

Outcome of Patients with Infantile Spasms

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ORIGINAL PAPER SUMMARY

Purpose: To assess outcome of children diagnosed with infantile spasms (IS) during the six-year-period (2002-2006), at the Pediatric Clinic of Clinical Center of University of Sarajevo, as well as to present other important clinical characteristics in this group of patients. **Methods:** All patients had medical histories with detailed description or video recordings of their seizures, as well as profound neurological exam, series of video-EEG registrations, neuroimaging studies and laboratory studies that were possible to perform. **Results:** Total of 19 patients with IS were treated (14 male, 5 female). Etiologically symptomatic IS were present in 78.9% of cases, cryptogenic in 21.1%. Flexor and mixed spasms were the most common (47.4% and 31.6% respectively). Therapeutic response was satisfactory: 42.1% of patients were seizure-free, 47.4% had partial response with more than 50% decrease of seizures, 10.5% had poor therapeutic response. Most of the patients were treated with polytherapy. The follow-up period was 15-70 months (mean 42.5

months). At last check-up four patients had normal development and were without seizures, two were lost to follow-up, two patients have died (21.4%, 10.5% and 10.5% respectively). Out of remaining patients seven (36.8% of total) had a severe psychomotor retardation with spastic tetraparesis, while the rest had hemiparesis and developmental difficulties. **Discussion:** Treatment of infantile spasms presents a great challenge, especially in the developing countries like Bosnia and Herzegovina in which the treatment modalities are limited. Our results indicate that despite the lack of the proper treatment options, outcome of the patients regarding control of seizures and latter psychomotor development did not differ significantly from the reports from the other countries. **Conclusion:** Although prognosis for most patients with infantile spasms remains poor, further studies identifying predictors of favorable prognosis and recent advances in understanding the pathophysiology of infantile spasms offer hope of safer and more effective therapies that improve long-term outcome.

Keywords: infantile spasms, etiology, prognosis

cyanosis, flushing, sweating etc). According to patterns of muscle involvement during the seizure and postural manifestations spasms have been categorized into three major subtypes: flexor, extensor and mixed flexor-extensor (2, 5). Spasms rarely persist into young adulthood; they cease spontaneously by five years of age and are frequently replaced by other seizure types (2).

Patients with IS usually have characteristic interictal EEG pattern, so called "hypsarrhythmia", originally described by Gibbs and Gibbs in 1952 (1, 2). Treatment goals for patients with IS are the best possible quality of life with cessation of seizures, the fewest adverse effects from treatment, and the least number of medications. Various medical treatment options can be divided into two major groups: commonly used first-line treatment (i.e., ACTH, prednisone, vigabatrin, pyridoxine) and second-line treatment (i.e., benzodiazepines, valproic acid, lamotrigine, topiramate, zonisamide). Unfortunately, there is no medical treatment that gives satisfactory therapy for all infants with IS. In some patients, surgical resection can lead to freedom from seizures (1, 2, 6).

The long-term implications of infantile spasms are significant, with frequent occurrence of intellectual impairment and persistent seizures in survivors, and increased incidence of early mortality (4).

Prognosis is poor and is related directly to the etiology of the disease, and maybe to success of the first given drugs in controlling seizures (4). Prognosis appears to be worse in infants

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1. INTRODUCTION

The term "infantile spasms" (IS) has been used to address both a distinctive seizure type and an age specific epilepsy syndrome that is characterized by specific type of seizures, well defined changes in electroencephalogram (EEG) and delay in psychomotor development (1,2). Standardization, established by the International League against Epilepsy (2,3) states that a seizure type (spasms or epileptic spasms) must be distinguished from the epilepsy syndrome of infantile spasms (West syndrome).

Infantile spasms are divided into 3 main groups according to ILAE classification. Symptomatic infantile spasms occur when an identifiable factor (prenatal, perinatal, or postnatal) is re-

sponsible for the syndrome. Patients with cryptogenic disorder are actually symptomatic, but the specific etiology is unknown. A small percentage of patients have idiopathic infantile spasms, with no identifiable cause and normal growth and development premorbidly (1, 2). In this article, the term "infantile spasms" (IS) is synonymous with West syndrome.

Infantile spasms affect children worldwide, with a reported incidence of 1 in 2000 to 4000 live births (4).

