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Long term response to steroid therapy in Rasmussen encephalitis

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Summary Rasmussen encephalitis (RE) is a severe and progressive focal epilepsy of unknown origin that leads to deterioration of motor and cognitive function. In a previous study, we described positive effect of high doses of steroids during the first year after the onset of RE. The objective of this study was to evaluate this therapy at long term.

We reviewed 11 patients (7 girls and 4 boys) with RE of the right hemisphere (7) and the left (4) at a follow-up of 9 ± 2 years. Age at onset of RE ranged from 2 to 14 years.

Six patients had no benefit from steroid therapy and underwent hemispherotomy. Five had significant reduction of seizure frequency with disappearance of epilepsia partialis continua, and improved motor function. Of these, two died of unexpected sudden death 5 and 7 years after seizure control. Two others with initial response experienced progressive recurrence of seizures 1 to 4 years after the end of steroid therapy and required hemispherotomy. Finally, only one patient exhibited total cessation of seizures with steroids for 3 years, but seizures progressively recurred although the frequency was moderate.

Our data confirm that although steroid treatment can be useful when given early in the course of RE, long term relapse can occur among the good responders requiring delayed hemispheric disconnection.

Introduction

Rasmussen's encephalitis (RE) is a chronic inflammatory brain disorder leading to unilateral hemispheric brain destruction. This process is accompanied by progressive impairment of neurological functions

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associated with the affected hemisphere and intractable seizures.[1,2]

Usually, a progressive course of focal onset seizures, characteristically epilepsia partialis continua (EPC)[3] as well as neurological deterioration (more often progressive motor defect) occurs. The diagnosis of RE is also based on neuroradiological findings, with characteristic MRI features of areas of cortical hyperintense T2/fluid attenuated inversion recovery (FLAIR) signal and atrophy of the affected hemisphere.[4,5] Even though, clinical and radiological finding are sufficient for diagnosis of RE, histology is still regarded as the gold standard for establishing the diagnosis of RE. Histopathologically, chronic inflammation, astrogliosis and microgliosis, neuronal loss and hemispheric atrophy are found mainly in the cortex.[1,6,7] The pathogenesis of RE has been linked to autoimmune process including antoantibodies[8] and cytotoxic T cells.[9]

Although hemispherectomy/hemispherotomy (disconnection of one hemisphere) may interrupt the seizure activity, such an indication is only acceptable to the patient and parents when hemiparesis has developed. Thus, there is a need for an effective treatment in early stages for both control of seizures and prevention of neurological deterioration. Various broad spectrum immunosuppressant treatments, including corticosteroids and cyclophosphamide as well as therapies directed primarily against humoral immune reaction like plasmapheresis/immunoabsorption or intravenous immunoglobulins have been applied with moderate success (for a review,[10]).

In a previous study, we proposed to treat these patients with high dose steroids, at doses usually given to patients with multiple sclerosis. At short term, there was improvement of motor function in half the patients, and favorable factors for response to treatment comprised early administration of high doses of steroids.[11,12] We now reviewed critically the course of the disorder following steroid therapy with a follow-up of up to 11 years (9 ± 2 years).

Patients and methods

Over the past 20 years (1983—2003), we identified 14 patients with the clinical and radiological characteristics of RE, including intractable focal seizures, EPC[3] and progressive neurological deficit, according to literature criteria.[13] Bilateral EPC was excluded. We also excluded the patients who had EPC from metabolic (i.e. MERRF or Alpers disease) or viral (measles) diseases.

These RE patients were treated with high doses steroids (including intravenous bolus and oral steroids) as part of their treatment, including conventional antiepileptic therapy. Among the 14 RE patients, 3 patients did not respond to steroid therapy within the 2 months after its introduction, since they developed intractable epilepsy and lost the ability to walk.[12] Therefore, we also excluded these patients and we selected the 11 remaining patients (7 girls, 4 boys) for the present long term follow-up study. They had unilateral EPC together with the criteria of Rasmussen syndrome and still had the ability to walk independently when steroid therapy was started.

The files were studied retrospectively with a particular emphasis given to (a) the age of onset of first seizures as well as the seizure types, the age of onset of epilepsia partialis continua, and the hemisphere affected by RE; (b) the time lag between the onset of first seizures and onset of epilepsia partialis continua and neurological deficit to initiation of steroid treatment; (c) the course of epilepsia partialis continua and of neurological condition, with special emphasis on walking and speech; (d) the time lag from relapse after steroid to surgery, and the age at surgery; (e) the course of epilepsy and neurological deficits at 6 month steroid therapy and (f) the course of epilepsy and neurological deficits at the last visit.

