JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 4(22): CASE22410, 2022
DOI: 10.3171/CASE22410

Cognitive outcome after left functional hemispherectomy on dominant hemisphere in patients with Rasmussen encephalitis: beyond the myth of aphasia. Patient series

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BACKGROUND Rasmussen encephalitis is a rare chronic neurological pathology frequently treated with functional hemispherectomy (or hemispherotomy). This surgical procedure frees patients of their severe epilepsy associated with the disease but may induce cognitive disorders and notably language alterations after disconnection of the left hemisphere.

OBSERVATIONS The authors describe longitudinally 3 cases of female patients with Rasmussen encephalitis who underwent left hemispherotomy in childhood and benefited from a favorable cognitive outcome. In the first patient, the hemispherotomy occurred at a young age, and the recovery of language and cognitive abilities was rapid and efficient. The second patient benefited from the surgery later in childhood. In addition, she presented a reorganization of language and memory functions that seem to have been at the expense of nonverbal ones. The third patient was a teenager during surgery. She benefited from a more partial cognitive recovery with persistent disorders several years after the surgery.

LESSONS Recovery of cognitive functions, including language, occurs after left hemispherotomy, even when performed late in childhood. Therefore, the surgery should be considered as early as possible to promote intercognitive reorganization.

https://thejns.org/doi/abs/10.3171/CASE22410

KEYWORDS Rasmussen encephalitis; functional hemispherectomy; hemispherotomy; language; reorganization; plasticity

Rasmussen encephalitis is a rare childhood neurological pathology characterized by progressive alteration of the structure and function of an entire cerebral hemisphere with an inexorable installation of drug-resistant epilepsy.[1] After normal development, patients progressively develop unilateral hemispheric atrophy resulting in severe seizures with contralateral hemiparesis and intellectual and cognitive function impairments.[2] The curative treatment is hemispherotomy, a surgical procedure consisting of functional disconnection of the affected hemisphere, allowing favorable seizure and quality-of-life outcomes.[3] Such a surgical decision remains debatable due to the risks of permanent impairment for functions sustained by the affected hemisphere. The most challenging situation is for patients who are candidates for left hemispherotomy, which may lead to aphasia due to the disconnection of the specialized hemisphere for language. These neurological sequelae might constrain the surgical decision,[4] especially for patients older than 5 years old, because language lateralization is already established in the brain[5] and neuroplastic potential tends to decrease.[6]

A large amount of knowledge has shed light on a left hemispheric specialization for language already established at birth.[7] However, in the context of early left-side injury and hemispherotomy, most patients are able to develop normal or subnormal language skills.[8–10] These findings support Lenneberg's[11] theory of a hemispheric equipotentiality for language before the development of left specialization in infancy until adolescence. Altogether, these paradoxical hypotheses suggest that in early development, language networks involve typical left perisylvian regions but also homologous regions in the right hemisphere, allowing its development

ABBREVIATIONS fMRI = functional magnetic resonance imaging; LEXTOMM = Language, Executive Functions, Theory of Mind, Episodic Memory; PIQ = performance intelligence quotient; SD = standard deviation; VIQ = verbal intelligence quotient; WMI = Working Memory Index.

INCLUDE WHEN CITING Published November 28, 2022; DOI: 10.3171/CASE22410.
SUBMITTED September 23, 2022. **ACCEPTED** October 19, 2022.

even in the case of left-side lesions.[12] Moreover, this hemispheric specialization does not deprive the right hemisphere of all language functions.[13] In patients with Rasmussen encephalitis after left hemispherotomy, recovery of normal verbal intelligence efficiency has been highlighted with some dissociation in linguistic profiles, reflecting relative left specialization for language and potential of recovery,[14,15] which may also be based on cognitive reserve.[16] Indeed, premorbid intellectual level and nonverbal functions (including executive abilities) might also be predictors of recovery from aphasia.[17,18]

Considering these theoretical contexts, language and cognitive outcomes of patients with Rasmussen encephalitis who underwent functional hemispherectomy must be analyzed from an interactive perspective. A better understanding of patients' recovery and cognitive status would allow neurosurgeons to better consider operative decisions and rehabilitation methods. Here we present 3 adult patients with Rasmussen encephalitis who underwent left hemispherotomy in childhood. These prospective cases make an important contribution to the study of these issues and illustrate a global, interactive, and dynamic perspective of cognitive outcomes.

