

Informative Value of Magnetic Resonance Imaging and EEG in the Prognosis of Infantile Spasms

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Summary: *Purpose:* To investigate the informative value of EEG and cranial magnetic resonance imaging (cMRI) in the prognosis of infantile spasms (ISs); 86 patients with ISs were included in this study.

Methods: All cases had epileptic spasms, psychomotor retardation, and hypsarrhythmia in at least one of their EEGs. cMRIs and laboratory tests necessary for etiologic diagnosis were completed in all cases. Patients were followed up periodically both clinically and by video-EEGs for >1 year. Clinical information was categorized on the basis of four spheres as epilepsy, psychosocial development, motor development, and overall clinical condition, with each category being evaluated under three levels of involvement as good, moderate, and severe, depending on selected parameters. A similar scale was applied for the EEG results and for the cMRI findings. Clinical parameters were correlated to EEG and cMRI results, by Spear-

man test. Other statistical tests used were Kruskal–Wallis χ^2 and Mann–Whitney *U* analysis as multiple comparison by post hoc Bonferroni correction.

Results: A severe overall clinical course was observed in 64% of patients, whereas this incidence was 58% and 44% in the EEG follow-up and cMRI parameters, respectively. In regard to prognosis, a significant correlation was determined between the clinical and the EEG course. This relation was the most prominent in psychosocial developmental parameters and least prominent in the motor development. cMRI findings, however, were correlated only with motor development.

Conclusions: cMRI and repeated EEG recordings, especially when assessed together, may provide complementary information regarding the prognosis in ISs. **Key Words:** Infantile spasms—Electroencephalography—Magnetic resonance imaging—Prognosis—Hypsarrhythmia.

Infantile spasms (ISs), one of the most common epileptic syndromes in infancy, is characterized by a triad composed of clusters of spasms, a distinctive EEG pattern, called hypsarrhythmia, and an arrest or regression in psychomotor development (1–3). Patients with ISs generally have a poor neurologic prognosis, as intellectual outcome deteriorates, and seizures often persist (4); however, a minority may preserve normal intelligence and even display academic performance (5). This study in a group of patients with ISs questioned the prognostic informative value of cMRI and serial EEGs as compared with the clinical course of the disease.

METHODS

A total of 86 patients with epileptic spasms, psychomotor developmental delay, and hypsarrhythmia in at least one of the serial EEGs was included in the study. There were eight (9.3%) cryptogenic and 78 (90.7%)

TABLE 1. Patient distribution in clinical severity scales

	No. of pts	% of pts
SF		
Severe (none or >50% decrease in seizure frequency)	28	32.6
Moderate (between 50 and 74% decrease in seizure frequency)	32	37.2
Good ($\geq 75\%$ decrease in seizure frequency)	26	30.2
PSD		
Severe (no development in cognitive and affective reactions, autism inc.)	41	47.7
Moderate (<50% of app. age)	26	30.2
Good ($\geq 50\%$ of app. age)	19	22.1
MD		
Severe (no development)	35	40.7
Moderate (>50% of app. age)	28	32.6
Good ($\geq 50\%$ of app. age)	23	26.7
OCC		
Severe (at least one of these parameters is severe)	55	64
Moderate (all three parameters moderate or two moderate, one good)	13	15.1
Good (Three parameters good or two good, one moderate)	18	20.9

SF, seizure frequency; PSD, psychosocial development; MD, motor development; OCC, overall clinical course; inc, included; app, appropriate.

