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Research Paper

Extended Glasgow Outcome Scale to Evaluate the Functional Impairment of Patients With Subcortical Band Heterotopia: A Multicentric Cross-sectional Study

Irene Toldo, MD, PhD [a, *], Francesco Brunello, MD [a], Paola Cavasin, MD [a], Margherita Nosadini, MD, PhD [a], Stefano Sartori, MD [a], Anna Chiara Frigo, MD [b], Roberto Mai, MD [c], Veronica Pelliccia, MD [c], Maria Margherita Mancardi, MD [d], Pasquale Striano, MD [d], Marisavina Severino, MD [e], Federico Zara, MD [f], Romana Rizzi, MD [g], Susanna Casellato, MD [h], Gabriella Di Rosa, MD [i], Mario Mastrangelo, MD [j], Alberto Spalice, MD [k], Mauro Budetta, MD [l], Luca De Palma, MD [m], Renzo Guerrini, MD [n], Dario Pruna, MD [o], Duccio Maria Cordelli, MD [p], Vito Sofia, MD [q], Amanda Papa, MD [r], Valentina Chiesa, MD [s], Francesca Ragona, MD [t], Pasquale Parisi, MD [u], Alfredo D'Aniello, MD [v], Pierangelo Veggiotti, MD [w], Filippo Dainese, MD [x], Lucio Giordano, MD [y], Laura Licchetta, MD [z], Paolo Tinuper, MD [z], Giuseppe D'Orsi, MD [aa], Matteo Cassina, MD, PhD [ab], Renzo Manara, MD [ac]

[a] *Child Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy*
[b] *Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy*
[c] *'Claudio Munari' Centre for Epilepsy Surgery, ASST GOM Niguarda, Milan, Italy*
[d] *Child Neuropsychiatry Unit, Clinical and Surgical Neurosciences Department, IRCCS Istituto Giannina Gaslini, Genova, Italy*
[e] *Pediatric Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy*
[f] *Laboratory of Neurogenetics and Neuroscience, IRCCS Istituto G. Gaslini, Genova, Italy*
[g] *Neurology Unit, Department of Neuro-Motor Diseases, Azienda Unità Sanitaria Locale IRCCS, Reggio Emilia, Italy*
[h] *Child Neuropsychiatry Unit, University Hospital of Sassari, Sassari, Italy*
[i] *Child Neuropsychiatry Unit, Department of Human Pathology of the Adult and Developmental Age, University Hospital "G. Martino", Messina, Italy*
[j] *Unit of Child Neurology and Psychiatry, Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy*
[k] *Department of Pediatrics, Child Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy*
[l] *Pediatric and Child Neurology Unit, Cava de' Tirreni AOU S. Giovanni di Dio e Ruggiero d'Aragona Hospital, Salerno, Italy*
[m] *Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[n] *Pediatric Neurology, Neurogenetics and Neurobiology Unit and Laboratories, Meyer Children's Hospital, University of Florence, Florence, Italy*
[o] *Pediatric Neurology and Epileptology Unit, "Brotzu" Hospital, Cagliari, Italy*
[p] *IRCCS Institute of Neurological Sciences of Bologna, UOC Neuropsychiatry of the Pediatric Age, Bologna, Italy*
[q] *Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy*
[r] *Department of Child Neurology and Psychiatry, AOU Maggiore della Carità Novara, Novara, Italy*
[s] *Epilepsy Centre-Child Neuropsychiatry Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy*
[t] *Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*
[u] *Child Neurology, Faculty of Medicine & Psychology, NESMOS Department, Sapienza University, Rome, Italy*
[v] *IRCCS "NEUROMED", Pozzilli, Italy*
[w] *Pediatric Neurology Unit, V. Buzzi Hospital, University of Milan, Milan, Italy*
[x] *Epilepsy Centre, SS. Giovanni e Paolo Hospital, Venice, Italy*
[y] *Child Neuropsychiatric Division, Spedali Civili, Brescia, Italy*
[z] *Department of Biomedical and Neuromotor Sciences, University of Bologna, Milan, Italy*
[aa] *Epilepsy Centre, Clinic of Nervous System Diseases, Ospedali Riuniti, University of Foggia, Foggia, Italy*
[ab] *Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, Padova, Italy*
[ac] *Neuroradiology, Department of Neuroscience, University of Padova, Padova, Italy*

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* Communications should be addressed to: Dr. Toldo; Child Neurology and Neurophysiology Unit; Department of Women's and Children's Health; University Hospital of Padua; via Giustiniani, 3; Padova 35128, Italy.
E-mail address: irene.toldo@unipd.it (I. Toldo).

