Journal of the Neurological Sciences 277 (2009) 37–49

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Treatment of epilepsy in severely disabled children with bilateral brain malformations

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ARTICLE INFO

Article history:
Received 3 July 2008
Received in revised form 7 October 2008
Accepted 8 October 2008
Available online 26 November 2008

Keywords:
Magnetoencephalography
Single photon emission computed tomography
Positron emission tomography
Potassium bromide
Lissencephaly
Polymicrogyria

ABSTRACT

To determine a management strategy for the epilepsy in children with bilateral cortical malformations, clinical data of 23 patients (age, 3–23 years, M:F=7:16) were retrospectively reviewed. Among these patients, 15 were bedridden and 16 were profoundly retarded and could not even smile. The patients were categorized into the following five groups based on the findings of neuroimaging, seizure types, and electroencephalographic patterns. Group 1: Diffuse cortical malformation with epileptic spasms and secondarily generalized tonic seizures, group 2: diffuse cortical malformation with erratic twitches, group 3: bilaterally extended but not diffuse cortical malformations, group 4: bilateral polymicrogyria with persistent epileptic spasms (Aicardi syndrome), and group 5: bilateral cortical malformation with drop attacks (subcortical band heterotopia and congenital bilateral perisylvian syndrome). Eleven patients suffered from infantile spasms; adrenocorticotropic hormone was effective in group 1 but ineffective in group 4. Treatment of tonic seizures in groups 1–3 and erratic twitching in group 3 with phenobarbital, zonisamide and potassium bromide was beneficial. Epileptic spasms and tonic seizures were prominent in group 4 and were refractory to medical treatment, except that zonisamide, clobazam, and a ketogenic diet were partially or transiently effective. Complex partial and astatic/atonic seizures in group 5 were refractory to medications other than that carbamazepine and clobazam provided limited benefits. Total callosotomy resulted in better seizure control for three patients in group 5, and functional hemispherectomy was effective for one patient in group 4. These results provide the basis for the appropriate choice of medical and surgical treatment for managing bilateral, widespread cortical malformations.

1. Introduction

Cortical malformations can have either focal or bilateral/diffuse distributions. The latter group encompasses several types of pathologies, including lissencephaly (agyria/pachygyria), polymicrogyria, and subcortical band heterotopia. A high proportion of children with these malformations present with epilepsy, which is often resistant to medical treatment. Several mechanisms underlying the pathogenesis of intractable epilepsies in cortical malformations have been proved: decreased number of inhibitory neurons [1–3], up-regulated expression of receptors for excitatory neurotransmitters on the dysmorphic neurons [4], aberrant innervation of the excitatory efferents to the surrounding area of dysplastic lesions [5], and alteration in the intrinsic membrane property of ectopic neurons [6]. These can explain the high epileptogenesity within and outside the malformed cortex. In addition, the different extents to which these pathomechanisms are involved in each subgroup of cortical malformations may also be related to the distinct characteristics of the clinical course of epilepsy in each malformation syndrome. For example, the disrupted migration of inhibitory interneurons may result in the early emergence of seizures in the first few days of life, specifically in the case of individuals with X-linked lissencephaly with abnormal genitalia [7], and postnatal excitatory axonal growth and its synaptogenesis may participate in the epileptogenesis at a particular period during infancy [5].

Presumably, since different pathophysiologies are involved in the etiologies of cortical malformations, and there are certain anatomical connections between the dysplastic and normal structures, each malformation syndrome has propensity to develop a distinctive type of epilepsy. This includes infantile spasms in lissencephaly [8], temporal lobe epilepsy in periventricular nodular heterotopia [9], and Lennox–

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doi:10.1016/j.jns.2008.10.009

Table 1
Patients with bilateral cortical malformation and epilepsy

Patient	Age	Sex	Diagnosis	Motor outcome	Intellectual disability	Onset age of epilepsy	Seizure type at onset
Group 1							
1	16 years	F	Pachygyria	Bedridden	Profound	2 months	Tonic spasm
2	3 years	F	Pachygyria	Bedridden	Profound	10 months	Tonic–clonic
3	6 years	F	Lissencephaly (Miller–Dieker syndrome)	Rollover	Profound	4 months	Tonic–clonic
4	16 years	M	Lissencephaly	Bedridden	Profound	2 months	Tonic
5	5 years	M	Holoprosencephaly	Bedridden	Profound	2 days	Tonic–clonic/myoclonic
Group 2							
6	8 years	M	Holoprosencephaly	Bedridden	Profound	Neonatal period	Twitching/myoclonic
7	1 years	F	Cobblesonte lissencephaly	Bedridden	Profound	0 days	Tonic/eyelid twitching
8	5 years	M	Simplified gyral pattern	Bedridden	Profound	0 days	Writhing/twitch/clonic
9	3 years	M	XLAG	Bedridden	Profound	0 days	Tonic/twitching
Group 3							
10	8 years	F	F-T-P pachygyria	Stand with help	Severe	3 months	Ocular deviation
11	10 years	F	F-T simplified gyri/pachygyria	Bedridden	Profound	3 months	Staring/eyelid twitch
12	10 years	F	F-T simplified gyri/pachygyriay	Bedridden	Profound	3 months	Focal twitch/tonic
13	3 years	M	F-T-P polymicrogyria	Bedridden	Profound	3 days	Tonic/clonic
14	8 years	F	Bitemporal cortical dysplasia	Walk with help	Severe	1 month	Eyelid twitching
Group 4							
15	3 years	F	Aicardi syndrome	Bedridden	Profound	3 months	Tonic spasm
16	4 years	F	Aicardi syndrome	Bedridden	Profound	1 month	Tonic
17	3 years	F	Aicardi syndrome	Bedridden	Profound	3 months	Tonic spasm
18	8 years	F	Aicardi syndrome	Bedridden	Profound	2 months	Tonic
Group 5							
19	19 years	F	Band heterotopia	Ambulant	Moderate	6 years	CPS
20	22 years	F	Band heterotopia	Ambulant	Moderate	8 years	Brief visual loss
21	9 years	F	Band heterotopia	Ambulant	Normal	2 years	Conscious loss/vomiting
22	11 years	M	Bilateral perisylvian syndrome	Crawling	Severe	2 months	Pedaling
23	23 years	F	Bilateral perisylvian syndrome	Ambulant	Moderate	8 years	CPS