Spasms include brief muscle contractions involving the neck, trunk and the extremities in a symmetric bilateral fashion. They occur in clusters of couple to more than hundreds of seizures and are usually followed by different ictal phenomena (screaming, crying, pallor,

with various seizure types, persistent EEG abnormalities, poor response to ACTH, and delayed initiation of the treatment, which is now put under the further investigation (4). To the opposite, a later onset, normal-to-mild psychomotor delay at the time of diagnosis, and a good seizure control were related to better prognosis (1, 2, 6).

Aim of our study was to assess outcome of children diagnosed with IS during the six-year-period (2002-2006), at the Paediatric Hospital Sarajevo, as well as to present other important clinical characteristics in this group of patients.

2. METHODS

Nineteen patients with the diagnosis of IS, set at Pediatric Hospital Sarajevo in a period January 1st, 2002 – December 31st, 2006, were retrospectively studied. Diagnosis of IS was set according to international classification (The 1989 International League Against Epilepsy classification scheme for epileptic syndromes (7) and disorder was defined as a triad of symptoms: infantile spasms, specific interictal EEG pattern, and developmental delay. Diagnosis was established even if one of three elements were missing.

All patients had medical histories with detailed description or video recordings of their seizures. Thorough neurological exam, series of video-EEG recordings, neuroimaging studies (MRI scans, brain ultrasound, rarely CT scan) and laboratory studies (lack of metabolic testing). Lumbar puncture was performed only in infants with suspected infection of central nervous system.

Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, version 13.0) was used for the statistical analysis, as well as CIA (Confidence interval analysis version 2.1.2.).

	n =	%
Male	14	73.7%
Female	5	26.3%
History of prenatal and perinatal events	10	52.6%
Symptomatic Infantile spasms	15	78.9%
Cryptogenic Infantile spasms	4	21.1%
Positive family history of neurological disorders	3	15.8%
Motor and/or psychic delay	17	89.5%

TABLE 1. Descriptive statistics of assessed patients

3. RESULTS

Total of 19 (100%) patients with IS were treated. Descriptive statistics of this group can be found at Table 1 and 2.

	Range	Average
Birth weight 2700 g	1800-4200	2790 g
Gestational age 35,6 weeks	31-42	35.63
Age at diagnosis 3 – 9 months	3-9	4.93

TABLE 2. Descriptive statistics of assessed patients

Several types of seizures were recognized in assessed patients. Types were classified mainly according to seizures seen by doctors, and in some cases on video recordings. Clinical characteristics are summarized at Table 3.

Type of spasms	n =	%
Flexor	9	47.4%
Mixed	6	31.6%
Extensor	4	21.1%

TABLE 3. Clinical characteristics of patients seizures

Some patients had seizures that were accompanied with ictal automatisms, and the most notable were seizures followed by crying in 26.3% of the patients.

Diagnostic workup was tailored individually, but all patients had neuroimaging studies, EEG recordings and ophthalmologic examinations. Changes seen on diagnostic procedures are shown at Table 4.

	n =	%
Changes at brain ultrasound	10	52.6
MRI changes	15	78.9
EEG recordings "hypsarrhythmia"	15	78.9
"burst suppression"	2	10.5
multifocal activity	2	10.5
Changes at eye fundi	16	84.2

TABLE 4. Diagnostic characteristics of assessed patients

Therapy was given according to availability of antiepileptic medications, started as monotherapy, but usually second antiepileptic drug was needed for seizure control, and in some cases three drugs had to be used. Valproate was widely used since it was the only drug that can play a role in controlling infantile spasms readily available. Summary of therapy given and results of seizure control are shown at Table 5.

Outcome of patients with infantile spasms was assessed after follow-up period that lasted 15-70 months (mean 42.5 months). Results are summarized at Table 6.

	n =	%
Therapy		
Monotherapy	4	21.1%
Polytherapy	15	78.9%
Drugs used		
ACTH	3	15.8%
Prednisone	3	15.8%
Valproate	16	84.2%
Vigabatrin	10	52.6%
Topiramate	7	36.8%
Seizure controle:		
good	8	42.1%
more than 50% decrease of seizures	9	47.4%
poor	2	10.5%

TABLE 5. Therapy and seizure control

Outcome	n =	%
Normal	4	21.1%
Spastic tetraparesis, moderate or severe mental retardation	7	36.8%
Hemiparesis	2	10.5%
Mental retardation with/without mild motor impairment	2	10.5%
Died	2	10.5%
Lost at follow-up	2	10.5%

TABLE 6. Outcome of patients with infantile spasms

4. DISCUSSION

Infantile spasms always present great challenge for treatment. There are lots of controversies and despite all efforts outcome is often not satisfactory.