Study Description

Participants

Three patients with Rasmussen encephalitis in the left specialized language hemisphere at different periods of childhood development participated in this study. They were female French natives and presented typical cognitive and motor development until epilepsy onset (Table 1). They benefited from a vertical parasagittal hemispherotomy between 2005 and 2013 at a mean age of 9.3 years (standard deviation [SD] 4.3 years) after a similar duration of epilepsy (mean 1.5 years, SD 0.3 years; see Table 1) at the Rothschild Foundation Hospital in Paris and became seizure free after the surgery (Engel class I). Between 2005 and 2021, patients were seen in follow-up for clinical, neuropsychological, and cognitive evaluations (Table 1).

Clinical Neuropsychological and Cognitive Assessment

Clinical neuropsychological and cognitive evaluations were prospectively proposed to assess the cognitive abilities of patients several weeks before the surgery (T1) and 1 or 1.5 (T2), 3 (T3), and more than 8 (T4) years after hemispherotomy. We retrospectively analyzed patients' preoperative and postoperative scores (Table 2).

General intellectual abilities were assessed using age-appropriate Wechsler Intelligence Scales.[19] Scores of the Verbal Comprehension Index or verbal intelligence quotient (VIQ), Perceptual Reasoning Index or nonverbal performance IQ (PIQ), and Working Memory Index (WMI) were reported. Considering the language domain, patients also performed picture naming, semantic, word repetition, and syntactic comprehension tasks from the ELOLA (Evaluation du Langage Oral de L'Enfant Aphasique),[20] BILO (Bilan Informatisé de Langage Oral),[21] or NEPSY[22] batteries, depending on the patient's age and evaluation available. Furthermore, they performed a verbal and nonverbal episodic memory evaluation from the BEM-144 (Batterie d'Efficience Mnésique).[23]

For the last clinical follow-up (T4; Tables 2 and 3), in addition to a neuropsychological evaluation, an in-house computerized cognitive battery was proposed. This battery, called LEXTOMM (Language, Executive Functions, Theory of Mind, Episodic Memory),[24] allows measurement of cognitive performances for language (naming, semantic, phonology, and syntax), executive functions with nonverbal tasks (inhibition, flexibility, and sustained attention), theory of mind (false beliefs attribution), and a control task of visual low-level categorization. All tasks were developed with E-prime 3.0 running on a laptop computer (1,366 × 768 pixels per inch [PPP]). Participants were asked to provide manual responses with their functional hand by pressing a computer mouse, except for the lexical naming task, for which they had to provide oral responses. In parallel, we also examined with the LEXTOMM battery an age-matched control group, including 85 healthy French-speaking adult participants (65 females) between 18 and 30 years old (mean 20.6 years, SD 1.8 years). Task execution was measured in terms of percentage of correct responses and reaction times (in milliseconds).

Data Analyses

Clinical Neuropsychological Evaluation

To determine preserved or impaired cognitive abilities, we compared obtained scores (expressed as z-scores) for patients in each test to the standardized clinical norm (mean 0, SD 1). Specifically, IQ scores were expressed as standard scores (mean 100, SD 15), except for WMI, which was transformed into a z-score. In agreement with clinical practice, an IQ score under 70 or a z-score under −1.65 was considered significantly impaired.[25]

Cognitive LEXTOMM Evaluation

Individual patients' performances for each task were directly compared with the control group's performances with a modified *t* test using Singlims software.[26] The significance threshold was set at 0.05.

