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REVIEW

Treatment of Rasmussen encephalitis half a century after its initial description: Promising prospects and a dilemma

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Summary   Rasmussen encephalitis (RE), initially described half a century ago, is an inflammatory unihemispheric brain disorder. Its two clinical key facets are the progressive tissue and function loss and the epilepsy, often in form of epilepsia partialis continua. For both, treatment options are available. Anti-seizure effect of anti-epilepsy drugs is usually limited to secondarily generalized seizures and complex partial seizures whereas epilepsia partialis continua usually is totally refractory. Hemispherectomy in one of its modern variants offers a very high chance of seizure freedom, however at the price of irreversible loss of functions located in the affected hemisphere. In a proportion of patients, long-term immunotherapy is able to prevent or slow down hemispheric tissue loss and the associated functional decline. It does, however, mostly not improve the epilepsy. Whereas for many patients unequivocal treatment proposals can be readily made, a dilemma may emerge in those with severe epilepsy but still preserved hemispheric function.
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Contents

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Introduction

Half a century ago, three physicians from the Montreal Neurological Institute — the neurosurgeon Theodore Rasmussen, the neuropathologist Jerzy Olszewski, and the neurologist Donald Lloyd-Smith — reported on three patients who suffered from, as these authors summarized, ''focal seizures due to chronic localized encephalitis'' (Rasmussen et al., 1958). This index publication is indeed a ''classic paper''. In an exemplary way, it assembles the viewpoints of three key disciplines concerned with the disorder (today to be amended by neuroradiology and neuroimmunology). The authors masterly describe the key features of presentation and course of the disorder, its neuropathology and the effect of conservative and surgical treatments. Since the late 1980s, most researchers and clinicians have adopted the term Rasmussen encephalitis (RE) or Rasmussen syndrome for this condition (Piatt et al., 1988; Andermann, 1991).

What did Rasmussen and co-workers — and other researchers after them — observe clinically, and which pathogenic and therapeutic insights have been made available since 1958?

RE is a rare disease. Information on its frequency and occurrence may, however, be deduced from existing case reports and patient series. Patients with the disease from different parts of the world have been published, mostly from Northern America and Europe, but also from South America (Yacubian et al., 1997), Australia (Vadlamudi et al., 2000) and different parts of Asia (Korn-Lubetzki et al., 2004; Yang and Luan, 2004; Tekgul et al., 2005; Deb et al., 2005; Takahashi et al., 2006). It is estimated that two new cases are identified in large epilepsy centres per year. Gender predominance has not been noted.

RE is — in almost all patients — a disease of one cerebral hemisphere, which undergoes progressive atrophy. It mainly but not exclusively affects children. The typical disease course can be described as follows (Oguni et al., 1992; Bien et al., 2002c; Chiapparini et al., 2003): After a variable ''prodromal period'' characterized by relatively minor disease signs and symptoms, the patient enters the ''acute stage''. This is characterized by a progressive decline of functions associated with the affected hemisphere, i.e. hemiparesis, hemianopia, cognitive deterioration and (if the dominant side is affected) aphasia. Often, patients experience frequent intractable unilateral simple partial focal motor seizures, complex partial seizures or secondarily generalized seizures. Epilepsia partialis continua (EPC), i.e., unilateral myoclonic twitching of the distal extremities or the face for at least 1 h and with intervals of no more than ten seconds (Thomas et al., 1977), is observed in approximately half of the patients. Cases with very few or even no seizures at all have been observed (Korn-Lubetzki et al., 2004; Bien et al., 2007). After an average period of 8 months, most of the functional decline is over, and the patient passes into the ''residual stage'' with a stable neurological deficit. During this stage, seizure frequency is still high but lower compared to the acute stage.

Brain pathology of RE is characterized by infiltration of T lymphocytes, neuronal loss, microglia activation, microglial nodules, and astrogliosis (Rasmussen et al., 1958; Robitaille, 1991; Farrell et al., 1995; Pardo et al., 2004). In their index paper, Rasmussen and co-workers suggested a slow-virus infection as the causative factor. Despite several studies along this route, a causal association of RE with a specific virus has not been established [for a summary of the respective literature, see Bien et al. (2005)]. This, however, does not mean that the possibility of a viral etiology has been excluded (Theodore et al., 2008).