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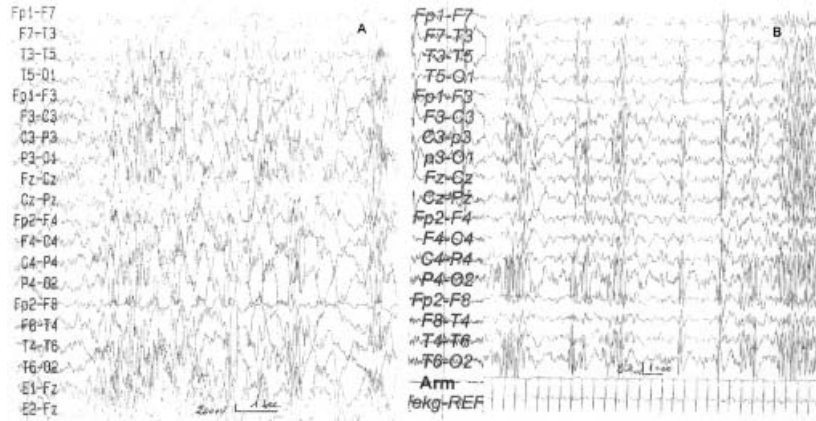


FIG. 1. Bilateral fast discharges as an indicator of “severe course” in the EEGs of an infant with nesidioblastosis and infantile spasms: (a), at 10 months, and (b), at 22 months throughout the evolution into Lennox-Gastaut syndrome.

symptomatic cases, as described in the International Classification of Epilepsies and Epileptic Syndromes (6) with a male/female ratio of 1.75/1.

Clinical evaluation protocol

Follow-up examinations, after the diagnostic procedures completed, were carried on a monthly basis within the initial 3 months, followed by once in 3 months during the first year and once in 6 months, later. The shortest follow-up period was 1 year, the longest was until 10 years of age. Mean age of the patients was 34.6 ± 21.5 months, the median age was 29.5 months at the last visit. Clinical evaluations of the patients included specific information regarding the seizure frequency (SF), motor development (MD) and mental and psychosocial development (PSD) during the initial and follow-up visits. After a detailed examination of the initial video-EEGs, all documented partial seizures and epileptic spasms of the infant were shown to the parents during another visit, and a common semiologic understanding and naming of the seizure types was achieved. Seizure types were later assembled under a single category for statistical reasons.

Developmental milestones were determined by Denver II (7) screening test. Parameters as eye contact and following objects, communicative smiling, reaching objects, and responsive utterings were carefully noted within the context of PSD. A rating scale was adjusted for frequency and severity of seizures, as for psychosocial and for motor performances; and differences throughout the initial visit to the latest one were noted. A common clinical follow-up prognostic scale (good, moderate, severe) was later developed on the basis of evolutionary scales for each individual modality (Table 1).

EEG recordings and the evaluation protocol

EEGs of ≥ 2 -h duration during sleep and waking, synchronized with video monitoring was conducted by a 32-channel digital machine. A total of 386 video-EEGs (mean, 4.5 ± 2.6 per individual) recorded with regular intervals from the onset of the disease to the last follow-up visit were evaluated by the authors. EEG parameters included were presence of sleep spindles, hypsarrhythmia, bilateral fast discharges (8), and epileptogenic foci after disappearance of hypsarrhythmia, as well as asym-