Case Descriptions

Patient 1

This female patient presented with a diagnosis of Rasmussen encephalitis at the age of 4.0. Preoperatively, she was right-handed and had a normal psychometric evaluation (VIQ 98, PIQ 111). She experienced an epilepsy aggravation with multiple seizures each

TABLE 1. Demographic and clinical information

Case No.	Sex	Age at Onset (yrs)	Epilepsy Duration	Age at Op	Postoperative FU at Last Evaluation	Age at T1 Preoperative	Age at T2	Age at T3	Age at T4
1	F	4.0	1.5	5.5	13.0	5.5	7.0	9.4	18.5
2	F	7.3	1.2	8.5	15.0	8.5	9.1	10.3	23.4
3	F	12.3	1.8	14.0	8.1	13.11	15.3	17.1	22.1
Mean (SD)		7.8 (4.1)	1.5 (0.3)	9.3 (4.3)	11.1 (3.5)				

FU = follow-up; Op = operation.

TABLE 2. Clinical neuropsychological scores for prehemispherotomy (T1) and posthemispherotomy (T2–T4) evaluations

			IQ		Cognitive z-scores						
Case No.	TA	Age (yrs)	VIQ	PIQ	Naming	Syntax	Phonology	Semantic	Verbal Memory	Nonverbal Memory	Working Memory
1	T1 preoperative	5.5	**IMP**	**IMP**	**IMP**	**IMP**	**IMP**	**IMP**	**IMP**	**IMP**	**IMP**
	T2	7.0	96	90	0.19	0.11	0.11	0.27	0.00	−0.67	−1.60
	T3	9.4	108	84	−1.07	−1.39	0.28	0.23	−1.55	0.71	−1.40
	T4	18.5	102	92	−0.33*	**−1.70***	−0.11*	0.82*	1.50	1.50	−0.60
2	T1 preoperative	8.5	**72**	**IMP**	1.15	**−3.00**	0.33	−0.03	**IMP**	**IMP**	**−2.67**
	T2	9.1	**67**	84	−0.63	**−3.80**	−1.00	1.60	−1.62	NT	**−2.80**
	T3	10.3	83	105	−0.60	0.33	−1.33	0.53	0.55	**−3.05**	**−2.53**
	T4	23.4	107	**68**	2.41*	**−4.43***	**−2.33***	0.82*	0.80	−0.70	**−2.07**
3	T1 preoperative	13.11	78	82	**−4.40**	**−1.80**	**−7.70**	−0.70	**−2.18**	−1.35	**−2.93**
	T2	15.3	**55**	81	**−7.20**	**−1.80**	**−18.00**	−1.60	**−2.85**	−0.09	**−3.33**
	T3	17.1	77	96	**−1.80**	NT	NT	NT	0.10	−0.05	**−2.47**
	T4	22.1	84	86	**−7.87***	**−6.74***	**IMP**	−0.52*	−0.95	−1.45	**−3.00**

IMP = assessment impossible due to the epilepsy severity; NT = not tested; TA = time of assessment.
Scores in boldface indicate clinically impaired scores compared with the norm (IQ mean 100, SD 15; z-score mean 0, SD 1).
* LEXTOMM battery at T4.

day associated with a deterioration of her general condition characterized by progressive right hemiparesis and language regression to aphasia. Preoperatively (T1), she was too impaired by epilepsy to undergo the neuropsychological assessment (Table 2). She benefited from left hemispherotomy at 5.5 years old, 17 months after epilepsy onset. Postoperatively, she presented with mutism, right hemiparesis, and right hemianopsia. She became seizure free and could be weaned from any antiepileptic treatment. A follow-up 18 months after surgery (T2) revealed satisfactory recovery with normal scores for VIQ and nonverbal IQ and all language and memory tasks. However,

TABLE 3. Cognitive LEXTOMM scores in adulthood (T4)