Another mechanism potentially involved in the pathology of RE may be an antibody-mediated immune response directed to antigens of brain resident cells. Antibodies to subunit 3 of the AMPA receptor (GluR3 antibodies) had been suggested to dominate pathogenesis. More recent work, however, revealed that they are neither a sensitive nor a specific marker of RE (Wiendl et al., 2001; Mantegazza et al., 2002; Watson et al., 2004). Nevertheless, plasmapheresis and immunoabsorption have beneficial effects in some patients. Therefore, non-GluR3 directed antibodies may contribute to the pathogenesis in some patients. Recently, antibodies to the neuronal alpha7 acetylcholine receptor (Watson et al., 2005) and to the presynaptic protein Munc18-1 have been suggested as potential candidates (Alvarez-Baron et al., 2008).

Most robust evidence, however, links RE pathogenesis to cytotoxic T cells causing apoptotic death of neurons and astrocytes (but not oligodendrocytes or myelin). The intraparenchymatous density of T lymphocytes is inversely correlated with disease duration (Bien et al., 2002b). About 10% of the T cells in the inflammatory lesions are Granzyme-B positive cytotoxic T lymphocytes (Bien et al., 2002a). Part of these cells are found in close apposition to neurons (Bien et al., 2002a) and astrocytes (Bauer et al., 2007). Their Granzyme-B containing cytotoxic granules are oriented towards neural or astrocytic membranes. Cytotoxic attacks due to release of Granzyme-B result in the apoptotic death of neurons and astrocytes. The T cells in RE brains have expanded from oligoconal precursor T cells. This suggests a specific immune-reaction directed to a few specific antigenic epitopes (Li et al., 1997). Spectratyping analysis of T cell receptors reveals clonal expansions of distinct subsets of CD8 positive T cells in blood and brain tissue of RE. Upon immunohistochemical testing of brain tissue,

V-beta specific T cells containing the cytotoxic molecule granzyme B and lying in close appositions to NeuN+ neurons and GFAP+ astrocytes indicating that indeed the expanded T cells contribute to pathogenesis of RE. Longitudinal analysis of peripheral blood samples showed dominance but also longitudinal persistence of specific CD8 T-cell clones over time. Taken together, data suggested a cytotoxic T cell reaction to a common driving antigen or several antigens without shared clones (Schwab et al., 2009). The protein/s containing these antigenic epitopes, however, is/are still not known.

For definite diagnosis of RE, consensus criteria as reproduced in Table 1 have been proposed (Bien et al., 2005). They have been used in subsequent studies and are a valuable and valid tool in clinical practice.

Epilepsy and functional decline: the two faces of RE

The clinical phenotype of RE is dominated by two aspects: the functional decline on the one hand and the epilepsy on the other hand. At some time during the early disease course, there may be an overlap between these two when unilateral motor seizures cause a transient postictal paresis. With time, however, fixed motor, sensory, visual field and — if the dominant hemisphere is affected — language deficits come about. There are interindividual differences in the endpoints of neurological deficits after several years of disease duration (Bien et al., 2002c). As a rule of thumb: the earlier the disease starts, the more severe the outcome in terms of functional decline is (Hart et al., 1997; Bien et al., 2002c; Villani et al., 2006). Epilepsy, too, can be of interindividually different severity. On the one end, there are the patients with highly distressing and handicapping pharmacoresistant EPC. On the other end, there are patients with mild, infrequent or even absent seizures (Korn-Lubetzki et al., 2004; Bien et al., 2007). So far, no prognostic markers for the evolution of epilepsy severity have been proposed. Our experience with patients undergoing long-term immunotherapy is as follows: the severity of epilepsy during the early disease course — as graded according to the Baltimore ''Burden of disease'' scale (Vining et al., 1997) — in most patients predicts the severity of epilepsy a few years later (Bien, in preparation).

A summary on the ''two faces'' of RE — functional decline and epilepsy — is given in Table 2.

Therapeutic principles

In contrast to a common belief, RE is a disorder with several, in part very promising, therapeutic options. In accordance with the previous considerations, the ''two faces'' of RE need to be addressed by different treatment approaches:

Table 1 Diagnostic criteria for Rasmussen encephalitis [reproduced with permission from Bien et al. (2005)]. RE can be diagnosed if either all three criteria of part *A* or two out of three criteria of *B* are present. Check first for the features of part *A*, then, if these are not fulfilled, of part *B*. In addition: if no biopsy is performed, MRI with administration of gadolinium and cranial CT needs to be performed to document the absence of gadolinium enhancement and calcifications to exclude the differential diagnosis of a unihemispheric vasculitis (Derry et al., 2002).