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ABSTRACT

Background: Subcortical band heterotopia (SBH) is a rare malformation of the cortical development characterized by a heterotopic band of gray matter between cortex and ventricles. The clinical presentation typically includes intellectual disability and epilepsy.
Purpose: To evaluate if the Extended Glasgow Outcome Scale-pediatric version (EGOS-ped) is a feasible tool for evaluating the functional disability of patients with (SBH).
Method: Cross-sectional multicenter study of a cohort of 49 patients with SBH (female n = 30, 61%), recruited from 23 Italian centers.
Results: Thirty-nine of 49 (80%) cases showed high functional disability at EGOS-ped assessment. In the poor result subgroup (EGOS-ped >3) motor deficit, language impairment, and lower intelligence quotient were more frequent ($P < 0.001$, $P = 0.02$, and $P = 0.01$, respectively); the age at epilepsy onset was remarkably lower ($P < 0.001$); and the prevalence of epileptic encephalopathy (West syndrome or Lennox-Gastaut-like encephalopathy) was higher ($P = 0.04$). The thickness and the extension of the heterotopic band were associated with EGOS-ped score ($P < 0.01$ and $P = 0.02$). Pachygyria was found exclusively among patients with poor outcome ($P < 0.01$).
Conclusions: The EGOS-ped proved to be a reliable tool for stratifying the functional disability of patients with SBH. According to this score, patients could be dichotomized: group 1 (80%) is characterized by a poor overall functionality with early epilepsy onset, thick heterotopic band, and pachygyria, whereas group 2 (20%) is characterized by a good overall functionality with later epilepsy onset and thinner heterotopic band.

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Introduction

Subcortical band heterotopia (SBH) is a rare malformation of the cortical development characterized by a heterotopic band of gray matter between cortex and ventricles. The subcortical band can be localized in only one lobe, or it can extend to the entire hemisphere, usually bilaterally; the thickness varies from a few millimeters to more than a centimeter.

The clinical presentation typically includes intellectual disability and epilepsy, but the phenotypic spectrum varies from healthy carriers to patients with a severe neurological and cognitive impairment.[1]

Previous works evaluated the relationships existing between specific neuroradiological parameters and clinical features in patients with SBH,[2,3] but an overall assessment of functional disability as well as studies focused on the association between global functional disability and neuroradiological features are still lacking in the literature.

The Extended Glasgow Outcome Scale-pediatric version (EGOS-ped) is an interesting and validated tool used for classifying the overall neurological outcome in pediatric patients who suffered from head trauma,[4] mostly comparing the level of daily life autonomy of affected patients with normal healthy controls of the same age. Despite its potential, until now its use has not been extended to other types of patients with social, psychic, and neurological impairment.

Aim of the study

This study aims to evaluate if the EGOS-ped assessment is an easy and effective semiquantitative tool able to classify the functional disability and correlate with clinical phenotype and/or neuroradiological parameters of patients with SBH.

Materials and Methods

Participants

This was a cross-sectional multicenter study in patients with neuroradiological confirmed diagnosis of SBH, recruited from 23 Italian centers of Child Neurology.

Inclusion criteria were

(1) confirmed neuroradiological diagnosis of SBH and
(2) availability of the clinical data and the EGOS-ped assessment.

The patients' records were handled with respect of confidentiality, and the study protocol was approved by the Institutional Review Board of the Department of Woman's and Child's Health of Padua (10-03-2014, protocol number AOP0353). The study was conducted according to good clinical practice recommendations of the local Ethics Committee.

Clinical data

The clinical data collected for each patient included.

(1) Gender and age;
(2) Genetics: genetic testing and results, focusing on double-cortin gene (*DCX*) and lissencephaly 1 gene (*LIS1*) mutations;
(3) Neurological examination: head circumference, motor and/or language disorders, cognitive assessment;
(4) Epilepsy: age of onset, clinical evolution and features, number and type of antiseizure medications (ASMs) used.

A clinical report form, created *ad hoc* for this study, was used to standardize the collection of patients' clinical data (Supplementary Material S1).