Case No.	Naming	Syntax	Phonology	Semantic	Control Task	Inhibition	Flexibility	Attention	Theory of Mind
1									
ACC	94.17	78.57	86.67	100	100	89.17	100	81.78	100
t-Score	−0.33	**−1.70**	−0.11	0.82	0.92	**−3.48**	0.79	−1.10	1.10
RT	NA	1,561.98	**2,969.92**	577.47	**895.27**	**1,223.98**	1,467.10	469.94	3,201.53
2									
ACC	82.2	61.6	63	100	83	84.17	75	64.67	73.33
t-Score	2.41	**−4.43**	**−2.33**	0.82	**−3.42**	**−5.56**	**−5.73**	**−3.09**	**−3.39**
RT	NA	**1,945.02**	2,054.32	**994.81**	**1,320.48**	**1,044.08**	**4,158.83**	483.4	**3,972**
3									
ACC	76	47.32	IMP	96.88	96.67	87.5	100	50	46.67
t-Score	**−7.87**	**−6.74**	**IMP**	−0.52	0.07	**−4.18**	0.79	**−4.79**	**−7.87**
RT	NA	1,065.28	**IMP**	**867.56**	**1,048.14**	**978.23**	**2,329.58**	**607.75**	**6,689.14**
CG									
ACC (SD)	CG1: 64.05 (7.41); CG2: 94.96 (2.38)	89.1 (6.16)	87.8 (10.6)	98.1 (2.3)	96.4 (3.9)	97.55 (2.39)	96.96 (3.80)	91.29 (8.56)	93.45 (5.89)
RT	NA	1,311.91 (174.22)	1,638.71 (257.05)	659.57 (112.26)	619.21 (104.5)	542.59 (45.53)	1,433.75 (254.96)	421.30 (103.40)	2,266 (694.7)

ACC = accuracy (in terms of percentage of correct responses); CG = control group; CG1 = control group for the naming task used for the patient 2 comparison; CG2 = control group for the naming task used for the patient 1 and the patient 3 comparisons; IMP = impossible to perform the task; NA = not available; RT = reaction time (milliseconds).
Scores in boldface indicate significantly impaired performance compared with a matched healthy control group.

her working memory ability remained subnormal (Table 1 for score details). Furthermore, cognitive recovery progressed for VIQ, as found 3 years postoperatively (T3), highlighting a discrepancy between a normal VIQ and a lower nonverbal IQ. Indeed, cognitive scores were normal, except for syntactic comprehension, verbal declarative memory, and working memory, which remained in the low average range. At 18.5 years old (T4; Table 3), both intellectual and memory efficiencies indicated normalized scores (Fig. 1A and C). Language and executive scores did not differ from those of the control group, except for syntactic and inhibition tasks, in which she was impaired. However, she performed with significantly higher reaction times than control participants on the phonology, inhibition, and visual categorization tasks.

Overall, the patient showed a great progression of all cognitive functions with normal language and memory performance as early as 1.5 years postoperatively, which were maintained in adulthood, despite some specific language and executive deficits (syntax and inhibition respectively, Fig. 2).

Patient 2

This young female patient was diagnosed with Rasmussen encephalitis after epilepsy onset at the age of 7.3 years. She was right-handed and had normal schooling. Epileptic crises were progressively associated with significant degradation of her general functioning with continuous partial epilepsy on her right hemibody and daily right hemiclonic epileptic seizures. She also presented with important language impairments. Preoperatively (T1), only language neuropsychological tests could be administered because of the epilepsy severity (Table 2). Evaluation using motor tasks was impossible to carry out. She presented with subnormal VIQ but normal semantic, phonological, and naming abilities (Fig. 1B). However, she exhibited deficits in syntactic comprehension and working memory (Fig. 1C). She benefited from a left hemispherotomy at 8.5 years old, 14 months after the seizure onset. Postoperatively, the patient became free from seizures and antiepileptic medication. One year after hemispherotomy (T2), her verbal profile was the same as preoperatively. Assessment also noted a weak verbal declarative memory and a normal nonverbal IQ. Three years postoperatively (T3), her intellectual efficiency had improved in both verbal and nonverbal domains (Table 2). Only nonverbal declarative memory and working memory remained clinically impaired. We received her again at the age of 23 (T4) for the last assessment (Fig. 2). A heterogeneous profile of performances was observed. Indeed, she

