ORIGINAL ARTICLE

Infantile Spasms in Children with Down Syndrome: Detroit Experience

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ABSTRACT

Background: Children with Down syndrome (DS) frequently develop infantile spasms (IS); however, variable seizure outcome has been reported and not much is known about the clinical-electrophysiological factors affecting these outcomes. Therefore, we evaluated the clinical, neuroimaging and electrophysiological data in our DS with IS patient cohort, with a relatively long follow-up duration, to address some of these issues.

Methods: This was a retrospective cohort study. Clinical, diagnostic, including radiological, therapeutic and treatment outcome details of 15 children (F: M=7:8) with IS and DS (follow up duration: 10-197 months) were obtained from their clinical records and analyzed.

Results: The median age at onset of spasms was 7 (2-16) months. EEG showed hypsarrhythmia in 10 infants, and patterns of diffusely disorganised background with multifocal independent spike-wave activity in the remaining five. Brain MRI (n=8) revealed no abnormality in 3, delayed myelination in 1, minimal changes in brain volume in 2, and simplified gyral pattern in 2 patients. PET scans (n=5) showed diffuse glucose hypometabolism in 3, focal hypo- or hypermetabolism in 1 and 2 patients, respectively, and increased or decreased basal-ganglia metabolism in one each. Spasms disappeared in 8 patients (53.3%; six off medication), with girls (5/7; 71%) responding slightly better than boys (3/8; 37.5%). Seven of the 8 responders had shown hypsarrhythmia. Cessation of spasms was achieved by ACTH alone (n=1) or in combination with vigabatrin or zonisamide (n=1, each), and monotherapy with zonisamide (n=2), topiramate (n=1), prednisone (n=1), and ketogenic diet (n=1). Two patients showed evolution into complex partial seizure or Lennox-Gastaut syndrome. One child had dystonic cerebral palsy associated with perinatal asphyxia.

Conclusions: Spasms developed relatively later in patients with IS and DS, compared to unknown IS patients, and showed modest response to treatment. Girls appear to have a better treatment response, with presence of hypsarrhythmia may signal a better treatment outcome.

Keywords: Epileptic spasms, Epilepsy, FDG PET, Pediatric, Hypsarrhythmia.

BACKGROUND

The incidence of infantile spasms (IS) is reported to be 1 in 2,000 - 4,000 live births [1, 2]. The long-term sequels associated with IS make it one of the major underlying causes of cognitive impairment following early onset epilepsy. Both motor and cognitive outcomes of IS are strongly related to the underlying etiology of the disorder. Down syndrome represents 17% of prenatal etiologies in structural-metabolic cases of IS and overall accounts for 5 % of patients with IS [3, 4]; however, variable seizure outcome has been reported and not much is known about the exact clinical-electrophysiological factors affecting these outcome.

The majority of earlier studies have reported relatively good treatment outcome of IS in infants with Down syndrome [5-9]. However, there are a few studies that showed persistence of spasms in Down syndrome patients despite receiving seemingly appropriate/adequate treatment [10]. Overall, these investigations are varied in many aspects, including the demographic characteristics, number of patients, associated comorbidities, and selection of drug treatment regimens. For instance, most of the studies did not include ketogenic diet in their treatment regimen and also did not use more sophisticated imaging tests such as high resolution MRI scans in evaluation of the subjects. Previous studies also reported different relationships between EEG findings and the prognosis of seizures [5-10]. It would be useful to determine whether IS has an impact on the prognosis of epilepsy in Down syndrome so that the parents can be counselled more accurately. We examined the clinical, neuroimaging and electrophysiological data in our DS with IS patient cohort, with a relatively long follow-up duration, to evaluate the effect of various clinical-electrophysiological factors on seizure outcome, including the response of IS to anti-epileptic medications and the ketogenic diet in a cohort of patients with Down syndrome evaluated over a 17-year period at two medical centers in the state of Michigan, USA.

METHODS

Between 1997 and 2014, a total of seventeen patients with infantile spasms associated with Down syndrome were seen at the Children's Hospital of Michigan, Detroit (n=15) and the Hurley Medical Center, Flint, (n=2) Michigan. At least one of the other concomitant disorders associated with Down syndrome was also present in every patient of the group, including congenital heart defects, hypothyroidism, hearing deficits, sleep apnea, aspiration pneumonia and gastroesophageal reflux disease. We excluded the data of two patients who were diagnosed with malignancies (glioblastoma, acute lymphoblastic leukemia) shortly after onset of the spasms. The medical records of a total of fifteen patients were reviewed and data on demographics, semiology of seizures, diagnostic tests, and treatment response were extracted (follow-up duration, 10-197 months). The data were subsequently updated, if necessary, by telephone interviews with the family.