Extended Glasgow Outcome Scale-pediatric version (EGOS-ped)

During the last follow-up, the overall neurological and functional outcome of each patient was evaluated using the EGOS-pediatric version.

Even though this scale was initially created and validated to assess the neurological outcome in patients with head trauma, a previous study showed that the EGOS-ped is comparable with the Vineland Adaptive Behavior Scales assessment, as it concerns the evaluation of the overall functionality of patients.[4] The Vineland Adaptive Behavior Scales analyze five functional domains: communication, daily activities, socialization, motor skills, and adaptive behavior; they require a specific preparation of the

evaluator, and they take a remarkable amount of time (up to two hours) to be performed. EGOS-ped is easy to administer, and it takes less than 10 minutes to be completed: it is a simple flow chart of questions, which can be easily answered by patients' caregivers; the assessment defines a numerical score, which indicates the level of functional disability, from 6 (severe disability) to 1 (normal overall functionality) (Supplementary Material S2). The original score included a seventh class (corresponding to vegetative state), which has not been considered in the present study because it was not applicable.

Even though the study population also included adults, the EGOS-ped assessment was applied to the whole cohort because the structure and the final score system are the same in both adult and pediatric versions of the EGOS questionnaire, except for the formulation of each question, which, in the EGOS-ped, is adjusted to fit any age, from the early childhood to adulthood.

Neuroradiological data

Each patient with SBH recruited in this study was diagnosed using brain magnetic resonance imaging (MRI) (1 T, 1.5 T, or 3T depending on the MRI device available at each center).

In the majority of cases, patients' MRI was reviewed in the leading center of the study (University of Padua) by a neuroradiologist with a consolidated clinical experience in brain malformations diagnosis (R.M.).

The following neuroradiological parameters were calculated, according to the classification system created by Barkovich[2]:

(1) Localization, extension, and maximum thickness of the SBH, measured in the frontal, parietal, temporal, and occipital lobes. The thickness of the band was classified into four categories: 1= <4 mm, 2 = 4 to 8 mm, 3 = 8 to 12 mm, 4= >12 mm;
(2) Frontal horn ratio ([FHR] the ratio of the distance between the lateral tips of the frontal horns to the distance between the inner tables of the frontal horns at the level of the frontal horns) was classified as 1 = normal (FHR < 35%), 2 = mildly dilated (35% < FHR < 40%), 3 = moderately dilated (40% < FHR 5 50%), or 4 = severely dilated (FHR > 50%);
(3) T2 prolongation in the cerebrum was graded as 1 = normal, 2 = periventricular, 3 = subcortical, or 4 = both subcortical and periventricular;
(4) Presence of pachygyria (1 = normal gyri, 2 = slightly broad gyri, 3 = pachygyria).

Furthermore, white matter hyperintensity (absent/present) and polymicrogyria (absent/present) were taken into consideration, due to the high prevalence of these findings during the MRI evaluation process.

Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows. Statistical significance was declared for $P < 0.05$.

As we found a bimodal distribution of the outcome variable in our cohort (as shown in Fig), to simplify and make more consistent the statistical analysis, we decided to dichotomize the outcome variable into (1) good outcome (EGOS-ped classes 1 and 2); and (2) poor outcome (EGOS-ped classes 3 to 6).

Quantitative variables were summarized with median and interquartile range; for categorical variables we used number and percentage of patients in each category. Mann-Whitney test and chi-square or Fisher exact test were applied to compare patients with good and poor outcome.

Results

The study population included 49 patients (female n = 30, 61%) with neuroradiological diagnosis of SBH (Table 1). Thirty-nine of 49 (80%) cases had a poor outcome at EGOS-ped assessment, whereas 10 of 49 (20.4%) had a good outcome. The median age at the study enrollment in the overall cohort was 21 years (Q1 = 12 y, Q3 = 31 y), and it was significantly lower among the poor outcome subgroup ($P = 0.002$).

As shown in Table 1, the EGOS-ped assessment was significantly associated with the neurological examination and the intelligent quotient (IQ) score. In particular, motor deficit, language impairment, and lower IQ score were more frequent among patients with poor outcome ($P < 0.001$, $P = 0.02$, and $P = 0.01$, respectively).