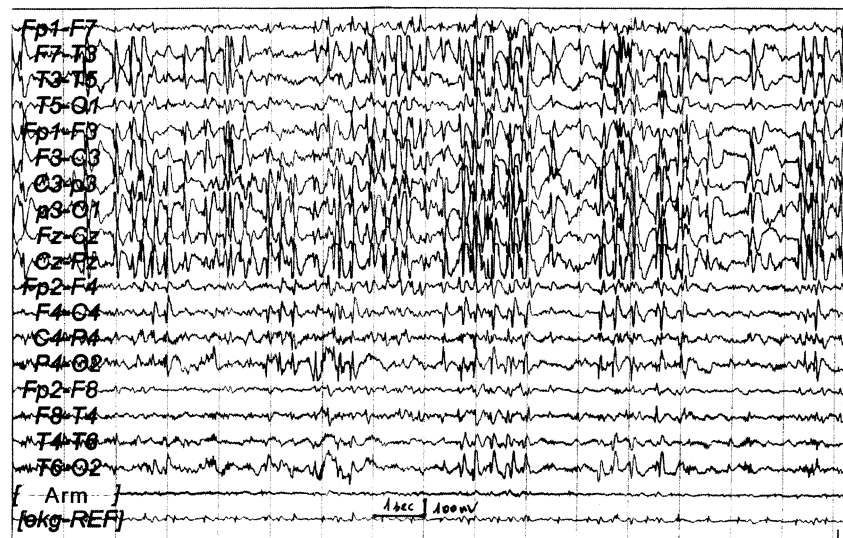
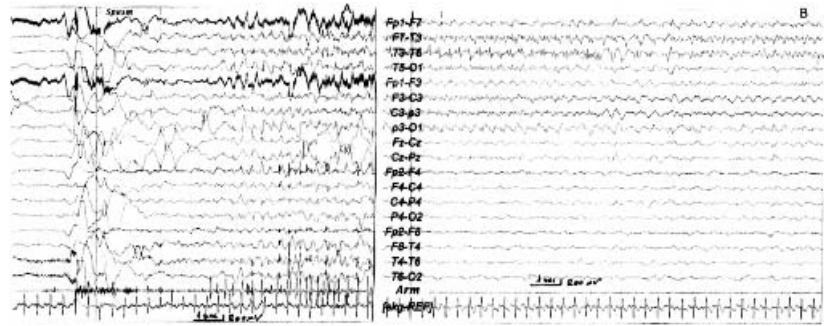


FIG. 2. Asymmetric hypsarrhythmia with depression on the right hemisphere leads, as a marker of “severe course” from an infant (11-month-old) with hypoxic-ischemic encephalopathy and bilateral clastic lesions in the cranial magnetic resonance imaging, larger on the right.

FIG. 3. EEG sample of an epileptic spasm (A) followed by an ictal pattern (B) predominant on T3 with extension to adjacent regions (as a marker for severe course). Clinically, a right-sided motor seizure in a 10-month old infant, with bilateral pachygyria in the cranial magnetic resonance imaging.



metry of sleep spindles and of hypsarrhythmia. Presence of interhemispheric asymmetry in the background activity, if not hypsarrhythmic, as well as additional ictal patterns and various abnormal rhythms also were noted. Those were considered as accessory criteria for classification of EEGs with in-between features of severity levels. (Example: An EEG that could not be clearly rated as good or moderate was classified as moderate if focal ictal patterns would exist.) See sample EEGs showing diagnostic indicators of various severity scales in Figs. 1–4.

A conclusive format for video-EEG data was then completed on the basis of those parameters. Final stage of this evaluation process was the production of a severity scale similar to that of the clinical outcome (Table 2).

Evaluation protocol for cMRIs

A total of 103 cMRIs was available with at least one for each patient and repeated examinations to follow either the maturational changes of the brain or to avoid diagnostic suspicion. They were evaluated by two independent neuroradiologists, and the following parameters were noted: presence of a lesion, its localization, its distribution (ranging from + to ++++), presence of white (subcortical, deep) and gray matter (cortex, deep nuclei) involvements, and morphology of corpus callosum and cerebral ventricles, enlargement of subarachnoid space, diffuse cerebral or cerebellar atrophy, and pattern of myelination and its appropriateness for age. A severity scale prepared on the basis of these cMRI parameters is seen in Table 3. Figures 5 and 6 illustrate some examples of different levels of involvement.

No EEG or cMRI data were included in the study if the

patient was taking adrenocorticotrophic hormone (ACTH) or was within 6 months after treatment because of the reported side effects of the drug (9,10).

Statistics

Rating results of SF, PSD, MD, and overall clinical course (OCC) were correlated to EEG and cMRI ratings individually by Spearman correlation analysis. Median values for each severity level in clinical parameters (SS, PSD, MD, OCC, individually) and corresponding EEG groups were compared by Kruskal–Wallis χ^2 analysis. Mann–Whitney *U* test was performed to assess significance among group differences and by post hoc Bonferroni correction. Similar procedures were performed for cMRI findings.