Part A		
1.	Clinical	Focal seizures (with or without Epilepsia partialis continua)
		and
		unilateral cortical deficit(s)
2.	EEG	Unihemispheric slowing with or without epileptiform activity
		and
		unilateral seizure onset
3.	MRI	(1) Unihemispheric focal cortical atrophy *and at least one of the following:*
		(2) Gray or white matter signal T2/FLAIR hyperintense signal
		(3) Hyperintense signal or atrophy of the ipsilateral caudate head
Part B		
1.	Clinical	Epilepsia partialis continua
		or
		progressive[a] unilateral cortical deficit(s)
2.	MRI	Progressive[a] unihemispheric focal cortical atrophy
3.	Histopathology	T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis
		Numerous parenchymal macrophages, B cells or plasma cells or positive signs of viral infections (viral inclusion bodies or immunohistochemical demonstration of viral protein) exclude the diagnosis of RE

[a] ''Progressive'' means that at least two sequential clinical examinations or MRI studies documenting increasing deficits or tissue loss are required to meet the respective criteria.

Table 2 The ''two faces'' of RE.

	Progressive neurological deficit	Epilepsy
Underlying cause	Progressive cerebral hemiatrophy, caused by chronic inflammation	Lesion-related + not further determined pro-epileptic (immunologic?) factor
Duration	8—12 months	Whole disease duration
Additional remarks	Decline in children more severe than in adolescents and adults	RE cases without epilepsy occur
Therapeutic options	Long-term immuno-tx	AEDs ''Short-term high-intensity'' immuno-tx HE

tx: therapy.

Firstly, epileptic seizures shall be controlled, and secondly, the progressive tissue loss during the acute disease stage shall be counteracted in order to improve the functional long-term outcome of the patients. These treatment aims and approaches are summarized in Table 3. In our experience, the two most frequent sources of therapeutic disappointment are (1) ambiguity regarding the therapeutic aims of a given intervention and (2) underuse of treatment options.

Severity and rarity of the disorder are the reasons why up to now no prospective controlled treatment data have been published. However, trials are underway and may guide treatment decisions in the near future (see Section ''Pharmacological prevention of functional decline'').

Seizure treatment

Anti-epilepsy pharmacotherapy
Published data on the effect of anti-epilepsy drugs (AEDs) in RE are from the 1980s to 1990s. The drugs available at this time have consistently been found to be ineffective against EPC, but to have some effect against the other seizure types (Piatt et al., 1988; Dubeau and Sherwin, 1991; Topcu et al., 1999). No anticonvulsive mono- or combination-therapy has been described to be superior to other regimens (Dubeau and Sherwin, 1991). Since these studies, several new AEDs have been licensed. Of note, no data indicating higher efficacy of these drugs in RE compared to the older ones have been published. As with other difficult to treat epilepsies, however, improved tolerability and a reduced potential for pharmacokinetic interactions will often argue in favor of the new compounds. The latter point may be of particular importance if long-term immunotreatment is applied (see Section ''Pharmacological prevention of functional decline''). Enzyme-inducing drugs reduce blood-levels of corticosteroids and tacrolimus; enzyme-inhibiting drugs, on the other hand, confer the risk of tacrolimus intoxication and encephalopathy. Substances with high albumin bound fraction may be difficult to keep at a constant blood level if in parallel with plasma exchange. As a general rule, number and dose of AEDs should be kept as low as possible, i.e., one should try to abolish secondarily generalized tonic-clonic and, possibly, complex partial seizures; EPC, however, is almost never suppressed by AEDs and it provides little benefit to the patients if one tries to suppress this focal motor status epilepticus. In cases of localised EPC, botulinum toxin

has been successfully injected (Lozsadi et al., 2004; Browner et al., 2006).

''Short-term intense'' immunotherapy for alleviation of seizures
In some cases, a beneficial anti-seizure effect has been reported for steroid boluses or plasma exchange (PEX) with subsequent maintenance therapy at reduced doses or PEX intervals (Granata et al., 2003). Intravenous immunoglobulins (IVIG), too, have been reported to be effective against seizures in RE (Walsh, 1991), best described in adults (Leach et al., 1999). It is unclear, however, how often a sustained effect against seizures can be achieved by these means (Vining, 2006).