The six month follow-up data of eight patients of this series have been reported in a previous study.[12]

Results

Patients characteristics (Table 1)

Clinical, EEG, and neuroimaging in the first 4 months after onset are summarized in Table 1. Age at onset ranged from 2 to 14 years (mean 6 ± 3.7). RE affected the right hemisphere in 7 cases and the left one in 4 cases. Disease onset was marked in all cases by partial epileptic seizures that constituted the first manifestation of RE: they consisted of simple partial motor seizures in eight cases, and of complex partial seizures in three cases. Epilepsia partialis continua rapidly followed in 9/11 patients, 1—30 months after the first seizures (mean 9.7 ± 11.08). Neurological deficit was never the first manifestation of the disease. Before steroids, nine patients had developed focal motor deficit, involving one limb in five cases, and consisting of hemiparesis in the 4 others. On starting steroids, five patients were able to walk alone. Three patients had cognitive impairment consisting of motor aphasia (cases # 3 and # 10) frontal behavior (case # 3), and attention deficit (case # 5).

Table 1 Main individual characteristics at onset

Patient/ Sex	Age of seizure onset (y)	Time lag between the seizure onset and EPC onset (m)	Seizure type	CSF oligoclonal bands	EEG at onset (within the first 3 months)	MRI at onset (within the first 6 months)
1/M	2	1	CPS motor	No	R centro-temporal SW and sp	R GWA/WMA
2/M	6	24	SPS motor FS	Yes	R SW and sp	R CA
3/M	6	5	CPS motor	No	L frontal sp	L CA
4/F	3	1	SPS motor atonic	Yes	R fronto-temporal SW and sp	R GWA
5/F	8	0	SPS motor absences	No	R fronto-parietal SW and sp	R CA
6/F	3	12	SPS motor	No	R occipital SW and sp	R CA and GWA/WMA
7/F	9	36	SPS motor	No	R SW and sp	R CA and GWA/WMA
8/F	3	6	SPS motor FS	No	R frontal SW and sp	R CA
9/M	14	1	CPS motor	No	L SW and sp	L GWA and CA
10/M	9	3	SPS motor	Yes	L SW and sp	L CA
11/F	3	24	SPS motor hemitonic	No	L SW and sp	L CA/GWA

F: female; M: male; y: years; m: months. EPC: epilepsia partialis continua; SPS: simple partial seizures; CPS: complex partial seizures; R: right; L: left; SW: slow waves; sp: spikes; FS Focal Spike. CA: cortical atrophy; GMA: gray matter intensity abnormalities; WMA: white matter intensity abnormalities.

Steroid treatment schedule

The steroid treatment schedule is summarized in the Table 2. It was not exactly the same for each patient, as four of them were referred from another hospital. 7/11 patients received steroid therapy consisting in a series of 3 intravenous bolus of methylprednisolone, (400 mg/m^2 of body surface) during the first 6 days (on alternate days), repeated 2 months later, together with oral prednisone at 2 mg/kg of body weight daily. Among the four remaining patients, three received intravenous bolus of methylprednisolone followed by oral prednisone whereas one only received oral prednisone.

Steroid treatment was started 3 months to 3 years following the first seizures (mean 10.6 months $\pm$ 11.7), less than 1 year in 8 cases and before the third year of evolution for the remaining 3 cases. If seizure frequency decreased, EPC disappeared and motor function recovered within the first 2 months of steroid treatment, treatment was maintained for 2 years, with progressive decrease of dose of oral prednisone, bolus of prednisolone being administered every 2 months for 6 months. The total steroid bolus ranged from 3 to 19 bolus (mean 10.7 $\pm$ 7.7). The total steroid duration was 24.3 months $\pm$15.1, during which bolus of methylprednisolone lasted 7.4 months $\pm$5.4.