RESULTS

A severe OCC was detected in 64% (Table 1) of patients of whom seven (8.13%) died during the evaluation period. A prognostic profile indicating severity was prominent in the EEGs of 58% of patients (Table 2), whereas 44% revealed such degree of involvement in their cMRIs (Table 3) versus 25.5% with no remarkable cMRI changes. A strongly positive correlation was found between all parameters of clinical course (SF, PSD, MD, OCC) and EEG ratings for severity (Table 4). Comparison of group differences of median values revealed that the most significant relation existed between PSD and EEG. Subgroups of severity levels strictly corresponded for PSD and EEG course. Although significantly related in global evaluation, SF was rated moderate in the EEG

FIG. 4. EEG samples indicating “good course” in an infant with tuberous sclerosis. **A:** Hypsarrhythmia at age 4 months. **B:** Presence of sleep spindles along with bilateral spike-wave discharges, at 8 months, with vigabatrin. **C:** Organized non-rapid-eye-movement sleep, stage 2, with well-developed sleep spindles, at 3 years, receiving vigabatrin.

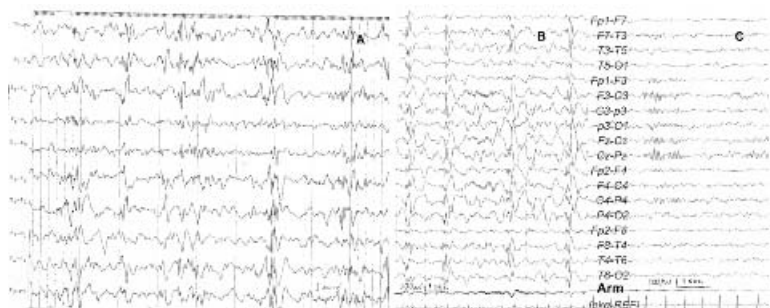


TABLE 2. EEG follow-up scale and the incidence of patients

Course of EEG: No. of pts	Description
Severe: 50 (58.1% of pts)	Bilateral fast discharges present Asym hyps cont Asym hyps → mef Asym hyps → fea + sl sp Abs/asym
Severe or moderate (as determined by accessory ^a criteria and later placed in other groups)	Sym hyps cont + sl sp abs/asym Sym hyps → mef + sl sp abs/asym
Moderate: 26 (30.2% of pts)	Sym hyps cont + sl sp sym Sym hyps → mef + sl sp sym Sym hyps → fea + sl sp abs/asym
Good: 10 (11.6% of pts)	Sym hyps → fea + sl sp sym Sym hyps → no ea

asym, asymmetrical; hyps, hypsarrhythmia; cont, continuous, mef, multiple epileptogenic foci; sym, symmetrical; fea, focal epileptogenic activity; abs, absent; sl, sleep; sp, spindle; ea, epileptogenic activity; →, changed to.

^a See EEG recordings and the evaluation protocol, in Methods.

subgroup with severe changes. MD was the modality with least significant relation with the degree of severity in the EEG (Table 5).

Correlative analyses of clinical-severity subgroups, however, showed that MD was the only parameter significantly related to cMRI changes (Table 6). As is shown by the median values of clinical parameters corresponding to each cMRI severity subgroup, MD was good in patients with normal cMRI findings, and it was the worst in the group with severe imaging findings (Table 7).