Notably, microcephaly was found exclusively among patients with poor outcome, even though this association did not reach statistical significance ($P = 0.17$).

Forty-six of 49 (94%) cases had epilepsy. Three cases still did not have epilepsy, but two of them were younger than two years at last follow-up and already had many multifocal electroencephalographic epileptiform abnormalities.

The median age at epilepsy onset was remarkably lower in the poor outcome subgroup (3 y vs 14 y, $P < 0.001$). Epileptic encephalopathy (West syndrome or Lennox-Gastaut-like encephalopathy) was diagnosed at onset in 37% of patients with poor outcome, whereas none of the patients in the good outcome group had this severe presentation ($P = 0.04$). However, the frequency of seizures, the effectiveness and the number of ASMs used during their lifetime did not show remarkable differences in the two groups of patients.

Thirty-eight of 49 (78%) patients were tested for *DCX* and *LIS1* mutations: 15 of 38 (38%) cases carried a *DCX* mutation, whereas only four of 38 (10%) cases carried a *LIS1* mutation. In one case a deleted chromosomal segment on Xq22.3 spanning 538 kb was found; the deletion allowed the loss of the entire p21 Protein-Activated Kinase 3 Gene (*PAK3*) gene and the interruption of the *DCX* gene with the loss of 3' portion gene sequence. In three cases, mutations were found in different genes: Dynein Cytoplasmic 1 Heavy Chain 1 Gene (*DYNC1H1*), Tubulin Alpha 1A Gene (*TUBA1A*), and Beta-Actin Gene (*ACTB*). In another case a mutation in the Neural Precursor Cell Expressed Developmentally Downregulated Gene 4-like (*NEDD4L*) gene was found in heterozygosis, and the same proband also presented a mutation in the TSC Complex Subunit 2 Gene (*TSC2*); the pathogenicity of these mutations is unclear, and it was not possible to extend the analysis to the parents. Interestingly, mutations of the *NEDD4L* gene have been found to be associated with periventricular nodular heterotopia.[5] We did not observe significant differences in distribution of the *DCX* and *LIS1* mutations between the poor and the good outcome subgroups (Table 2).

Brain MRI was available for review in 40 of 49 (82%) cases: eight of 10 (80%) of the good outcome group and 32 of 39 (82%) of the poor outcome group.

The associations between EGOS-ped assessment and neuroradiological parameters have been summarized in Table 3. The frontal, parietal, temporal, and occipital thickness of the heterotopic band were associated with EGOS-ped evaluation; in particular, a thicker band was more likely to be found among patients with poor outcome in all four lobes ($P = 0.02$, $P < 0.01$, $P = 0.02$, $P < 0.01$). Moreover, the maximum thickness of the heterotopic band, regardless of its localization, was associated with EGOS-ped assessment ($P < 0.01$). As it concerns the extension

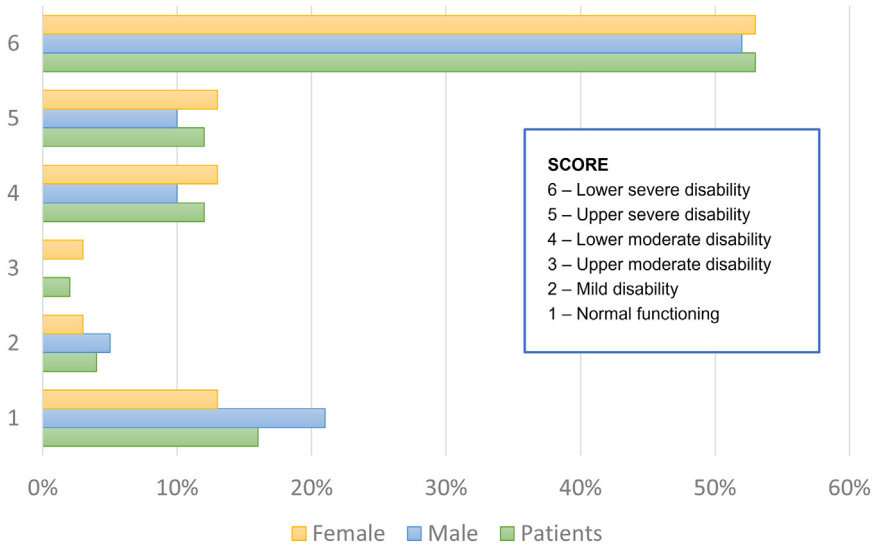

FIGURE. Distribution of patients (female, male, and total number) among EGOS-ped classes. The color version of this figure is available in the online edition.

of the band, the involvement of three or more lobes for hemisphere was significantly more frequent among patients with poor outcome ($P = 0.02$). Pachygyria, even in its milder form (slightly broad gyri), was found exclusively among patients with poor outcome ($P < 0.01$), as far as T2 prolongation in the ventricular or subcortical area ($P = 0.14$).