Table 2 Individual steroid treatment schedule

Patient/ Sex	Time between first symptoms and introduction of high doses of steroids (m)	Total number of steroid bolus	Total bolus duration (m)	Total steroid treatment (IV + oral) duration (months)
1/M	1	15 bolus	13	17
2/M	30	6 bolus	10	No
3/M	8	6 bolus	3	3
4/F	3	6 bolus	3	3
5 /F	4	No		29
6/F	12	15 bolus	12	21
7/F	12	6 bolus	3	15
8/F	12	19 bolus	11	48
9/M	7	18 bolus	12	24
10/M	1	3 bolus	1	22
11/F	36	24 bolus	14	17

F: female; M: male; y: years; m: months.

Table 3 Short and long-term course on steroids

Patient/ age (y)	Just before treatment		RE course between 2 and 6 months		Long term course			
	Epilepsy/EPC	Deficit	Epilepsy/Seizure reduction (%)	Deficit motor/ behavioral recovery	Time lag introduction of steroids − relapse	Epilepsy	Deficit	Steroid treatment duration (m)
1/12	LUL (EPC)	L H did not walk	<50	Partial; walks with assistance	4 m	Relapse L UL	L UL frontal behavior	17
2/15	LH (EPC)	LH; walks with assistance	90	No improvement	3 m	Relapse L UL + face	L H walks unstable	No
3/14	RUL (EPC)	RH motor aphasia; did not walk	90	Partial; walks alone	7 m	Relapse RUL	RH walks with assistance frontal behaviour	3
4/11	LUL (EPC)	L H Did not walk	90	Complete	1 y	Relapse RUL	L H walks with assistance	3
5/18	LH	Attention deficit	90	No	3 y	Relapse	L H did not walk	29
6/13	LH (EPC)	L H	50—90	Partial	6 m	Relapse LH	L H Walks with assistance	21
7/12.5	LH	No motor deficit	<50	N/A	3 m	LUL	L UL Walks alone	15
8/16	L Foot (EPC)	L Lo Walks with assistance	90	Complete walks alone (5 m)	4 y	Relapse LH	Does not walk atonic falls	48
9/21[a]	RH (EPC)	R Lo walks with assistance	90	Complete; Walks alone	4 m	Relapse RH		24
10/16[a]	RUL (EPC)	RUL motor aphasia	90	Partial; language improvement	2 y	Relapse RUL	Walks alone	22
11/14	RUL (EPC)	RUL walk alone	>90	Partial	3 y	Relapse RUL	R UL walk alone	17

y: years; m: months; EPC: epilepsia partialis continua; L: left; R: right; H: half of the body; UL: upper limb; Lo: lower limb.

[a] For patient 9 and 10, age of death.

2—3 month follow-up (Table 3)

Nine patients (cases # 2, 3, 4, 5, 6, 8, 9, 10, 11) had more than 50% reduction of seizure frequency on steroids within the first 6 months, with eight having at least 90% seizure reduction. Among them, three had complete motor, but one patient (case # 2) remained with severe motor deficit despite seizure control. In addition, one patient (case # 5) who exhibited neither EPC, nor permanent motor deficit before the initiation of steroids, kept behavioral disorders unchanged with steroids.

No severe side effects were observed. However, all 11 patients exhibited mild to moderate steroids related side effects. They consisted of Cushing syndrome in 11, osteoporosis in 3 (with fracture of the femur in one patient), hypertension in 1, and infection in 1 (oral and vaginal candidosis).

Over 6 month follow-up—last visit (Table 3)

The age of the patients ranged from 11 to 18 years (mean 13.9 $\pm$ 2.15) at last visit. The mean follow-up was 9 $\pm$ 2 years. Table 3 summarizes the evolution of the 11 patients before and after steroids.

Six patients (cases # 1, 2, 3, 4, 6, 7) experienced a progressive relapse of epilepsy and EPC between 3 and 12 months after the introduction of steroids. These patients underwent early hemispherotomy. Seizures completely disappeared between the age of 4 and 13 years (mean 7.8 $\pm$ 4.1). Time lag for surgery ranged from 1 to 7 years (mean 3 $\pm$ 2.1), according to the time lag to the development of hemiparesis and the acceptability of the operation by the patient and its parents (Table 4).