DISCUSSION

Our results suggest that mental and communicative skills are the most consistently affected behavioral aspects of the infant with IS, whereas seizures may decrease or increase in the time course. Only 22% of our patients have a relatively good PSD, which is not far from the results of similar studies (5,11). Contributions of aggressive use of antiepileptic medication (AEDs) along with the introduction of newer agents may play a

role in this fact; however, maturational changes in neuronal excitability may be even more effective. A question may emerge at that point: Is it epilepsy that bears more future risks for the child, or is it the cognitive involvement? Nevertheless, it is obvious that management should be directed to all behavioral modalities. However, the general approach to the patient with IS, at least in our country, has been directed mainly to seizure control and to motor rehabilitation to a lesser extent. Physicians frequently overlook the cognitive and psychosocial impairment of the child until it becomes very evident to the family, by the near-school ages.

Numerous EEG findings have been evaluated and discussed regarding their prognostic value in IS (9,12–17). Presence of physiologic background activity and sleep spindles within hypsarrhythmic periods has been proposed as indicating a good prognosis in one study (18), whereas controversial reports in relation to the spindles exist (19,20). Our study was not designed to question the informative value of sleep spindles in the prognosis; rather, both presence and interhemispheric symmetry of those physiological elements were included as parameters contributing to the classification of any EEG under “good” category in addition to other relevant data. Hypsarrhythmia with prominent interhemispheric asymmetry (if the nonhypsarrhythmic hemisphere lacked physiologic activities and showed a depression in the background activity as the difference in the amplitudes was >50%), bilateral fast discharges (suggestive of Lennox–Gastaut syndrome) were categorized as criteria for severe prognosis (21). Asymmetric hypsarrhythmia seems a reliable sign of lesional involvement (12), and when the bioelectrical activity is definitely depressed, the lesion is located solely or predominantly in the non- or less-hypsarrhythmic hemisphere. A parameter included as evidence for a good prognosis, in this study, was the early disappearance of hypsarrhythmia after treatment, a fact reported earlier (1,5).

Our results revealed that 58% of our cases had a trend toward malignancy in their EEGs, and 11% had a good course. Those results were statistically correlated with the clinical course of the patient and very strictly corre-

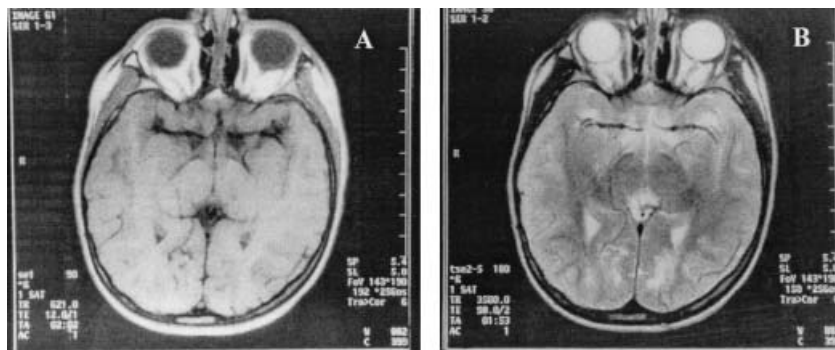
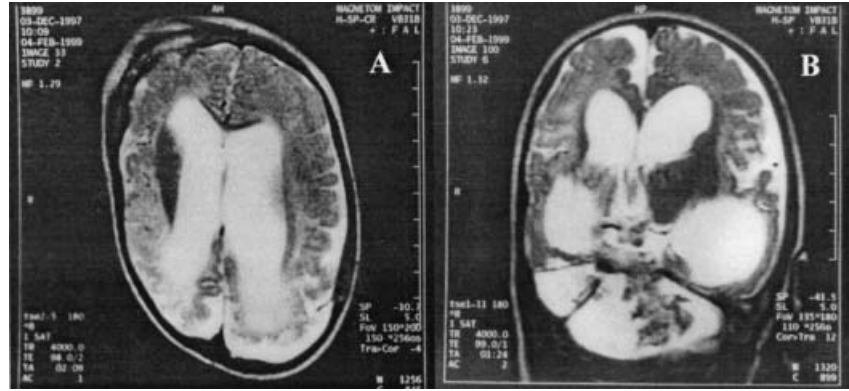


FIG. 5. Example of “moderate” degree of involvement in cranial magnetic resonance imaging (3-year-old boy with hypoxic–ischemic encephalopathy): Bioccipital subcortical gliotic lesions, prominent in T₂-weighted image. **A:** T₁-weighted image. **B:** T₂-weighted image.