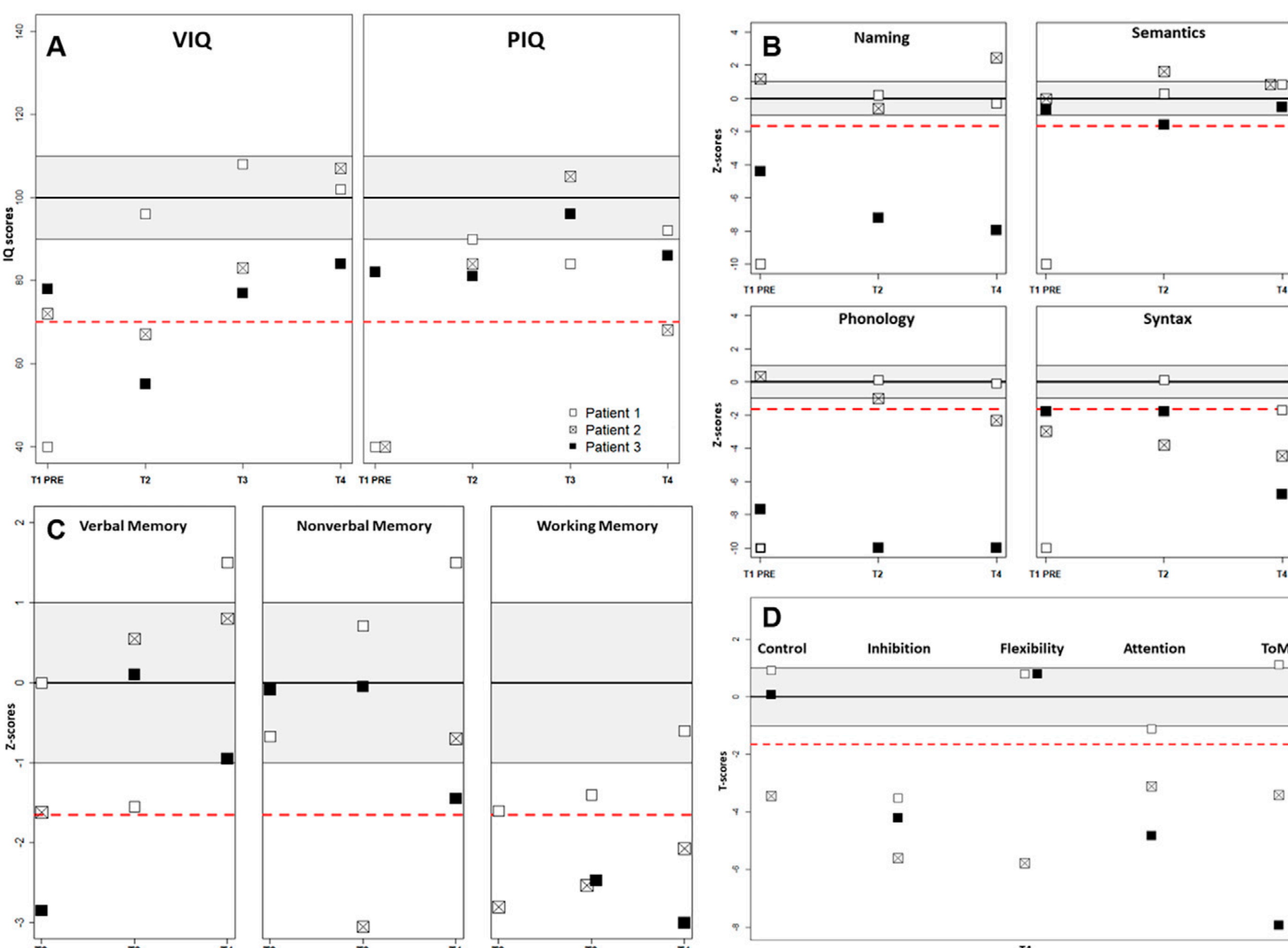

FIG. 1. Performance before (T1) and during the follow-up after left hemispherotomy (T2–T4) for IQ (**A**), language (**B**), memory (**C**), and executive functions (**D**). The *gray area* represents the norm (mean 100, SD 15 for IQ scores; mean 0, SD 1 for z- and t-scores). The *dotted line* represents the clinical threshold. ToM = theory of mind.