### Presurgical assessment and surgical epilepsy therapy
Types of epilepsy surgery in RE. Only one epilepsy surgery approach is effective in RE: hemispherectomy, either performed in the traditional meaning of anatomical hemispherectomy or in one of the modern variants (in the following, all surgical types are abbreviated to HE). Advanced variants of HE, often collectively referred to as ''functional HE'' techniques (Binder and Schramm, 2006), are disconnetive rather than resective in nature (Oppenheimer and Griffith, 1966; Rasmussen, 1993; Villemure et al., 2000; Schramm et al., 2001; Delalande et al., 2007; Schramm, 2008). The classic technique was anatomic HE which was replaced in the early 1980s by Rasmussen's functional HE technique. This included removal of two larger brain segments, i.e. a central suprasylvian tissue block and the temporal lobe and a combination of disconnection procedures (callosotomy and disconnection of frontal, occipital, and parietal lobe). Since considerable late mortality was observed in anatomic HE, to a considerably lesser degree also in functional HE, several centers independently developed newer techniques in the 1990s. The basic principle of the modern techniques is to replace resection by disconnection. In the so-called perisylvian techniques parts of the temporal lobe and parts or all of the operculum are resected and these resections are combined with disconnection of the frontal, parietal, and occipital lobe, and a callosotomy. Two techniques resect very little brain indeed, and mostly disconnect: Delalande's vertical hemispherotomy and Schramm's keyhole transsylvian hemispherotomy. See a detailed review in Schramm (2002). The modern disconnective hemispherotomy procedures are associated with shorter operation times, less blood loss, less intraoperative

Table 3 Principle treatment aims and options.

	Realistic therapeutic aim	Particular recommendation	Side effects	Further remarks
Anti-seizure treatment				
AEDs	Suppression of CPS and SGTCS	Non-enzyme inducing or inhibiting drugs preferable in case of immunotherapy	If ≥2 AEDs: frequently sedation, ataxia, diplopia, tremor	No effect on functional decline. EPC particularly resistant to AEDs
Epilepsy surgery	Seizure freedom	Only HE effective	Hemiplegia, hemianopia, aphasia (if language dominant hemisphere is disconnected)	Secondary affection of contralateral side after HE has never been reported
''Short-term high-intensity'' immuno-tx	Improved seizure control	High-dose steroids, IVIG (especially adults), PEX	In case of response, this tx may become a long-term option	Seizure reduction should be evident within days to weeks; if not, the ''short-term'' immuno-tx should be discontinued
Prevention of structural and functional decline				
Long-term immuno-tx	Prevention of structural and functional decline	Tacrolimus, IVIG, long-term oral steroids, repeated PEX. Relative effect indeterminate, prospective study underway	Substance specific	Usually not effective against seizures

Abbreviations in alphabetical order—AED: anti-epilepsy drug; CPS: complex-partial seizures; EPC: Epilepsia partialis continua; HE: hemispherectomy in one of its modern variants; IVIG: intravenous immunoglobulins; PEX: therapeutic plasma exchange; SGTCS: secondarily generalized seizures; tx: therapy.
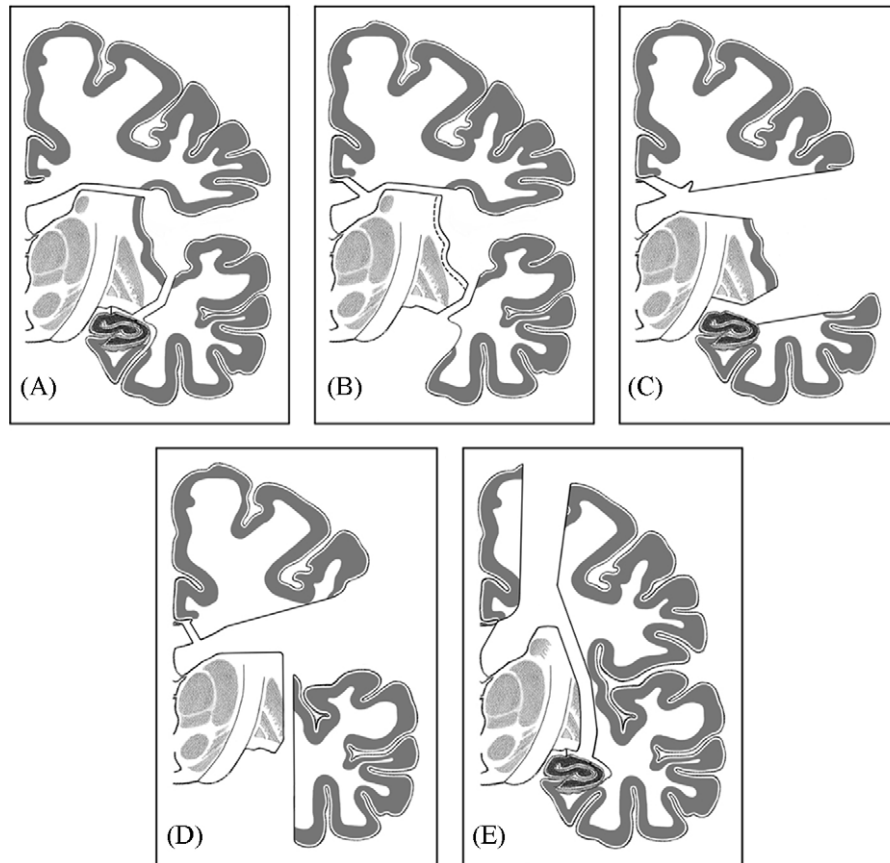
Figure 1   Modified functional hemispherectomy techniques. (A) Trans-sylvian trans-sulcal keyhole approach to ventricle. (B) Second part in trans-sylvian key hole approach: temporomesial resection, mesial disconnection, and insular cortex removal. (C) Peri-insular window technique. (D) Variant of peri-insular window technique. (E) Dorsal transcortical subinsular hemispherotomy.