This is an age related syndrome. Infants start with seizures usually in first 6 months of age. Ninety percent of IS begun in patients younger than 12 months (1, 4). In our study age of diagnosis was 3-9 months with the mean of 4.93 months, which is in concordance with results found in literature. IS were diagnosed in males more frequently than in females although the difference was not statistically significant.

Etiology of seizures is of primary interest for prognosis. Nearly 79% of patients in our study were classified as symptomatic IS, others as cryptogenic, with no idiopathic cases. In the study that was conducted by Partikian and Mitchell (4), the majority of the patients (74%) had a symptomatic etiology, with only about one quarter fulfilling criteria for cryptogenic categorization. The most common symptomatic etiologies in their study included congenital brain

malformation, perinatal encephalopathy from various causes, and tuberous sclerosis. Eighteen patients were designated as having a symptomatic etiology due to nonspecific magnetic resonance imaging (MRI) findings demonstrating abnormal myelination pattern or due to developmental delay clearly preceding the onset of spasms.

Prenatal and perinatal factors play an important role in etiology of West syndrome. The most common brain damage in patients with West syndrome is periventricular leukomalacia (PVL). Okumura et al. (8) suggested that a late-onset circulatory dysfunction might be a risk factor for various neurological sequelae including West syndrome, even without gross brain lesions. These findings may explain the anatomical association between the West syndrome onset and PVL and intellectual and cognitive deficit in premature infants with PVL. Yoshinaga et al. 2007 (9) proposed that preterm infants with PVL who showed epileptic discharges before 3 months of corrected age should be treated with the antiepileptic drugs to prevent the onset of WS syndrome but this was not widely accepted.

In our study prenatal and perinatal factors were considered as a potential cause in 52.6% of cases. The average birth weight results in our study indicated a prematurity as an important risk factor in development of West syndrome (9).

EEG registration showed that most of the patients in our study had pattern of "hyparrhythmia" (78.9%) in the beginning of the disease. Patients with symmetric hyparrhythmia and infantile spasms rarely had focal or asymmetric cerebral lesions on imaging studies (most had structural diffuse brain lesions) and overall had better chances for a normal outcome. Drury et al. (10) conducted a study of 26 patients with infantile spasms, and found that 6 patients (23%) had asymmetric hyparrhythmia. All 6 had symptomatic infantile spasms and 5 had focal abnormalities on examination or imaging study. These focal abnormalities may identify a subset of patients with West syndrome who are candidates for epilepsy surgery, focal cortical resections.

Careful ophthalmologic examination of children with infantile spasms can help establishing etiologic diagno-

sis. Ophthalmic examination can reveal chorioretinitis from congenital infections (1, 4). In our study 84% of patients had changes on eye's fundus, mainly pale discs, but they were nonspecific, so it was not possible to identify the cause only by ophthalmologic examination. Ophthalmic examination often reveals chorioretinitis from congenital infections, chorioretinal lacunar defects in patients with Aicardi syndrome, or retinal tubers in patients with tuberous sclerosis (1).

Treating West syndrome is usually controversial. Adrenocorticotrophic hormone (ACTH) remains the treatment of choice for many neurologists (2), but some controlled studies recommended vigabatrin as a first-line therapy, namely in patients with tuberous sclerosis complex. Elterman et al. (11) who conducted a randomized clinical trial of vigabatrin in 32 patients with infantile spasms concluded that their results confirmed previous reports of the efficacy and safety of this drug in patients with infantile spasms, particularly among those with spasms secondary to tuberous sclerosis. Conversely, a multicentric randomized controlled trial, a part of the United Kingdom Infantile Spasms Study, compared vigabatrin with prednisolon or tetracosactide at 14 days and revealed that cessation of spasms was more likely in infants given hormonal treatments than those given vigabatrin, while adverse effects were common with both treatments (12). Mackay et al. 2002 (13) in their evidence-based approach supported the use of ACTH and vigabatrin as the most effective agents in the treatment of infantile spasms in non-tuberous sclerosis patients, but concerns remained about the risk/benefit profiles of these drugs. Reports on visual field defects may limit the use of vigabatrin, but Willmore, Abelson, Ben-Me-nachem et al reported that the prevalence of visual field defects in children on vigabatrin therapy was 15% and retinal defect in infants ranged from 15% to 31%, so they recommended cognitive age-appropriate visual field testing at baseline and repeated at intervals in patients who continue therapy (14).