TABLE 1.
Distribution of Clinical Variables Among Poor Outcome and Good Outcome Groups

Variable	N°	Good Outcome (N = 10)	Poor Outcome (N = 39)	Combined (N = 49)	*P* Value
Gender	49				0.479
Male		50% (5)	36% (14)	39% (19)	
Female		50% (5)	64% (25)	61% (30)	
Age at study enrollment (years) median (IQR)	49	31 (26-38)	18 (10-25)	21 (12-31)	**0.002**
Head circumference	46				0.171
Normocephaly		100% (9)	76% (28)	80% (37)	
Microcephaly		0% (0)	24% (9)	20% (9)	
Motor deficit	49				**<0.001**
Absent		100% (10)	36% (14)	49% (24)	
Present		0% (0)	64% (25)	51% (25)	
Speech disorder	49				**0.015**
Absent		90% (9)	46% (18)	55% (27)	
Present		10% (1)	54% (21)	45% (22)	
IQ	21				**0.006**
Normal (>85)		100%(3)	6% (1)	19% (4)	
Borderline (70-85)		0% (0)	6% (1)	5% (1)	
Mild mental retardation (55-69)		0% (0)	28% (5)	24% (5)	
Moderate mental retardation (40-54)		0% (0)	56% (10)	48% (10)	
Severe mental retardation (<40)		0% (0)	6% (1)	5% (1)	
Epilepsy	49				1.000
Absent		0% (0)	8% (3)	6% (3)	
Present		100% (10)	92% (36)	94% (46)	
Age at epilepsy onset (months) median (IQR)	42	168 (102-108)	36 (8-72)	47 (13-108)	**<0.001**
Type of epilepsy at onset	44				**0.040**
Focal epilepsy		100% (9)	63% (22)	71% (31)	
Epileptic encephalopathy		0% (0)	37% (13)	29% (13)	
N° of ASMs median (IQR)	46	5 (2-9)	5 (4-8)	5 (3-8)	0.841
Seizure occurrence	45				0.226
No seizures in the last 12 months		20% (2)	6% (2)	9% (4)	
Monthly		40% (4)	37% (13)	38% (17)	
Weekly		40% (4)	34% (12)	36% (16)	
More than daily		0% (0)	23% (8)	18% (8)	
Seizure control	45				0.397
Total		30% (3)	11% (4)	16% (7)	
Partial		60% (6)	74% (26)	71% (32)	
No improvement with therapy		10% (1)	14% (5)	13% (6)	

Abbreviations:
ASM = Antiseizure medication
IQ = Intelligence quotient
IQR = Interquartile range
N° = Number
Bold indicates statistical significance ($P \leq 0.05$).

TABLE 2.
Distribution of DCX and LIS1 Mutations Among Poor Outcome and Good Outcome Groups

Variable	N°	Good Outcome (N = 10)	Poor Outcome (N = 39)	Combined (N = 49)	*P* Value
DCX	39				1.000
Not mut		67% (4)	66% (20)	62% (24)	
Mut		33% (2)	39% (13)	38% (15)	
LIS1	39				1.000
Not mut		100% (6)	88% (29)	90% (35)	
Mut		0% (0)	12% (4)	10% (4)	
Total n° of genetic determined cases *(mutation of DCX, LIS1, DYNC1H1, TUBA1A, or ACTB)*	39				0.221
Not mut		67% (4)	39% (13)	44% (16)	
Mut		33% (2)	61% (20)	56% (22)	

Abbreviations:
Mut = Mutated
N° = Number

Discussion

Differently from previous studies,[2,3,6] in which single and specific clinical parameters (IQ, epilepsy severity, motor or language disorders) were associated with the neuroradiological and/or genetic features, in our study we searched for a quantitative and standardized method able to synthetize the functional profile of patients with SBH. So far, a specific functional evaluation score is not available for patients with brain malformations, so we decided to adopt the EGOS-ped given its characteristics.[4]