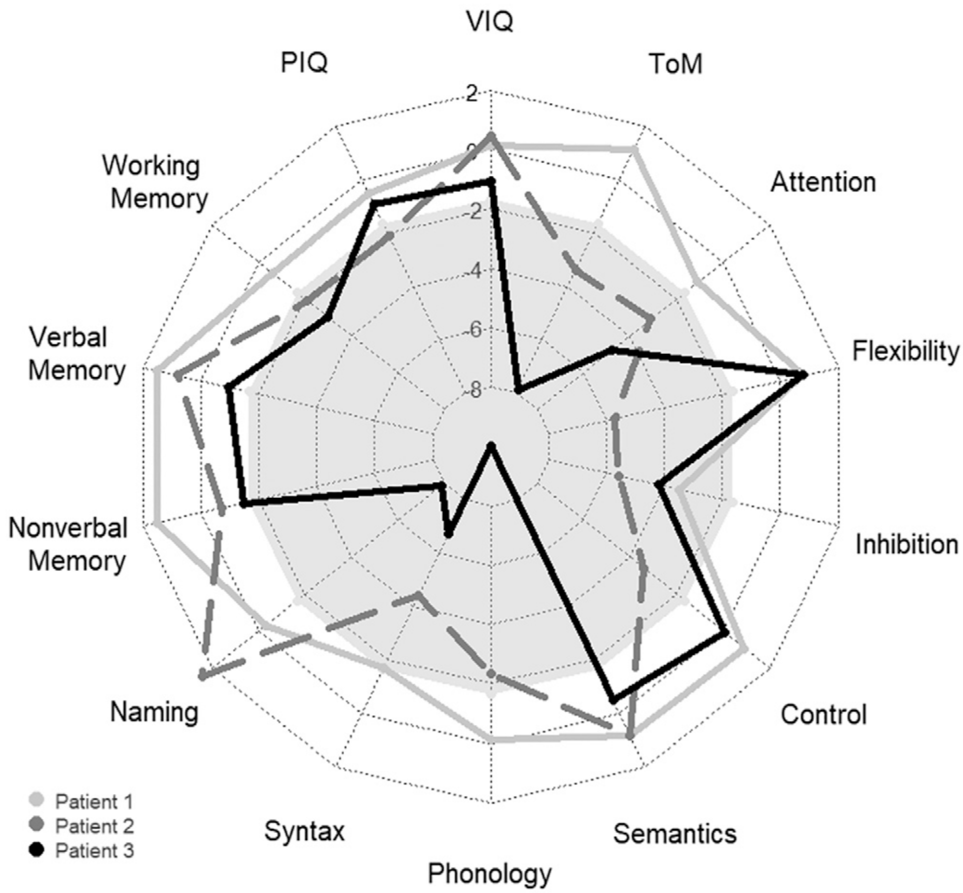

FIG. 2. Cognitive profile of patients in adulthood (T4), including both LEXTOMM battery performance and clinical neuropsychological scores. ToM = theory of mind.

showed a normal VIQ but an important decrease in nonverbal IQ, which became impaired (Table 2). Her declarative memory was normal, but her working memory remained impaired. This verbal–nonverbal discrepancy was also illustrated in her cognitive evaluation. Indeed, all her nonverbal functions (i.e., executive functions, theory of mind, and low-level categorization) were significantly impaired, whereas some language subdomains (i.e., lexicon and semantics) were utterly normal despite slower reaction times (Table 3). Her complex phonological and syntactic processing remained significantly affected, however.

Overall, the patient exhibited language function recovery, except for syntactic processes. In addition, her declarative memory progressed rapidly postoperatively until reaching normal performance. However, her reaction times tended to be significantly slowed down for most tasks. Furthermore, her VIQ progression seemed to be at the expense of nonverbal IQ, which was impacted in adulthood, as executive functions (Fig. 2).