RESULTS

Patients and Clinical Presentation

Current age of the patients (seven girls, eight boys) ranged from 2-17 years, and the median age at the onset of spasms was 7 months (range: 2-16 months). Spasms were either flexor (79%) or extensor (21%). Spasms were symmetrical in all patients except one who had asymmetric extensor spasms, more pronounced on the right side.

None of the patients were ill at the time when spasms began, except a ten-month-old boy who developed asymmetric extensor spasms while undergoing treatment for staphylococcal scalded skin syndrome. No other types of seizures were present in any of the patients prior to the onset of the IS.

Two infants were born pre-term due to premature rupture of membranes or intrauterine growth retardation. History of fetal distress syndrome was evident in two infants (one preterm, one full-term), of which one developed dystonic cerebral palsy.

Personal or family history for non-febrile seizures in first-degree relatives was negative in all but one patient. Two infants had one each of a second or third-degree relative diagnosed with epilepsy. A history of post-traumatic seizures was evident in third-degree relatives of two infants.

Five patients underwent surgeries for the repair of heart defects (n=2), atlanto-axial subluxation (n=1), esotropia (n=1), and hypospadias (n=1), which were all uneventful.

Electroencephalogram

The EEG performed in all patients shortly after the onset of spasms revealed hypsarrhythmia in ten infants, and patterns of diffusely disorganised or slow background with occasional interictal sharp waves in the others. In three patients with a relatively late onset of spasms (age at onset: 10, 8, and 16 months), interictal EEG showed frequent sharp wave activity in bilateral frontal regions. In one patient who had asymmetric spasms, hypsarrhythmia was more pronounced in the hemisphere contralateral to the major motoric involvement. However, none of the patients showed focal onset on the EEG.

Neuroimaging

Brain MRI was acquired in eight patients and was either normal or showed some non-specific changes. It revealed completely normal morphology in three, delayed myelination with diffuse volume loss in cortex and brain stem, likely related to recent ACTH, in one, subtle asymmetric changes in the volume of different brain areas in two and simplified gyral pattern in the remaining two patients with evident mild microcephaly.

Five patients underwent F-18-fluorodeoxyglucose (FDG) PET scans shortly after being diagnosed with IS. The FDG PET revealed diffuse hypometabolism in three patients; among these, two also showed a small focus of hypermetabolism in the left frontal cortex (Figure 1). The FDG PET scan in one infant, who was diagnosed with dystonic cerebral palsy at a later age, showed bilateral hypometabolism in temporal lobe, basal ganglia and thalamus. 11C-PK11195 (PK) PET scan, which binds to the translocator receptor protein expressed by activated microglia and therefore shows microglia-mediated neuroinflammation, was performed in one patient. It showed increased tracer binding in left caudate and left thalamus, suggesting underlying neuroinflammatory changes in these regions (Figure 2).
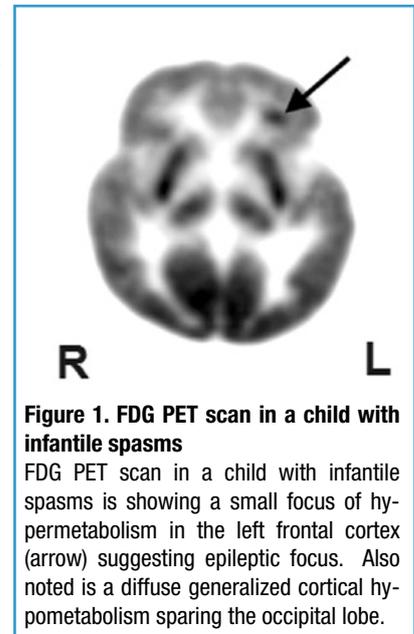

