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Long-term Neuropsychological Outcome and Quality of Life in Perinatal Ischemic Stroke

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Abstract

Background: Perinatal arterial ischemic stroke is an established risk factor for neuromotor and cognitive sequelae, but little is known about long-term neuropsychological implications. We aimed to evaluate long-term neuropsychological outcome and its effect on life quality in children with history of perinatal arterial ischemic stroke.

Methods: Seventeen children with history of perinatal arterial ischemic stroke, selected from the institutional cerebrovascular registry, were recruited for this study. Outcome was investigated using a battery of standardized neuropsychological tests and PedsQL questionnaire. A neuropsychological composite score (Cognitive Index) was calculated taking into account impaired performances.

Results: 47% of the patients had impaired Cognitive Index. Neuropsychological functions involved included: language, visuo-motor and executive functions, visual selective attention, with sustained attention as the most affected (59% of patients). Impairment in Cognitive Index was significantly associated with poor quality of life as perceived by parents.

Conclusion: In conclusion, minor impairments, such as neuropsychological deficits, can frequently occur in children with history of perinatal arterial ischemic stroke and may affect quality of life.

Keywords: Cognitive; IQ; Neonatal stroke; Arterial stroke; Cerebrovascular

Abbreviations IQ: Intelligence Quotient; PSOM-SNE: Pediatric Stroke Outcome Measure-Short Neuro Exam; WISC: Wechsler Intelligence Scale for Children; CI: Cognitive Index

Introduction

Perinatal arterial ischemic stroke is defined as "a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies" [1]. It is the most common cerebrovascular event of the perinatal period with an incidence of 1/1600-1/5000 neonates and with a high prevalence in those born at term (85% of all cases) [2-6]. In most cases the clinical onset is acute with neonatal seizures however, some infants present with abnormal use of one hand becoming evident in the first months of life and stroke is supposed to happen in the perinatal period [7].

Outcome studies indicate a high incidence of long lasting morbidity such as motor, sensory and cognitive deficits and epilepsy, while mortality rate is relatively low (3%) [8]. Neuromotor impairment has been extensively studied (for a review see Golomb), but little is known about cognitive sequelae, typically diagnosed at preschool or school age when complex skills are required, long after the pathogenic process has occurred [9]. Research on cognitive outcome mainly focused on Intelligence Quotient (IQ), while only few studies used the neuropsychological approach [10-15]. Neuropsychological assessment is able to reveal specific alterations in different domains and is particularly useful for evaluation of the outcome of focal brain lesions, unlike IQ, which is a nonspecific index of the general cognitive functioning.

Many instruments have been developed to evaluate health related quality of life in children with different neurological conditions including neonatal and pediatric stroke, but none evaluated the impact of neuropsychological impairments on life quality [16-18].

The aim of the present study was to assess long-term neuropsychological outcome and quality of life as perceived from children with history of perinatal arterial ischemic stroke and their parents, and to evaluate the influence of cognitive impairments on the quality of life.

Methods

Patients

Potential patients were identified from the institutional cerebrovascular disorders registry. The database includes patients treated at our Pediatric University Hospital since January 1990. Inclusion criteria for this study were: diagnosis of perinatal arterial ischemic stroke following international consensus criteria including both subcategories of acute and delayed presentation (presumed perinatal stroke) [1]; cerebral MRI or CT-scan evidence of ischemic injury in an arterial vascular territory; birth at ≥ 37 weeks gestational weeks; age at testing ≥ 5 years. Infants with associated global hypoxic–ischemic injury, metabolic injury or congenital cyanotic heart disorders, which could act as independent risk factors for neurodevelopment disabilities, were not included.

Out of 24 eligible patients, two were lost at follow-up and five denied consent to the study. The final study group included 17 children. Neonatal and neurological data of the group at the time of neuropsychological testing are summarized in Table 1. For neurological examination we used the Pediatric Stroke Outcome Measure-Short Neuro Exam (PSOM-SNE) Child Version (Children aged 2 years and older), scored according to Neuner et al. [16,19].