FIG. 6. Example for “severe” degree of involvement in cranial magnetic resonance imaging (2-year-old girl with hypoxic–ischemic encephalopathy): Biparieto occipital subcortical lesions and ventricular enlargement. Note the massive pathologic signals of cerebellum with pial hemosiderin deposit. **A:** Axial T₂-weighted image. **B:** Coronal T₂-weighted image.



lated with the cognitive behavior. Although EEG has been a popular means of search for the epilepsy in IS and the underlying pathophysiology (17,19,20) its relation to other modalities of well-being seems to deserve attention. In 33 (80.5%) of 41 patients with very poor psychosocial performance, the EEGs showed a consistent progress toward malignancy, and none toward good prognosis. Negative impact of the persistence of diffuse epileptogenic activity on the cognitive functions leading to mental deterioration has been reported before (22), where hypersarrhythmia may be considered a “bioelectrical status” seizing the yet immature brain and leading to irreversible functional changes, in this sense. Another probability, however, may be the direct effect of the primary etiologic factor on those modalities. Because IS is frequently a consequence of severe pre- or perinatal damage to the brain, as well as on developmental or metabolic abnormalities, there may not be enough reason to expect normal cognitive functioning.

A positive relation between a decrease in the severity of hypersarrhythmia and the SF has been reported (23). A similar observation as a 85.7% of severe EEG course in contrast to 3.5% good course was detected in patients with intractable seizures in our study. However, no significant difference in the seizure prognosis was existent between EEG groups with good and with moderate courses. Results were suggestive of a possibility for a

TABLE 3. Patient groups according to cMRI findings and incidences

Degree of Inv N: % of pts	Description
Severe: 38: 44.2%	Lesion +++/++++, sv atrophy and vol loss, delayed myelination, deep white and gray matter inv.
Moderate: 13: 15.1%	Lesion in two lobes, +/++ , atrophy and vol loss, delayed myelination
Mild–Normal: 35: 40.7%	Normal cMRI or lesion in one or two lobes, no atrophy/vol loss, normal myelination

sv, severe; vol, volume; inv, involvement; cMRI, cranial magnetic resonance imaging.

better prognosis of epilepsy independent of the EEG changes in time, although the probability of a later developing epilepsy can not be excluded.

Another positive but less significant relation was encountered between MD and the EEG course of the patients with IS. This relation was most prominent in the cases with severe motor deterioration. Malignant EEG changes were seen in 80% of that group. The EEG may serve as an indirect tool mainly by reflecting the negative effects of either diffuse or unilateral involvement of the brain on MD by means of the asymmetry or the absence of physiologic phasic or background activities.

Cranial MRI has a distinctive place in etiologic diagnosis in IS. A differentiation in prognostic consequences depending on the type of brain lesion was reported, and the best prognosis was attributed to the group with normal cMRI findings (24).

No available data in regard to the prognostic informative value of cMRI outside the etiologic perspective exists in the related field. The presence or absence of

TABLE 4. Correlation of clinical follow-up parameters and EEG course^a

Clinical parameters	EEG course (no. of pts)		
	Severe	Moderate	Good
SF (r _s , 0.44; p < 0.001)			
Severe	24	3	1
Moderate	17	14	1
Good	9	9	8
PSD (r _s , 0.51; p < 0.001)			
Severe	33	8	—
Moderate	12	12	2
Good	6	6	8
MD (r _s , 0.40; p < 0.001)			
Severe	28	7	—
Moderate	12	15	1
Good	10	4	9
OCC (r _s , 0.49; p < 0.001)			
Severe	41	13	1
Moderate	4	8	1
Good	10	4	9

^a Spearman Correlation Analysis test; SF, seizure frequency; MD, motor development; PSD, psychosocial development; OCC, overall clinical course.