Figure 1. FDG PET scan in a child with infantile spasms
FDG PET scan in a child with infantile spasms is showing a small focus of hypermetabolism in the left frontal cortex (arrow) suggesting epileptic focus. Also noted is a diffuse generalized cortical hypometabolism sparing the occipital lobe.
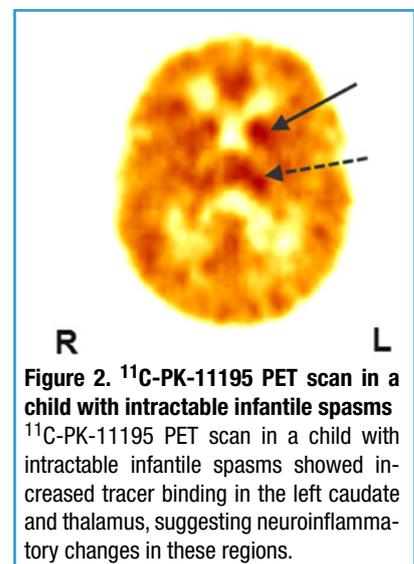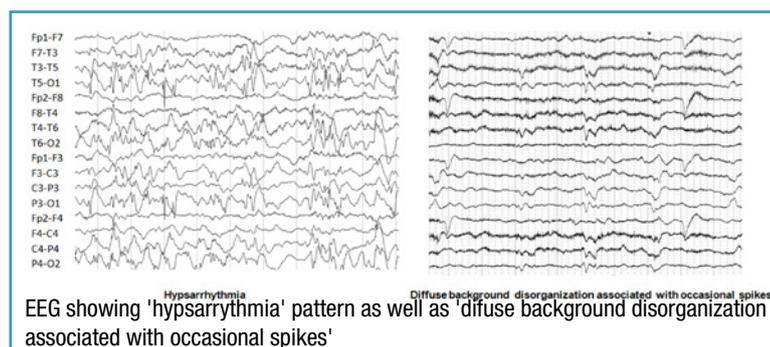

Figure 2. ^{11}C-PK-11195 PET scan in a child with intractable infantile spasms
^{11}C-PK-11195 PET scan in a child with intractable infantile spasms showed increased tracer binding in the left caudate and thalamus, suggesting neuroinflammatory changes in these regions.

Treatment Outcomes

Table-1 summarizes the administered treatments, and seizure outcomes at the most recent follow-up. Anti-epileptic treatments were admin-

EEG showing 'hypsarrhythmia' pattern as well as 'diffuse background disorganization associated with occasional spikes'

Table 1. Treatment details and outcome

Patients	Treatments in Order	Successful Treatment	Status at Last Follow-up Visit	Follow-up Duration (Month)
A	13	Zonisamide	Spasms Free	144
B	9	Topiramate	Spasms Free	76
C	14	Ketogenic Diet	Spasms Free	79
D	1,9,10,7,13,10	ACTH+ Zonisamide	Spasms Free	47
E	13	Zonisamide	Spasms Free	18
F	9, 7, 10	ACTH+ Vigabatrin	Spasms Free	99
G	16, 10	ACTH	Spasms Free	46
H	3, 9, 16	Prednisone	Spasms Free	57
I	13, 7, 1	None	Persistent Spasms	10
J	10,14,6,7	None	Persistent Spasms	23
K	6, 7, 4, 10, 14	None	Persistent Spasms	30
L	1, 6, 9, 15,7	None	Persistent Spasms	18
M	1, 2, 3, 4, 5,6	None	Lennox Gastaut Syndrome	191
N	7, 2, 8, 4, 9, 10, 3, 1, 11, 12	None	Complex Partial Seizure	182
O	10,7,1,4	None	Deceased	12

1: Valproic acid, 2: Lamotrigine, 3: Levetiracetam, 4: Clobazam, 5: Rufinamide, 6: Clonazepam, 7: Vigabatrin, 8: Phenytoin, 9: Topiramate, 10: ACTH, 11: Lacosamide, 12: Oxcarbazepine, 13: Zonisamide, 14: Ketogenic diet, 15: Prednisolone, 16: Prednisone

istered to 14 out of 15 children. Ketogenic diet was tried in three children, including one female patient whose family refused the use of any medication. In this patient, clusters of two to three flexor spasms began at the age of six months. After multiple counselling, the family accepted ketogenic diet treatment which started at the age of seventeen months. The spasms then gradually decreased in frequency and eventually disappeared within few days after introducing the high ratio (4:1) ketogenic diet. This girl also received potassium citrate and multivitamins and showed no diet-induced side effects except occasional nausea and vomiting. Seizures did not recur over the following two years after the administration of high ratio ketogenic diet and multiple follow-up video-EEG recordings performed were normal. The patient was gradually put back on a normal diet after two years and was still seizure-free at the time of evaluation (duration= 56 months). The other two children did not respond to the ketogenic diet.