Patient 3

This female patient presented with Rasmussen encephalitis, occurring when she was 12.3 years old. She was right-handed with normal schooling until 11.5 years of age, when she experienced unexpected academic disorders. She progressively dropped out of school due to the severity of her seizures. A first language functional magnetic resonance imaging (fMRI) performed at age 12.8 exhibited left-hemispheric lateralization. Her condition further deteriorated, and she became left-handed with progressive right hemiparesis. Preoperatively (T1), she was left-handed and had an intellectual efficiency in the low average range. All her linguistic skills were strongly impaired, compromising her reading level, except for semantic abilities, which were normal. Her memory was also affected with subnormal nonverbal declarative memory scores and deficits for verbal declarative and working memory tests (Table 2 and Fig. 1C). A second language fMRI was performed at the age of 13.7 years, which showed activations on the left inferior frontal gyrus and on the right temporoparietal and inferior frontal gyri. She underwent a left hemispherotomy at 14.0 years after 20 months of epilepsy duration. Eighteen months after surgery (T2), she exhibited a discrepancy in her intellectual efficiency, with a very deficient VIQ but a subnormal nonverbal IQ (Fig. 1A). As observed preoperatively, her memory and language capacities were largely compromised. Three years after surgery (T3), she had a normalizing IQ with nonverbal IQ in the average range and VIQ at a lower limit of normal. Her declarative memory was well recovered for verbal and nonverbal aspects, but her working memory remained largely impaired. Finally, she came to our center at 22 years of age (T4) to perform cognitive assessments (see Fig. 2). From a neuropsychological standpoint, she exhibited a homogenized normalized IQ for both verbal and nonverbal domains. She recovered a nondeficient declarative memory but an impaired working memory. Her language performance remained altered except for semantic skills, which were still within the norm. Her scores were impaired in inhibition, attention, and theory of mind, whereas she performed with normal scores in the control categorization and flexibility tasks. Her cognitive profile was also characterized by slow reaction times in all tasks, except for the syntactic task, for which responses were given at the chance level.

Overall, this patient's cognitive profile revealed a partial cognitive recovery associated with a slow task execution (Fig. 2). After surgery, a normalization of IQ and declarative memory was observed. Nevertheless, she remained with aphasic symptoms, except for semantic abilities. Her executive abilities seemed relatively preserved with heterogeneous scores, however, specifically satisfactory performance in cognitive flexibility but impairments in other executive domains.

Common and Divergent Findings

Overall, the patients showed a favorable cognitive recovery despite a significant slowness. Three years postoperatively, verbal intellectual efficiency, declarative memory, and semantic abilities were normalized for the 3 patients. However, syntactic abilities, working memory, inhibition, and attention remained weak in the long term. Nevertheless, various outcomes were identified for other functions evaluated. Phonological abilities were recovered only for patient 1. Nonverbal IQ, flexibility, and low-level visual categorization were normal in adulthood for patient 1 and patient 3 but impaired for patient 2.

Discussion

Observations

This study is the first to investigate complete long-term cognitive recovery following left dominant hemispherotomy to treat Rasmussen encephalitis. We report the cases of 3 patients who benefited from hemispheric surgery at ages 5.5, 8.5, and 14 years and who were prospectively followed until adult age with an extensive assessment at ages 18, 23, and 22 years, respectively. They all demonstrated favorable cognitive recovery, despite different cognitive trajectories and outcomes. Postoperatively, they benefited from average intellectual efficiency and declarative memory capacities, whereas language and executive functions were recovered differentially.

This favorable long-term intellectual recovery has also been demonstrated in the population of hemispherectomized patients without considering the side and the age of hemispherectomy or the etiology. This literature suggests that both hemispheres can underlie cognitive functioning even after surgery performed late in childhood and highlights some prognostic factors, such as postoperative seizure control, normalization of electroencephalogram, shorter disease duration, and longer recovery periods.[27] The decision to perform left hemispherotomy in patients with Rasmussen encephalitis is still too specific to compare these patients with the whole population of hemispherectomized patients.

In our study, the 3 patients recovered language after surgery on the dominant hemisphere, even though some domains remained altered. Lexical-semantic abilities were recovered quite rapidly, whereas phonological abilities were compromised (except for patient 1, operated earlier), and complex syntactic processing remained impaired for all patients. These results are consistent with previous work and suggest that the right hemisphere is not devoid of language abilities but that some subdomains (i.e., syntax and phonology) require the left hemisphere to be fully functional.[14,28,29] Nevertheless, the disconnection of the language dominant hemisphere, even when performed late, does not lead to permanent aphasia, allows stopping of cognitive decline, and may induce an important cognitive recovery.