complications, and most likely a lower rate of hydro-cephalus. It should be noted that anatomic HEs, functional HEs, hemispherotomies or hemispheric deafferentation procedures are all similarly effective, if performed correctly (Cook et al., 2004). For a graphic illustration and a schematic overview of the different techniques, see Figs. 1 and 2. In most series, RE patients achieve a seizure freedom rate of >70% after HE (Honavar et al., 1992; Vining et al., 1997;

Figure 2   From hemispherectomy to hemispherotomy.

Delalande and Bulteau, 2002; Granata et al., 2003; Devlin et al., 2003; Kossoff et al., 2003; Pulsifer et al., 2004; Delalande et al., 2007). Our total series of 111 cases so far included 15 cases with Rasmussen's encephalitis. There had been 1 death from an unrelated traffic accident as a pedestrian and 2 cases with unavailable follow-up. Seizure outcome in the 12 remaining cases was 85.7% Engel class I. For more details see Schramm (in press). These seizure-free outcome rates are higher than that of the average of epilepsy surgical patients (Tellez-Zenteno et al., 2005). Of note, any type of more focal resections (instead of HE) has at best lead to transient seizure freedom (Olivier, 1991).

The Baltimore group has emphasized the improvement of the general condition and state of health in RE patients with severe epilepsies after HE as documented by quality of life measures or improvements in the performance on IQ tests; these beneficial effects are certainly in part due to alleviation of the AED burden possible after successful HE (Vining et al., 1997; Pulsifer et al., 2004). The elimination of continuous epileptiform discharges transmitted to the healthy hemisphere (Elger et al., 2004) may be another beneficial effect of HE.

Presurgical assessment of patients with RE.   Presurgical evaluation for hemispherectomy should be performed in all patients with pharmacoresistant and handicapping seizures due to RE. Some special considerations during this presurgical assessment arise from the fact that RE represents the

Figure 3   Therapeutic pathway in unilateral (typical) RE [reproduced with permission from Bien et al. (2005)]. HE: hemispherectomy in one of its modern variants. Numbers 1—11 refer to the explanations in the original text (Bien et al., 2005).

alternative (Thilo et al., in press); a formal trial is underway (Laxer, 2008). In randomized prospective trial, tacrolimus and IVIG are compared (Bien, 2008). Results of such studies are expected to better determine the relative efficacy of the above-mentioned immunointerventions.

During long-term immunotherapies, regular follow-up investigations are required to detect a potential disease progress or side effects as early as possible. If long-term immunotherapy is successful, i.e. that no or only minor disease progression occurs, it should be continued — for how long, however, is an open question. One might tentatively estimate that it would be reasonable to continue treatment until a patient's condition has been stable for at least 3—5 years, and then to taper carefully if the patient wishes.

Treatment choice for the individual patient situation

In the European consensus statement on RE, a therapeutic pathway for any patient with the diagnosis of RE — see Fig. 3 — has been suggested (Bien et al., 2005). As a further development and illustration of that scheme, we display characteristic treatment decision situations for RE patients in Table 4. They are arranged according to the two afore mentioned key aspects of RE, i.e. ''severity of epilepsy'' and ''severity of neurological deficit'' (in relation to the deficit to be expected as a result of HE). The resulting ''standard situations'' A—D are discussed in the following. This is done under the assumption of the diagnosis of typical unilateral RE.