TABLE 5. Comparison of median values for clinical severity ratings and EEG groups

Clinical parameters	EEG groups			p ^a
	Severe	Moderate	Good	
SF (median)	Moderate ab	Moderate a	Good b	p < 0.001
PSD (median)	Severe ab	Moderate ac	Good bc	p < 0.001
MD (median)	Severe a	Moderate b	Good ab	p < 0.01
OCC (median)	Severe ab	Moderate-severe ac	Good bc	p < 0.001

Paired letters (i.e., ab) indicate significant differences within groups sharing similar letters.

^a Kruskal-Wallis χ^2 test.

lesions and their extensiveness in the cMRI, rather than type, and also the severity of destruction was scored in this study, and no statistically significant correlation was found between the level of involvement in the cMRI and the questioned clinical parameters, except with MD (Table 4). In our patients with preserved motor functioning (27%), there were no or mild involvements in the cMRIs in 74%. Motor performance in all the symptomatic cases was affected in strict concordance with the underlying primary disease, as to its severity and extensiveness of the cMRI lesions.

Apparent independence of the clinical parameters such as cognitive and seizure condition of the patients from the cMRI-related scales may be related to various reasons. First, purely biochemical abnormalities without imaging findings as well as presence of lesions undetectable with available technical standards may play important roles in the prognostic profile of a certain group of patients with IS. Second, interfering frequent spontaneous or drug-facilitated infections (i.e., ACTH,

TABLE 6. Correlation of clinical follow-up parameters and cMRI involvements^a

Clinical parameters	cMRI involvement (no. of pts)		
	Severe	Moderate	Mild-Normal
SF (r_s , 0.10; p > 0.05)			
Severe	13	15	10
Moderate	6	4	3
Good	9	13	13
PSD (r_s , 0.07; p > 0.05)			
Severe	17	16	5
Moderate	8	2	3
Good	16	8	11
MD (r_s , 0.45; p < 0.001)			
Severe	22	13	3
Moderate	7	3	3
Good	6	12	17
OCC (r_s , 0.19; p > 0.05)			
Severe	27	7	4
Moderate	9	1	3
Good	19	5	11

^a Spearman correlation analysis test.

TABLE 7. Comparison of median values for clinical severity ratings and cMRI involvements

Clinical parameters	cMRI involvement			
	Severe	Moderate	Mild	Normal
SF (median)	Moderate	Moderate	Moderate	Moderate
PSD (median)	Moderate	Severe	Moderate	Moderate
MD (median) ^a	Severe	Severe	Moderate	Good
p ≤ 0.001	a			a
OCC (median)	Severe	Severe	Severe	Severe

^a "a" indicates significant group differences (Mann-Whitney U test as multiple comparison by post hoc Bonferroni correction).

^a significant in Kruskal-Wallis χ^2 test.

benzodiazepines), poor feeding or hygienic care, delayed diagnosis, and malpractice have been some of our observations complicating the clinical course, in our settings. Finally, because IS has a very heterogeneous character on both clinical and laboratory grounds, it is not very unlikely that quite different results might be achieved in different methodologic settings. Although maximal attention to be precise and objective in the design and interpretation of the results was paid in this study, unavoidable complexities may still be barriers for more conclusive decisions.

Finally, when the results are briefly summarized, cMRI findings in patients with IS seem to be related to the MD, whereas the EEG changes and their evolution in time apparently have informative value regarding especially the psychosocial development and, in decreasing order, the seizure outcome and the MD of the infant. Results indicate that valuable information regarding the prognosis of an individual patient with IS may be gained early in the clinical course of the disease when the cMRI and repeated EEG data are carefully examined and interpreted from an integrative perspective. Any means for management of the well-known severe consequences of the syndrome may, therefore, be reached earlier.

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