A total of eight patients (53.3%), five girls and three boys, became seizure-free in response to antiepileptic medications and/or ketogenic diet; four patients responded to the first anti-epileptic treatment, where as the remaining four re-

sponded after two or more medications. Subsequent EEGs, performed in all these responders, did not show any epileptic changes. No relapse was reported (follow-up duration, 46-144 months) in these responders, with six off any medication. It appears that girls responded slightly better; five out of seven girls (71%) versus three out of eight boys (37.5%) responded to treatments and became seizure free. Hypsarrhythmia was the most commonly seen EEG pattern among the responders, seen in 7 out of 8 responders (87.5%). No significant relation was noticed between the semiology of spasms and treatment response.

Seizures persisted in seven patients (two girls, five boys); of these, one girl and one boy showed seizure evolution to Lennox-Gastaut syndrome and focal seizure, respectively. Among the seven non-responders, temporary periods of cessation of spasms were noticed in three patients in response to ACTH (n=2) and vigabatrin (n=1). However, seizures relapsed in all three, and one died of complicated pneumonia within one year after the diagnosis of infantile spasms, while he was still being treated with vigabatrin, valproic acid, and clobazam.

DISCUSSION

Median age at the onset of IS in DS children was 7 months, at the higher end of the reported age range for unknown IS patients [11]. Our study showed a modest treatment outcome in IS associated with Down syndrome (53.3%), in response to antiepileptic medications and/or ketogenic diet, compared to several previous studies who demonstrated either a relatively better outcome compared to the general IS population [6, 7, 9, 12, 13], or extremely unfavorable outcome with 100% treatment failure [10, 14]. It also appears that female DS patients with IS responded relatively better compared to male patients and hypsarrhythmia was the most commonly seen EEG pattern among the responders.

The discrepancies between the results of previous studies could result from several reasons, including heterogeneity of the study population, variation in electroencephalogram findings, and differences in treatment options offered to the patients. For instance, in some of the studies with relatively good treatment outcomes, patients with concomitant congenital heart disease having required open heart surgery or with history of fetal distress were excluded from the study [9]. In addition, not all of the previous studies provide comprehensive data about accompanying medical problems in their population [10]. In our study, we included patients with concomitant disorders except for malignancies having required chemotherapy or radiotherapy, and our findings did not show any significant relation between history of congenital heart disease or surgery, and treatment outcome.

Previous studies suggest that the developmental outcome of IS associated with Down syndrome appear to be poorest in patients with a superimposed hypoxic insult [9]. In our study, two infants had shown respiratory distress at the time of birth. One of them was subsequently diagnosed with dystonic cerebral palsy, and the other later developed Lennox-Gastaut syndrome. Spasms in these patients (Patients 'I' and 'M' in table 1) never completely responded to appropriate anti-epileptic medications. This finding is consistent with the conclusions of former studies [9].

Electroencephalogram characteristics in IS have been studied in detail by various researchers. It has been shown that hypsarrhythmia is evident in 64% of structural-metabolic IS and has the most consistent association with Down syndrome [15]. Several studies have suggested a comparatively better outcome of IS in patients with Down syndrome who also show hypsarrhythmia on EEG. In a study that analyzed the results for nine patients, seven became seizure-free after receiving anti-epileptic medications [7]. Although that study concluded that there was no relationship between initial EEG patterns and response to treatment, all nine patients showed hypsarrhythmia (n=5) or modified hypsarrhythmia (n=4). In another study with 100% rate of successful treatment (n=9), eight patients showed hypsarrhythmia on their initial EEG [6]. Hypsarrhythmia was evident on the EEG of 100% of sample populations in other similar investigations that showed relatively better outcome of IS in patients with Down syndrome (rate of cessation of spasms, respectively : 93%, 80%, 72%, 91%, 67%) [4, 5, 8, 12, 16]. On the other hand, in an albeit small study reporting 100% failure in treatment of IS associated with Down syndrome (n=3), none of the patients showed hypsarrhythmia on their initial EEG [10, 17]. EEG reports included slow and unstructured background accompanied by multifocal spike-and-wave discharges in left quadrants (n=2) or bilateral parieto-occipital regions (n=1). The same study reported that despite early treatment with multidrug regimens, patients with Down syndrome who do not show hypsarrhythmia on EEG may fail to become seizure-free [10, 17]. In our analysis, seven out of eight responders had hypsarrhythmia evident on their initial EEG, and four out of seven patients who did not respond to multiple trials of medications showed EEG patterns other than hypsarrhythmia. It should be noted that some studies have demonstrated poor seizure outcome in unknown IS without hypsarrhythmia [18]. This might also be the case in patients with Down syndrome and further studies with larger numbers of patients are needed to verify the notion that hypsarrhythmia may be a good prognostic feature for IS in Down syndrome.

