizures, combined with radiological signs of vasogenic oedema predominantly affecting the parieto-occipital white matter.[16] This complication has also been associated with the use of calcineurin inhibitors, with poorly controlled arterial hypertension also being a risk factor. These drugs have a potential vascular toxicity secondary to mechanisms of cerebral vasoconstriction and/or cerebrovascular inflammation.[15–17] The incidence of PRES in patients receiving calcineurin inhibitors ranges from 1% to 10%.[17] In our series, only one patient presented this complication, in association with persistent, poorly controlled arterial hypertension and in absence of toxic levels of tacrolimus. PRES may be underrepresented in our series, as not all patients underwent MRI studies; however none of the remaining patients presented symptoms suggestive of this complication.

Previous studies analysing survival after liver transplantation report contradictory data regarding patients with neurological complications.[1–3,5] Therefore, it remains unclear whether this subgroup has a poorer survival prognosis. This is probably explained by the wide variety of possible neurological complications and their varying severity, contributing differently to mortality.[18,19] In our series, a longer survival was observed in the group of patients presenting no neurological complications, although the differences were not statistically significant.

Table 2 Comparison between patients with and without neurological complications.

	Patients with NC	Patients without NC	*P*
Median age, years (Q_1–Q_3)	6.7 (1–12.5)	1.2 (0.6–4.3)	**.03**
History of encephalopathy	50%	50%	.421
Type of liver failure			.314
Acute	60%	40%	
Chronic	35%	65%	
Graft failure	20%	80%	
Need for cardiopulmonary support before LT	43%	57%	1
MARS therapy before LT	60%	40%	.325
Toxic levels of tacrolimus	70%	30%	.189
Survival	69%	87%	.241

LT: liver transplantation; MARS: molecular adsorbent recirculating system; NC: neurological complications. Statistically significant differences are indicated in bold.

One limitation of our study the neuroimaging data available: not all patients underwent brain MRI scans, because it was no technically possible or viable (e.g., in patients receiving MARS therapy). Therefore, some radiological signs that are better assessed with brain MRI may have missed by non-contrast head CT. Furthermore, not all patients undergoing liver transplantation were monitored with video-EEG; as a result, the incidence of encephalopathy may be underestimated, and patients classified as having psychomotor agitation may in fact have presented episodes of encephalopathy that were not detected by conventional EEG. Another limitation of our study is derived from its design. Its retrospective approach and a small sample size may explain the lack of statistically significant differences in some of the potential risk factors analysed. Prospective studies including paediatric patients undergoing liver transplantation should be conducted to identify trigger factors or baseline conditions that may help predict higher risk of developing neurological complications.

In conclusion, neurological complications of liver transplantation are frequent in paediatric patients, and present a highly variable clinical spectrum. Certain pre-existing factors seem to be associated with a higher incidence of complications; these include encephalopathy, MARS therapy, acute liver failure, and circulatory or respiratory support. After transplantation,toxic levels of tacrolimus are associated with an increased risk of neurological complications. To minimise morbidity and mortality in these patients, the management of baseline clinical status should be optimised before the surgery and the patients should be closely monitored during the post-operative period to enable early detection of any complications.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.10.007.

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