Mild or absent epilepsy, with progressed functional deficit

A low dose AED therapy will usually suffice in these cases. If complete seizure freedom cannot be achieved but is a major goal of the patient, HE can be offered.

Handicapping epilepsy, and no findings predicting a relevant post-HE deterioration

Here, HE is clearly the treatment of choice. The patient and his family needs to be informed about the general risks of the procedure.

Mild or absent epilepsy with limited neurological deficit

If the patient is still in the acute disease stage, i.e., has recently experienced a functional decline (C1), this is certainly the ideal situation for long-term immunotherapy. The epilepsy is no or only a minor problem, and the functional decline may be stopped or at least slowed down by the immunotreatment.

If, however, the patient is already in the residual stage (i.e., no functional decline within the previous 6 months or so, C2), initiation of immunotherapy is no longer recommended.

Handicapping epilepsy, but prediction of significant functional deterioration after HE

This is certainly the most problematic situation. Early institution of long-term immunotherapy is recommended to prevent functional decline. If seizures remain severe and disabling, additional ''short-term/intense'' immunotherapy should be tried (e.g., an i.v. pulse of several days of methylprednisolone at 20 mg/(kg day) in children or 500—1000 mg/day in adults, or PEX, or IVIG). If no satisfying effect is achieved, this add-on immunotherapy should be discontinued, and the option of HE should be considered as discussed above. We have encountered several patients, in which immunotherapy stopped the functional decline but who continued having frequent, handicapping seizures for years (Bien, in preparation). In these patients, ''successful'' immunotherapy has apparently created a pre-

Table 4 Therapeutic approach to the individual RE patient considering his neurological function and severity of epilepsy.

Significant functional deterioration by HE expected?	Mild or absent epilepsy		Handicapping epilepsy
No (i.e., significant deficit already present)	**A** 1 AED or HE		**B** HE
Yes (i.e., no high-grade deficit present)	**C1** *Ongoing functional decline* Long-term immuno-tx	**C2** *No decline during last 6-12 months* 1 AED	**D** Long-term immuno-tx *plus* ≤2 AED If seizures remain intolerable: 1. Try "short-time/intense" immuno-tx for seizure alleviation 2. Consider HE

AED: anti-epilepsy drug; HE: hemispherectomy in one of its modern variants; tx: treatment. The lettering A, B, C1, C2, D is taken up in the text Section ''Treatment choice for the individual patient situation''.

viously unknown dilemma: The effect of one treatment — preservation of function — generates a contraindication to another highly effective therapy: to HE with its high anti-seizure efficacy. In our experience, the most appropriate way to deal with this is as follows: The severity of each of the expected deficits after HE should be weighed in relation to the severity of epilepsy. This requires extensive and in-depth discussions with the patient and his family. Whereas the prediction of postoperative aphasia in a still communicable child (RE of the language dominant hemisphere) will usually preclude surgery, the perspective of a fixed dense hemiparesis with preserved walking abilities may be an acceptable price for seizure freedom. This is particularly clear in cases, in which continuous or near-continuous motor seizures impair hand and leg function anyway. Regardless of the affected side, the probably least relevant consequence of HE is hemianopia, which is usually well compensated in everyday life. In conclusion, especially in patients with impairing seizures and affection of the non-dominant hemisphere, HE will often emerge as the superior long-term option compared to ongoing conservative treatment.

Summary

RE has two clinical key ''faces'' that may become a burden to affected patients: the epilepsy and the progressive neurological dysfunction. For both aspects, powerful treatment options have emerged: HE against seizures, and long-term immunotherapy against structural and functional deterioration. The most severe disease constellation in RE is the following: a patient with still largely preserved function of the affected hemisphere in the presence of severe epilepsy. Such a constellation often leads the treating clinician into a therapeutic dilemma: HE is usually discarded because of

the inevitable postoperative functional deficits; successful immunotherapy, on the other hand, may stabilize not only the functional properties but at the same time the severe seizure propensity. Such situations should not be considered absolute contraindications to HE. Rather, individual treatment decisions including the surgical option should be made after thorough discussion with the patient and his family. Such decisions should weigh the severity of deficits to be expected after HE in relation to the severity of epilepsy and the consequences of its treatment. In such patients with affection of the non-dominant hemisphere and with handicapping epilepsy, HE should be considered relatively early on.

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