TABLE 3.
Distribution of Neuroradiological Features Among Poor Outcome and Good Outcome Groups

Variable	N°	Good Outcome (10)	Poor Outcome (39)	Overall (49)	*P* Value
Frontal thickness	38				**0.022**
No band		25% (2)	3% (1)	8% (3)	
<4 mm		25% (2)	7% (2)	10% (4)	
4-7 mm		25% (2)	13% (4)	16% (6)	
8-11 mm		25% (2)	37% (11)	34% (13)	
>12 mm		0% (0)	40% (12)	32% (12)	
Parietal thickness	39				**<0.001**
No band		12% (1)	3% (1)	5% (2)	
<4 mm		63% (5)	0% (0)	13% (5)	
4-7 mm		25% (2)	19% (6)	20% (8)	
8-11 mm		0% (0)	29% (9)	23% (9)	
>12 mm		0% (0)	49% (15)	39% (15)	
Temporal thickness	39				**0.015**
No band		38% (3)	3% (1)	10% (4)	
<4 mm		50% (4)	26% (8)	31%(12)	
4-7 mm		12% (1)	29% (9)	26% (10)	
8-11 mm		0% (0)	29% (9)	23% (9)	
>12 mm		0% (0)	13% (4)	10% (4)	
Occipital thickness	39				**0.002**
No band		12% (1)	3% (1)	5% (2)	
<4 mm		63% (5)	10% (3)	21%(8)	
4-7 mm		25% (2)	26% (8)	26% (10)	
8-11 mm		0% (0)	42% (13)	33% (13)	
>12 mm		0% (0)	19% (6)	15% (6)	
Maximum thickness	39				**<0.001**
<4 mm		38% (3)	0% (0)	8% (3)	
4-7 mm		37% (3)	13% (4)	18% (7)	
8-11 mm		25% (2)	35% (11)	33% (13)	
>12 mm		0% (0)	52% (16)	41% (16)	
Band extension	39				**0.022**
<3 Lobes		38% (3)	3% (1)	10% (4)	
>3 Lobes		63% (5)	97% (30)	90% (35)	
Normotopic cortex	37				**<0.001**
No pachygyria		100% (8)	16% (5)	32% (13)	
Slightly broad gyri		0% (0)	25% (8)	20% (8)	
Pachygyria		0% (0)	59% (19)	48% (19)	
Frontal horn ratio	40				0.694
<35%		88% (7)	60% (19)	65% (26)	
35%-40%		12% (1)	31% (10)	28% (11)	
40%-50%		0% (0)	6% (2)	5% (2)	
>50%		0% (0)	3% (1)	2% (1)	
T2 prolongation	33				0.137
Absent		100% (8)	52% (13)	64% (21)	
Periventricular		0% (0)	8% (2)	6% (2)	
Subcortical		0% (0)	16% (4)	12% (4)	
Periventricular and subcortical		0% (0)	24% (6)	18% (6)	

Bold indicates statistical significance ($P \leq 0.05$).

In our study, the EGOS-ped score was significantly associated with almost all the clinical variables except for seizures' frequency and the ASM response. This finding is not surprising because the frequency of seizures can have a very highly variable impact on the neurological profile[7] and the EGOS-ped score is not specific for epilepsy. Nevertheless, the EGOS-ped proved to be a valid tool that consistently reflected the cognitive and the neurological characteristics of patients with SBH, and, for this reason, it can be reliably used as a clinical outcome measure in statistical analyses aimed to compare the clinical phenotype with the neuroradiological and the genetic data.

We found that several neuroradiological features, in particular, the presence of thick and extended heterotopic band and the presence of pachygyria, were associated with a poor outcome at EGOS-ped score. In a previous study, Barkovic et al.[2] found that pachygyria and occipital involvement of heterotopic band correlated with early onset of seizures, pachygyria also correlated with epileptic encephalopathy and abnormal neurological examination, while the parietal involvement was associated with delayed language acquisition. Bahi-Buisson et al.[3] showed that patients with thicker band are more likely to have epileptic encephalopathy and developmental delay; moreover, the band thickness was related to the age of seizures onset.