The five remaining patients (cases # 5, 8, 9, 10, 11) had a longer seizure remission, disappearance of EPC, and improved motor function, during 2—3 years after starting steroids protocols. However, their evolution was still negative since:

- Two of them (cases # 9 and 10) died of sudden unexpected death (SUDEP) respectively 5 and 7 years after seizure control (at the respective age of 16 and 21 years). Both were found dead in their bed, without evidence that a seizure was the cause of death. Neuropathological study performed in the boy showed severe hemispheric atrophy, but no evidence of reactivation of inflammation suggesting active encephalitis.
- The third patient (case # 11), initially right-handed and exhibiting EPC on the right side of the body, underwent total cessation of seizures with steroid therapy for 3 years. Progressively, seizures recurred but the frequency was moderate and did not affect the regularity of schooling, since at the age of 12 years they still occurred only at night. Functional MRI at that age showed that speech was still located on the left hemisphere.
- The two remaining patients with initial response (cases # 5 and 8) later relapsed, after the end of steroid therapy. The first one (case # 5) experienced total remission of epilepsy for 3 years, but relapsed 7 months after withdrawal of steroids. Seizures progressively became weekly, then several times a week with drop attacks, and then with repeated episodes of status epilepticus. The injuries produced by the drop attacks and the repeated episodes of status epilepticus requiring admission to hospital, precipitated the decision of disconnection of the affected hemisphere. Right hemispherotomy was performed at the age of 15. On the last examination, she was 18 years old, seizure-free since 3 years and without antiepileptic drugs. She had left hemiplegia, could walk alone and followed rehabilitation program.

Table 4 Course after surgery

Patient/ Sex	Age at onset (y)	Age at surgery (y)	Current Age (y)	AED treatment withdrawn after surgery	Follow up after surgery
1/M	2	4	12	No	8 y
2/M	6	13	15	Yes	2 y
3/M	6	9	14	Yes	5 y
4/F	3	4	11	Yes	7 y
5 /F	8	15	18	No	3 y
6/F	3	5	13	No	7 y
7/F	9	12	12.5	Yes	6 m
8/F	3	14	16	No	2 y
9/M	14	—	Death	No	Sudden death at 21 y
10/M	9	—	Death	No	Sudden death at 16 y
11/F	3	—	14	NA	NA

F: female; M: male; y: years; m: months.

- The second patient (case # 8) remained totally seizure-free for 4 years. Progressively, she experienced a slow and continuous relapse of RE, with hemianopsia, progressive motor deficit leading to left hemiparesis and recurrence of complex partial seizures and atonic falls that prevented her from walking alone. Hemispherotomy was performed at the age of 14 years. She was 16 years old at the last examination, and has been seizure-free since 2 years without antiepileptic drugs. She had left hemiplegia, walked alone and followed a rehabilitation program.

The mean age of the patients with a sustained response to steroids was 7.4 years compared to 4.8 years for the patients who relapsed before 6 months ($p < 0.02$). However, we did not find any correlation between the steroid treatment schedule and long term outcome: the mean time passed to steroids was respectively 10.2 months and 11 months for the two groups of patients without any statistical difference; there was no difference between the mean bolus steroids duration between the two groups (12.8 months versus 9 months), although the total duration was different with 33 months versus 17.2 months; the 8/11 patients early treated had either no improvement or severe late relapse independently of the steroid regimen and lag.

Discussion

This retrospective study addressing the long term evolution of RE after steroid treatment provides interesting data about the benefits and the limits of this therapy, and raises a number of issues.

These data suggest that steroid treatment may benefit to half the patients from the beginning, with recovery of motor function and good control of a very devastating epilepsy, permitting them to recover the ability to return to school. For the patients who do not benefit from steroid treatment from the beginning, surgery soon becomes an option because the motor deficit permits disconnection of the affected hemisphere without evidence of further defect.[14,15]

However, for the patients who benefit initially, long term benefit of steroids remains questionable. Indeed, in some cases (2/5 in our series), steroid response is transient with progressive seizure relapse and the need to proceed to surgery later in life, during adolescence, at an age at which the disconnexion of one hemisphere is likely to be perceived much more negatively.[14,16]

Whether progressive relapse is an expression of steroids tolerance or a consequence of decrease of steroids doses remains to be determined. However, longer steroids treatment with high doses might contribute to more side effects than we observed in our series. In the future, the development of new immunomodulatory treatment, such as Tacrolimus, might give new options for RE patients with initial remission under steroids.