A practice option recommendation for the use of oral corticosteroids in the treatment of infantile spasms was supported by limited and inconclusive data (13). Topiramate, lamotrigine, and

zonisamide might also be useful in treating spasms (2, 12, 15).

No recommendation could have been made for the use of pyridoxine, benzodiazepines, or the newer antiepileptic drugs in the treatment of infantile spasms (13). Cochrane Database systematic review stated that there was no single treatment proven to be more efficacious in treating infantile spasms than any of the others, but further studies need to be conducted (16).

In our study the therapeutic response to antiepileptic drugs was satisfactory since 42.1% of the patients had their seizures under control. Partial response with more than 50% decreased number of seizures was found in approximately half of the patients (47.4%), while only one fifth of patients (10.5%) had a poor therapeutic response. Most of the patients were on polytherapy, usually consisting of combination of Na-valproate (efficient as monotherapy in only 10.5% of patients) with vigabatrin or topiramate, and in 3 cases of corticosteroid therapy.

Treatment options in our study depended on availability of different antiepileptic drugs, so "standard antiepileptic drugs" were the first line of treatment and treatment while "newer antiepileptic drugs" and corticotrophin depended on possibility to obtain them in certain periods of time, meaning that they were not available for all children all the time. This is common problem in underdeveloped countries and should be addressed.

Surgical treatment has been used successfully in a selected subgroup of patients with secondarily generalized spasms from a single epileptogenic zone. (2, 17)

None of our patients underwent surgery.

Developmental outcome of patients with West syndrome is generally described in literature as poor (1, 2, 4). In our study 21.1% of children remained seizure-free and had normal development, while 57.9% of patients had developmental problems with motor and/or psychic delay. Etiology strongly predicts motor and cognitive outcomes. Patients with cryptogenic infantile spasms were much more likely to have good outcome than those with symptomatic spasms. In the study of Partikian and Mitchell (4) cognitive outcome was normal in 21% of cryptogenic versus 8% of symp-

tomatic patients. Similarly, motor outcome was good or mildly impaired in 57% of cryptogenic participants versus 33% of symptomatic patients. Some new studies (18) outline that cognitive outcome can not be easily attributed to certain antiepileptic drugs. Eighteen to fifty percent of patients will develop Lennox–Gastaut syndrome (1, 19). Croatian 10-year-clinical study showed that 35 of 37 patients with diagnosis of West syndrome had delay in development and various degree of mental retardation (20). Age of onset as well as gender was not predictive of developmental outcome in both symptomatic and cryptogenic patients, but good response to first medication had a good prognostic value (4).

Subsets of patients among the symptomatic West syndrome group seem to have a better prognosis, such as patients with Down syndrome and neurofibromatosis (1, 2, 21, 22)

Kivity et al. 2004 (23) suggested that early treatment of cryptogenic infantile spasms with a high-dose ACTH protocol was associated with favorable long-term cognitive outcome. Once major developmental regression lasts for a month or more, the prognosis for normal cognitive outcome is poor.

Our study showed mortality of 10.5% which correlates with the reported mortality range between 5-31% (1)

5. CONCLUSION

Treatment of infantile spasms presents a great challenge, especially in the developing countries like Bosnia and Herzegovina in which the treatment modalities are limited. Our results indicated that despite the lack of the proper treatment options, outcome of the patients in regard to the control of seizures and latter psychomotor development did not differ significantly from the reports from other countries.

Although the prognosis for most patients with infantile spasms remains

poor, further studies identifying predictors of favorable prognosis and recent advances in understanding the pathophysiology of infantile spasms offer hope of safer and more-effective therapies that improve long-term outcome.

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