NEONTAL DATA	N
GENDER (Male)	11/17 (65%)
GESTATIONAL AGE mean (range)	39 (37-41)
BIRTH WEIGHT mean gr (range)	3476.25 (2700-4440)
APGAR SCORE at 5 minutes, range	7-10
PRESENTATION	
acute neonatal	12/17 (71%)
presumed perinatal	5/17 (29%)
ARTERIAL INVOLVEMENT	
left middle cerebral artery	13/17 (76%)
right middle cerebral artery	3/17 (17%)
right posterior cerebral artery	1/17 (6%)
bilateral involvement	0/17 (0%)
BRANCH INVOLVEMENT	
main branch	0/17 (0%)
cortical involvement	8/17 (47%)
lenticulo-striate	1/17 (6%)
cortical and lenticulo-striate	4/17 (23%)
NEUROLOGICAL DATA AT THE TIME OF TESTING	
AGE mean years (range)	9.5 (5-16)
Epilepsy	2/17
PSOM abnormal scores	
right sensorimotor abilities	10/17 (6 severe, 1 moderate, 3 mild)
left sensorimotor abilities	2/17 (1 severe, 1 moderate)
linguistic production	2/17 (1 moderate, 1 mild)
linguistic comprehension	2/17 (1 moderate, 1 mild)
cognitive-behavioral attitude	6/17 (2 severe, 1 moderate, 1 mild)

Table 1: Neonatal data and neurological characteristic of the study group (17 patients) at the time of neuropsychological testing.

Test-manual standardized norms for the Italian population are available for neuropsychological assessment [20-23]. For quality of life assessment we recruited a control group of forty-two healthy children comparable for age and gender (age range 5-16 years, mean 9.1 years), with no neurological and psychiatric disorders in their family and personal history and good school achievements, and their parents, because test-manual standardized norms for the Italian population were not available.

The study was approved by Institutional Review Board. Parental consent was obtained from all participating parents.

Neuropsychological and quality of life measures

Neuropsychological assessment was conducted by a psychologist trained in test administration, scoring and interpretation (E.C.). The following cognitive domains were assessed: language, using the Wechsler Intelligence Scale for Children-3th edition (WISC-III) Vocabulary and Similarities tests and the semantic verbal fluency test, which evaluates the ability to access the lexicon according to specific semantic categories; selective and sustained attention, using the Bell's test; short-term verbal and visuo-spatial memory, using the digit span test and the Corsi block-tapping test; executive functions, using the phonemic verbal fluency test, which evaluates the ability to access the lexicon through a phonemic cue by setting up an adequate verbal search strategy, the Tower of London test, which evaluates planning and problem solving, and the backward digit span test, which evaluates the working memory; visuo-motor functions, using the WISC-III Block Design and Coding tests [20-23]. An estimation of IQ was obtained from the scores of four WISC-III subtests, i.e., Vocabulary, Similarities, Block Design and Coding, as described by Sattler and Dumont [24]. The entire test battery required nearly 1^{½} hour to be completed.

All neurocognitive test results were norm-referenced (based on age-related means and standard deviations from test standardization norms). Z scores were generated for analyses so that comparisons between tests could be made. Individual test scores were considered "impaired" when the score of the particular measure fell 1.5 standard deviations below the normative mean. This cut-off score would be expected to capture fewer than 7% of children in the nonclinical normative sample. The 1.5 standard deviation determination of impairment was selected to be consistent with studies on other pathological conditions in children [25,26]. A neuropsychological composite score (Cognitive Index–CI) was generated for each patients and was defined as impaired when having three or more pathological scores on the test battery, as defined by previous works [26,27].

Quality of life

The children's self-reports and the parent's reports on their children quality of life were assessed by administering the PedsQL questionnaires, which yield information on four scale scores: physical, emotional, social and school functioning of the child during the previous four weeks. Mean scores are calculated based on a 5-point response scale for each item and transformed to a scale ranging from 0 to 100 with higher score representing better quality of life. The sum of single scores gives three summary scores: a total scale score, a physical health summary score (correspondent to physical functioning) and a psychosocial health summary score (including emotional, social and school functioning) [28].

Given the small sample size, individual profiles were evaluated. The mean and standard deviation of scores obtained by self-reports and parent's reports in the control group were used as normative values in order to generate Z scores from PedsQL scores of the stroke groups. PedsQL individual scores were considered "impaired" when a score fell 1.5 standard deviations below the average of the control group.