Following an initial benefit of steroids, some patients were found dead in their beds, with no evidence that a seizure was responsible of this outcome. Epilepsy was under control with rare seizures, no episodes of status epilepticus, and no evidence of steroid deficiency syndrome. SUDEP occurs more likely during sleep, and is a well identified problem for patients with epilepsy. Although the literature suggests that SUDEP is more frequent in patients with severe epilepsy than in the general population, no correlation has been found with seizure frequency suggesting that unknown clinical indices may be important.[17]

By the end of the study, only one of the five responders was still under relative control at the age of 12 years, with rare nocturnal seizures, no motor defect although there was some right hand neglect. Since functional MRI showed location of speech area on the affected left hemisphere, there could be no indication for hemispherotomy at this age.

As previously recommended, steroid protocols were started less than 1 year following the first seizures in most cases, during the acute phase of RE that is the stage of active inflammation. In late stages, inflammation is no longer pronounced and irreversible tissue damage has already taken place.[5,12,18] Nevertheless, we did not find any correlation between the steroid treatment schedule and long term outcome.

Recently, the pathophysiologic concepts of RE have evolved, giving new insight into the mechanisms of action of steroids in RE.[10] According to this model, the pathogenic process is initiated by a focal event, such as a viral infection and/or other immune mediated brain damage.[19] After the disease process has begun, MHC-1 restricted antigen presentation and the entry of activated cytotoxic T lymphocytes (CTLs) into the brain would lead to an attack against neurons. The inflammatory process, including the release of soluble mediators like cytokines, causes a spread of the inflammatory reaction with recruitment of more inflammatory cells, including CTLs.[9,20,21] The release of Granzyme B by CTLs may cleave insufficiently glycosylated GluR3 (subunit 3 of the ionotropic glutamate receptor) in a way that gives rise to the generation of antibodies which by themselves may lead to an antibody mediated ''second way of attack''.[22,23]

Based on this pathophysiological scheme, high doses of corticosteroids may have many mechanisms of action that modulate both humoral and cellular immune processes.[11,12] They also have an anti-inflammatory effect. They may repair the blood brain barrier and as a result, could induce the decrease of entry of activated CTLs into the CNS. Finally, corticosteroids have a minor anti-epileptic effect.[11,12]

Our data show that steroids do not give a sustained effect on the course of childhood RE since at least 8/11 treated with high doses steroids experienced short or long term relapse. Initial results were encouraging especially for adolescents, long term evolution with steroid treatment resembles to the natural evolution of the process, since after an initial silent period, patient relapse with the same clinical feature.[1,2]

In the literature, two main studies report some encouraging results of steroids on childhood RE. Hart et al. reported 8 out of 17 patients with a favorable response having greater than 50% reduction in seizure frequency, while 2 other patients showed a 25% reduction in seizure frequency.[13] Similarly, Chinchilla reported 7/8 positive initial response to steroid treatment.[12] The response involved seizure reduction and improvement of focal deficit within 6 months. Five patients experienced a lasting effect although they had periodic episodes of transient relapse with extent of EPC and motor deficit. In this series, only 1/7 patients with EPC had persistent long term response to steroids. However, follow-up was very short in both series, less than one year in Hart's series,[13] and 42 months in average in Chinchilla's series.[12] The long term follow-up that we present shows that the prolonged course leads to surgery in nearly all the patients because of later relapse of EPC.

Our findings suggest that a long term follow-up is needed before assessing the efficacy of one drug or one protocol in RE. Early results should be reviewed some years later before concluding to the efficacy of one protocol.

Given the diversity of treatment schedule in our series and the lack of comparative data we can only refer to the previous strategy that consists of series of intravenous bolus of methylprednisolone together with oral prednisone as an early treatment, within the 2—6 first months of evolution. For the long term treatment, evaluations of immunomodulatory treatment are in process and might give new perspective in the RE.

Conclusion

Corticosteroids can be a useful treatment of RE, when started in the active phase of the disease, less than 2 years after the first signs. However, with the schedule we used steroid therapy did not produce long lasting recovery. In many cases, long term relapse can occur, leading to delayed hemispheric disconnection. New strategies for treatment of RE are therefore requested, for both control of seizures and prevention of the almost inevitable neurological deterioration.