CPS: complex partial seizure, XLAG: X-linked lissencephaly with abnormal genitalia, * severe: some activity present, i.e. able to smile or follow certain directions of parents, etc.

Gastaut syndrome in band heterotopia [10]. Despite this characterization of epilepsy in each malformation syndrome, the response to treatment trials is often described as merely refractory to medications. Surgical intervention has been a less promising option for managing of bilateral or diffuse malformations than for managing focal cortical dysplasia, although surgery can benefit epileptic individuals with bilateral or diffuse malformations in certain conditions [11,12]. In many cases of the severely disabled children with cortical malformations, it would be better if the treatment of intractable epilepsy aims to alleviate the severity of seizures rather than completely terminate the seizures. Seizures are described as refractory if there is a mere decrease in the duration of tonic seizures or reduced generalization of partial seizures. However, the treatment certainly benefits each sufferer of malformation-related epilepsy. In order to establish an effective treatment strategy, we reviewed our experience with patients with bilateral cortical malformations, with the focus on the results of treatment trials. Here, we present the basis for adopting different approaches for treating epilepsy in each subgroup of malformation syndromes.

2. Patients and methods

Data of patients with cortical malformations were collected retrospectively from the medical records at the National Center Hospital for Mental, Nervous and Muscular Disorders and Tottori University Hospital between 1999 and 2007. The diagnosis of malformed cortex and distribution of the malformations on the magnetic resonance (MR) images was confirmed by at least one child neurologist and one radiologist in each case. Since we aimed to focus on patients with bilateral cortical malformations, those with unilateral focal cortical dysplasia, Aicardi syndrome with unilateral polymocrogyria, unilateral schizencephaly, and hemimegalencephaly were not included in this study. Twenty-three children were identified, and we attempted to categorize these patients based on the distribution of cortical malformations and the predominant seizure types. Thus, the following groups could be recognized (see Table 1). Group 1: Diffuse cortical malformations with epileptic spasms and/or secondarily generalized tonic seizures (n=5): lissencephaly (agyria/pachygyria) (n=4) and holoprosencephaly (n=1). Group 2: Diffuse cortical malformation with erratic twitches (n=4): cobblestone lissencephaly (n=1), X-linked lissencephaly with abnormal genitalia (XLAG) (n=1), simplified gyral pattern (n=1), and holoprosencephaly (n=1). Group 3: Bilaterally extended but not diffuse abnormal gyration (n=5): fronto-parieto-temporal polymicrogyria/pacygyria (n=2), fronto-temporal polymicrogyria (n=1), fronto-temporal simplified gyri/pachygyria (n=2). Group 4: Bilateral polymicrogyria with persistent epileptic spasms: Aicardi syndrome (n=4). Group 5: Bilateral cortical malformation with drop attacks (n=5): band heterotopia (n=3) and bilateral perisylvian syndrome (n=2).

The age of the patients (M:F=7:16) ranged from 3 to 23 years, and the age of onset of epilepsy was between the day of birth to 8 years. Fifteen patients were bedridden and could not roll over, and 16 patients were so profoundly retarded that they could not even smile (Table 1). All 11 patients who suffered from infantile spasms were treated with adrenocorticotropic hormone (ACTH). Each patient was treated with 1–11 antiepileptic agents. Some of the clinical data from patients 8, 9, 11, and 12 have been presented previously [13–15].

2.1. Evaluation methods

Since the epilepsy was markedly refractory in most of the patients included in the study, the effect of treatment was scaled as follows: good (decrease of seizure frequency or duration by 50% or more and for more than 3 months after improvement), minor (a decrease in seizure frequency or duration by less than 50% and for less than 3 months), and poor (no apparent benefit). With the exception of the case of infantile spasms, strict assessment of the treatment effects for individual seizure types in a single patient with multiple seizure types was often difficult, since the decrease in seizure frequency was often