Statistical Analysis

To highlight impairments in quality of life as perceived by parents and children with history of stroke, we compared their scores with those of their healthy peers and the scores of their parents with those of healthy children parents. Comparisons were done using Mann Whitney U-Test for independent groups. Fisher exact test was used to evaluate the association between PedsQL scores and CI and between PedsQL scores and PSOM scores.

The significance was set at $p<0.05$. All analyses were performed using the Statistical Package STATISTICA 6.0 for Windows (StatSoft, Tulsa, Oklahoma).

Results

Neuropsychological outcome

Considering the neuropsychological results, eight of 17 (47%) patients met criteria for impaired CI. Both epileptic patients meet the criteria for impaired cognitive index (ID 2 and ID 15). Neuropsychological profiles of each patient are summarized in Table 2. Sustained attention test (accuracy parameter of the Bell's) was impaired in 59% of the patients and visual selective attention (rapidity parameter of the Bell's Test) in 41%; the remaining neuropsychological functions were less frequently involved. No significant differences were found between the mean of the patient's group and the theoretical average of the normative sample with the exception of sustained attention (M=-2.18 SD=1.14). Children with left hemisphere lesion had lower scores in the linguistic task Similarities (mean Z score=0.31) compared to children with right hemisphere damage (mean Z score=1.39). All children in the subgroup with history of presumed perinatal stroke had impaired sustained attention skills and some other deficits in other neuropsychological domains, while in the subgroup of those presenting acutely in the neonatal period, sustained attention was impaired in 50% of the cases.

Considering the estimated IQ performance, the mean of patient's group (M=98.33 SD=19.30) did not differ from the theoretical average of the normative sample. Examination of the individual subject data indicates that performance fell below the normal range (<70) in two children; these patients had a globally impaired neuropsychological profile (Table 2).

One patient (ID 2) had behavioral problems and poor cooperation and was able to complete only four tests of the battery, these were impaired meeting the criteria for impaired CI.

Neuropsy	Patient ID																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Domain	Test																	
Est. IQ		101	a	132	107	1077	93	68	103	102	93	59	82	105	89	88	114	130
Attention	Bell's Test rapidity	-0.7	-2.5	b	-2.5	-0.8	-0.8	-1.1	-0.9	-1.7	-0.8	-3.0	-2.5	-0.5	-2.5	-2.6	-0.1	-1.6
	Bell's Test accuracy	-0.1	-2.5	b	-2.5	-0.6	-2.2	-2.7	0.0	-3.5	-2.2	-3.0	-3.0	-1.0	-3.0	-2.6	-3	-1.8
Language	Sem.Fluen.	-0.6	-2.9	b	-1.4	-0.7	-0.2	-2.2	0.0	-0.5	-0.2	-1.6	-1.2	-0.2	-0.2	-1.7	0.9	a
	Similarities	0.6	a	2.0	2.6	1.0	0.3	-2.7	0.0	-1.0	0.3	-2.7	-0.7	0.3	-0.3	0.0	0.7	1.3
	Vocabulary	0.3	a	2.3	0.0	2.0	0.7	-2.7	1.0	-1.0	0.7	-1.7	0.0	1.3	-1.0	0.	1.3	0.3
Memory	Corsi block-tapping	0.1	-2.0	-0.4	-1.1	0.1	1.5	-1.6	-0.3	-0.8	1.5	-1.4	0.6	0.7	0.5	0.1	0.6	-0.5
	Digit span-forward	0.8	a	-1.4	-0.5	0.7	-1.3	-1.1	-0.6	-0.6	-1.3	-1.4	-1.3	0.4	0.7	-0.3	-1.3	-0.4
Executive func.	Digit span-back.	0.6	a	b	-1.4	-0.6	1.1	-0.4	-1.1	0.3	1.1	-0.9	a	0.2	-0.2	-0.9	-1.9	-0.5
	Tower of London	1.1	a	0.0	0.2	0.7	0.8	a	0.7	0.7	0.8	1.2	0.2	1.9	0.3	-0.9	0.4	1.1