Because cognitive functions are not isolated, memory and nonverbal outcomes must also be investigated. Our results highlight that declarative memory is rapidly recovered, whether verbal or nonverbal. These findings are also reported in the literature and indicate that surgery improves memory performance, especially starting from 3 years postoperatively.[30] This preservation of memory functions could also contribute to language recovery in the isolated right hemisphere.[31] Moreover, long-term executive functioning is marked by more alterations. Although impairments were not found in all patients, the profile seems to be consistent with the crowding hypothesis, claiming that recovery of language is to the detriment of visuoperceptual functions and those with later development.[32,33] Indeed, after hemispherotomy, better recovery of verbal functions has been demonstrated with a priority for language and memory.[34]

The case reports highlight a variety of cognitive recovery trajectories. Indeed, a better outcome was observed for patient 1 with good verbal and nonverbal abilities in adulthood. With an early age of seizure onset, she could have benefited from a better reorganization in her contralateral right hemisphere and thus from a better language recovery.[35,36] This important cognitive recovery corroborates studies showing that hemispherotomy performed at a younger age is related to a more favorable postoperative cognitive outcome.[37,38] Moreover, by presenting patient 2, this case series illustrates that favorable cognitive recovery could also occur for older children beyond the critical period, as previously reported.[15,39,40] Patient 2 presented, indeed, a discrepancy between good recovery of verbal aspects but alteration of nonverbal ones. From an intercognitive standpoint, the reorganization of essential functions could be done at the expense of others. With hemispherotomy having been performed at the age of 8.5 years in a less plastic brain, the right hemisphere may not be able to support all the cognitive functions sufficiently. Finally, a partial recovery remains possible when pathology and surgery occur later because of more limited neuroplastic mechanisms. As illustrated by patient 3, recovery would thus rely on preserved capacities (i.e., semantics, flexibility, and nonverbal abilities) that are on cognitive reserve,[16,41] because the right hemisphere is not able to sustain left-lateralized syntactic and phonological functions anymore. As highlighted in previous works, hemispherotomy can be beneficial with favorable cognitive and seizure outcomes even performed late during adolescence or adulthood.[42,43]

Finally, a similar pattern was found regarding the patients' reaction times. The 3 patients tended to be slowed down for most of the tasks. This slowdown has been found previously and might be explained by the lower attentional and processing speed capacities due to the neurological conditions of an isolated hemisphere.[44]

Taken together, these findings emphasize the importance of multidimensional cognitive assessment and suggest that early hemispheric surgery is beneficial.[35,36,39] The recovery reported here may also be due to a short presurgical delay,[3,38,45] and it must be stated that these are preliminary findings that should be investigated with a larger number of patients. However, they could constitute a good illustration of the long-term cognitive outcome of patients with Rasmussen encephalitis and demonstrate that favorable outcomes may occur after hemispherotomy of the dominant hemisphere.

Lessons

The main finding of our study on these 3 patients was that language is recoverable after left hemispherotomy performed late in childhood. The decision to perform a hemispherotomy of the language dominant hemisphere to treat Rasmussen encephalitis must therefore be made beyond aphasia criteria. Hemispherotomy could preserve cognitive functioning and prevent intellectual decline in patients, and surgery should therefore be considered as early as possible to promote intercognitive reorganization and recovery.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Borne, Perrone-Bertolotti, Jambaqué, Baciu, Bulteau. Acquisition of data: Borne, Perrone-Bertolotti, Jambaqué, Castaignede, Bulteau. Analysis and interpretation of data: Borne, Perrone-Bertolotti, Jambaqué, Bulteau. Drafting the article: Borne, Perrone-Bertolotti, Jambaqué, Bulteau. Critically revising the article: Borne, Perrone-Bertolotti, Jambaqué, Ferrand-Sorbets, Baciu, Bulteau. Reviewed submitted version of manuscript: Borne, Perrone-Bertolotti, Jambaqué, Dorfmüller, Ferrand-Sorbets, Bulteau. Approved the final version of the manuscript on behalf of all authors: Borne. Statistical analysis: Borne, Perrone-Bertolotti, Baciu, Bulteau. Administrative/technical/material support: Perrone-Bertolotti, Jambaqué, Ferrand-Sorbets, Baciu, Bulteau. Study supervision: Perrone-Bertolotti, Jambaqué, Baciu, Bulteau.

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