Our findings are difficult to compare with those of previous studies, because our work is the first one based on the comparison between the overall functional outcome and the neuroradiological parameters. However, all the clinical variables previously mentioned (neurological examination, age of seizure onset, type of epilepsy, cognitive profile) correlate with the EGOS-ped score, supporting the fact that the band thickness and the presence of pachygyria greatly influence the clinical severity and the functional outcome of patients.

Di Donato et al.[8] developed a systematic neuroradiological classification of LIS-SBH spectrum, distinguishing the main neuroradiological presentation patterns: partial SBH, diffuse thin SBH, diffuse thick SBH, and mixed pachygyria-SBH; these patterns were well correlated to genetic data. The authors also tried to fit the different neuroimaging patterns into a clinical severity scale, identifying three main categories: mild, moderate, and severe. However, these clinical-neuroradiological correlations lacked statistical analyses and the method used to evaluate the clinical variables were not clarified.

Regarding the genetic aspects, in a recent systematic work on the LIS-SBH spectrum[9] in which the study was focused on neuroradiological and genetic correlations, it emerges that in patients with SBH the percentage of patients with mutation affecting one of the known pathogenic genes is overall 80% (N = 146 of 181) and this percentage increases to 95% considering patients with diffuse thick SBH (N = 62 of 65).[9] In our series, the rate of mutated patients was 56% (22 of 38).

Differently from previous work, we searched directly for any relevant correlation between genetics and functional outcome. We did not find a significantly different distribution of *LIS1* and *DCX* mutations among the poor and the good outcome subgroups; nevertheless, we observed that the frequency of mutations in SBH-related genes was higher in the poor than in the good outcome group (respectively 61% vs 33%). These findings should be confirmed on larger series, but it is in line with what was found by Di Donato et al.[9] on the neuroradiological point of view: the more severe SBH patterns (diffuse thick 95%, N = 62 of 65; mixed pachygyria-SBH 88%, N 23 of 26) were associated with a higher incidence of gene mutations, whereas the genetic undetermined cases were more frequent in the less severe neuroradiological patterns (partial posterior: 62%, N = 16 of 26; diffuse thin: 29% N = four of 14).

Our study has some limitations: (1) the cross-sectional data collection from several centers might have hampered the phenotypic characterization; however, our approach included a shared, standardized method of collecting data and a central revision of MRI; (2) the small sample size precluded a multivariate analysis; and (3) genetic data and brain MRI were not available for all patients included in the study for central revision; however, many efforts were done to obtain complete data and perform the genetic analysis: in fact 10 cases followed by other centers underwent a genetic panel for brain malformations fine-tuned in our center and offered to the patients who had not yet done the genetic analysis.

In conclusion, we applied for the first time an overall functional disability score (EGOS-ped) in a cohort of patients with SBH. SBH is characterized by a complex and heterogeneous clinical phenotype, including several neurological aspects (intellectual disability, language and motor disorders, epilepsy), which are often difficult to correlate with genetic and neuroradiological data. The application of a quantitative and standardized method that reflects the patient's clinical phenotype could overcome these limits. In our study, the EGOS-ped proved to be an easy and reliable tool for synthesizing the clinical phenotype and classifying the degree of disability of patients with SBH.

We found that the distribution of the score was bimodal, reflecting two well-defined subgroups of patients, rather than a homogenous continuum spectrum: the first one (about four-fifths of patients) was characterized by a poor overall functionality with severe intellectual disability, early onset of epilepsy, thick heterotopic band, and pachygyria, which the second one (about one-fifth of patients) was characterized by a good overall functionality and mild intellectual disability or normal cognitive profile, later onset of epilepsy, and thinner heterotopic band.

The clinical and neuroradiological features that mostly correlated with poor outcome were: microcephaly, epileptic encephalopathy, thick and diffuse heterotopic band, and pachygyria. These features were not found in patients with good outcome. All these features are easy to assess at SBH diagnosis and can have a significant prognostic role. To confirm the clinical correlations of SBH with EGOS-ped, larger multicentric prospective series could be useful.

Moreover, how the cortical networks disarray impacts the functionality of patients with SBH largely remains unknown.[10,11] Further studies, involving the use of functional MRI on larger cohorts, are needed to better match genetic, neuroradiological, and clinical features of SBH.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2023.01.012.

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