Earlier treatment and good initial response have been associated with a favorable prognosis of IS in both unknown and structural-metabolic groups [5, 19, 20]. On the other hand, some studies have stated that the lag time to initiation of treatment was not predictive of outcome, even when controlling for etiology [21]. In our study, the longest lag time was for a girl who received ketogenic diet eleven months after the onset of spasms, and became seizure-free. All other patients received treatments within a few days or weeks after the onset of spasms. The spasms may not always be immediately noticed by parents and, therefore, the lag time reported in previous retrospective studies may not be totally free of bias. In the present study, we could not statistically analyze the relation between the treatment lag and the spasms outcome in patients with Down syndrome because of inadequate reporting.

Our results showed no clear relation between the type of applied anti-epileptic medications and seizure outcome, probably because of the small numbers. Our study suggests a beneficial role of ketogenic diet in DS patients with IS. The diet did not cause any significant side effects besides nausea and vomiting in three patients who tolerated and continued it. One patient completely responded to monotherapy with the ketogenic diet. Ketogenic diet has been well known as a good therapeutic option in IS refractory to anti-epileptic medications [2, 22]; however, the beneficial role of the diet in IS has rarely been investigated among patients with Down syndrome. Further investigations with a larger number of patients are necessary to evaluate the usefulness of the ketogenic diet as the initial treatment for IS in patients with Down syndrome.

The mean age at the onset of spasms in our patients (7 months; range: 2-16 months) was slightly higher compared to the onset of unknown spasms (5 months) [11]. The relatively later onset of spasms in patients with Down syndrome has also been reported in previous studies, such as at ages of 12, 13, 16, and 18 months [4, 5, 8, 23]. It has been suggested that the age of onset of spasms is related to the maturational state of the cortical region initiating the spasms through its interaction with subcortical structures, such as brainstem and basal ganglia [24-28]. In other words, frontal cortex, which shows maturational changes later than posterior cortical regions, would be expected to initiate spasms later than parietal, temporal and occipital regions. There are now substantial data to support this notion. For example, in a study that investigated the late onset of spasms in 34 patients with structural-metabolic or unknown spasms, 51.6% of patients exhibited focal anteriorly predominant interictal epileptiform activity, suggesting a possible pathogenicity of fronto-temporal regions in this age-dependent epileptic encephalopathy [28]. In another study, the age of onset of IS in patients with tuberous sclerosis was related to the localization of cortical tubers, with a later expression of spasms

in frontal compared to parieto-occipital tubers [29]. In our study, interictal generalized sharp-wave activity with frontal predominance was evident in the EEG of three patients in whom spasms started at 8, 10, and 16 months of age. Neuroimaging tests performed on two of them revealed no abnormality in the frontal cortex. One study that evaluated the video-EEG patterns of adults with epilepsy and Down syndrome (n=22) reported slowing of background activity with sharp-and-slow waves showing frontal predominance in most patients [30]. Some investigations that evaluated the neuroimaging aspects of frontal lobe in patients with Down syndrome reported shortened frontal lobe dimension in fetuses with this disorder [31], and significantly lower white matter integrity in frontal tracts [32]. Although the later onset of seizure has been investigated in unknown spasms [27, 33, 34], to our knowledge, this has not been analyzed in patients with Down syndrome. Therefore, our findings raises a possibility of the primary generator of infantile spasms in Down syndrome being located in the frontal cortex, which may be consistent with the reported preponderance of frontal lobe epileptogenicity in Down syndrome. However, further prospective studies in larger sample size are needed to verify this notion.

CONCLUSIONS

Spasms developed relatively later in patients with IS and DS, compared to unknown IS patients, and showed modest treatment response compared to previous studies reporting relatively better or extremely unfavorable response. Girls appear to have a better treatment response, and presence of hypsarrhythmia may signal a better treatment outcome.

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Cite this article as: Marandi et al: Infantile Spasms in Children with Down Syndrome: Detroit Experience. JICNA 2016 16:116