References

1. Rasmussen TB, Olszewski J, Lloyd-Smith D. Focal seizures due chronic localized encephalitis. *Neurology* 1958;**8**:435—45.
2. Bien CG, Widman G, Urbach H, Sassen R, Kuczaty S, Wiestler OD, et al. The natural history of Rasmussen's encephalitis. *Brain* 2002;**125**:1751—9.
3. Dulac O, Dravet C, Plouin P, Bureau M, Ponsot G, Gerbaut L, et al. Nosological aspects of epilepsia partialis continua in children. *Arch Fr Pediatr* 1983;**40**:689—95.
4. Yacubian EM, Marie SK, Valerio RM, Jorge CL, Yamaga L, Buchpiguel CA. Neuroimaging findings in Rasmussen's syndrome. *J Neuroimaging* 1997;**7**:16—22.
5. Bien CG, Urbach H, Deckert M, Schramm J, Wiestler OD, Lassmann H, et al. Diagnosis and staging of Rasmussen's encephalitis by serial MRI and histopathology. *Neurology* 2002;**58**:250—7.
6. Farrell MA, Droogan O, Secor DL, Poukens V, Quinn B, Vinters HV. Chronic encephalitis associated with epilepsy: immunohistochemical and ultrastructural studies. *Acta Neuropathol (Berl)* 1995;**89**:313—21.
7. Andermann F, Hart Y. Rasmussen's syndrome, with particular reference to cerebral plasticity: a tribute to Frank Morrell. *Int Rev Neurobiol* 2001;**45**:173—208.
8. Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. *Science* 1994;**265**:648—51.
9. Bien CG, Bauer J, Deckwerth TL, Wiendl H, Deckert M, Wiestler OD, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. *Ann Neurol* 2002;**51**:311—8.
10. Bien CG, Elger CE, Wiendl H. Advances in pathogenic concepts and therapeutic agents in Rasmussen's encephalitis. *Expert Opin Investig Drugs* 2002;**11**:981—9.
11. Dulac O, Robain O, Chiron C, Plouin P. High-dose steroid treatment of epilepsia partialis continua due to chronic focal encephalitis. In: Andermann F, editor. *Chronic encephalitis and epilepsy. Rasmussen's syndrome*. Boston: Butterworth-Heinemann; 1991.
12. Chinchilla D, Dulac O, Robain O, Plouin P, Ponsot G, Pinel JF, et al. Reappraisal of Rasmussen's syndrome with special emphasis on treatment with high doses of steroids. *J Neurol Neurosurg Psychiatry* 1994;**57**:1325—33.
13. Hart YM, Cortez M, Andermann F, Hwang P, Fish DR, Dulac O, et al. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients. *Neurology* 1994;**44**:1030—6.
14. Caplan R, Curtiss S, Chugani HT, Vinters HV. Pediatric Rasmussen encephalitis: social communication, language, PET and pathology before and after hemispherectomy. *Brain Cogn* 1996;**32**:45—66.
15. Maehara T, Shimizu H, Kawai K, Shigetomo R, Tamagawa K, Yamada T, et al. Postoperative development of children after hemispherotomy. *Brain Dev* 2002;**24**:155—60.

16. Pulsifer MB, Brandt J, Salorio CF, Vining EPG, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. *Epilepsia* 2004;**45**:243—54.
17. Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure* 2003;**12**:456—64.
18. Oguni H, Andermann F, Rasmussen TB. The natural history of the syndrome of chronic encephalitis and epilepsy: a study of the MNI series of forty-eight cases. In: Andermann F, editor. *Chronic encephalitis and epilepsy. Rasmussen's syndrome*. Boston: Butterworth-Heinemann; 1991.
19. Koustova E, Sei Y, Fossom L, Wei ML, Usherwood PN, Keele NB, et al. LP-BM5 virus-infected mice produce activating autoantibodies to the AMPA receptor. *J Clin Invest* 2001;**107**:737—44.
20. Levite M, Fleidervish IA, Schwarz A, Pelled D, Futerman AH. Autoantibodies to the glutamate receptor kill neurons via activation of the receptor ion channel. *J Autoimmun* 1999;**13**:61—72.
21. Ganor Y, Besser M, Ben-Zakay N, Unger T, Levite M. Human T cells express a functional ionotropic glutamate receptor GluR3, and glutamate by itself triggers integrin-mediated adhesion to laminin and fibronectin and chemotactic migration. *J Immunol* 2003;**170**:4362—72.
22. Gahring L, Carlson NG, Meyer EL, Rogers SW. Granzyme B proteolysis of a neuronal glutamate receptor generates an autoantigen and is modulated by glycosylation. *J Immunol* 2001;**166**:1433—8.
23. Andrade F, Casciola-Rosen LA, Rosen A. Granzyme B-induced cell death. *Acta Haematol* 2004;**111**:28—41.