	Phonetic fluency	0.32	a	1.4	-0.2	-1	0.8	-2.2	-0.2	-1.5	0.8	-2	0,1	-1	-2.5	-1	-0.2	-1.6
Visuo-motor f.	Coding	-1.0	a	1.0	-0.3	-2.0	-1.3	0.0	-0.7	1.3	-1.3	-2.7	-1.5	-0.3	1.0	-2.0	0.7	1.3
	Block Design	0.3	a	0.6	-1.0	0.3	-1.0	-0.7	0.3	1.0	-1.0	-1.3	-1.3	-0.3	-1.7	-0.3	0.0	2.7
PedsQL																		
PedsQL	Parent's reports	-1,9	-2,4	0,3	-0,5	1,3	0,7	-3	0	-1,8	-0,5	-2,7	-1,7	1,3	-1,8	-0,9	-0,3	c
Total	Self-reports	1,8	-0,6	1,4	1,2	1,4	0	-2,5	-0,4	-1,2	0,7	-0,3	-0,2	0,7	-0,5	-2	0	c
Physical Health	Parent's reports	-1,9	-2,1	0,4	0,3	0,8	-0,1	-3	0	-1,1	0,8	-1,9	-1,4	0,8	-1,6	-1,4	0,3	c
Summary score	Self-reports	1,4	1,1	1,4	0,9	0,5	-0,9	-1,1	0,3	-1,6	0,7	0,5	-0,4	0,7	-0,2	-1,8	0,3	c
Physico-Social	Parent's reports	-1,5	-2	0,4	-0,5	1,3	0,9	-3	0	-1,8	-1,2	-2,5	-1,5	1,3	-1,5	-0,3	0,2	c
Summary score	Self-reports	1,8	-1,6	1,2	1,2	1,8	0,6	-3	-0,8	-0,8	0,6	-0,8	-0,1	0,6	-0,7	-1,8	0,2	c

Table 2: Standardized values of estimated IQ (M=100, SD=15), neuropsychological scores (M=0, SD=1) and PedsQL Total and Summary scores. Values lower than 1.5 standard deviations compared to the theoretical average of the normative sample are in bold type ([a]poor cooperation to test; [b]no standardized data for age (>15 years); [c]no available data).

Quality of life outcome

16/17 children with stroke and their parents completed the PedsQL questionnaire. PedsQL scores of children with history of perinatal stroke were not significantly different from those of their healthy peers. By contrast, the perception of their sons quality of life was significantly lower in parents of children with stroke than that of parents of healthy children, in every scale, except for emotional functioning: physical functioning (mean scores and standard deviation of parents of children with stroke and of those of the control group, respectively 71 ± 10 vs. 82 ± 11, p=0.01), social functioning (69 ± 12 vs. 86 ± 10, p=0.001), school functioning (67 ± 14 vs. 81 ± 13, p=0.001), total scale score (69 ± 10 vs. 80 ± 9, p=0.001), physical health summary score (71 ± 15 vs. 81 ± 11, p=0.01) and psychosocial health summary score (69 ± 15 vs. 80 ± 10, p=0.01).

PedsQL scores of each patient and their parents are summarized in Table 2.

Association between impaired quality of life and CI is summarized in Table 3.

	PedsQL parents*		PedsQL children**	
Cognitive Index	Impaired	Not Imp.	Impaired	Not Imp.
Impaired	6	1	2	5
Not Imp.	1	8	0	9

Table 3: Chi-square tests (Fisher's Exact Test) of frequencies of PedsQL scores of parents and children and neuropsychological CI (*p=0.009; ** Not significant).

Since the severity of neuromotor impairment is known to influence quality of life [16]. We compared neuromotor outcome (as evaluated by PSOM scores) in patients whose parents showed impaired or not impaired quality of life perception and we didn't find significant differences.

Discussion

Results of this study indicate that children with history of perinatal arterial ischemic stroke can suffer from several neuropsychological deficits, even in the absence of severe neuromotor sequelae and mental retardation. Furthermore, these impairments may affect quality of life as perceived by parents of the patients.

Literature on neuropsychological outcome in children having suffered from perinatal stroke is scarce. Kolk's and colleagues found significant mean group differences between patients and an ad hoc control group, in all neuropsychological domains; sensorimotor, visuo-spatial and language skills were the most impaired functions. In the present study, we evaluated cognitive impairment at the individual level by means of a Cognitive Index obtained from impairments in the different neuropsychological tests and half of the patients meet the criteria for impaired Cognitive Index, with neuropsychological deficits involving language, visuo-motor, executive functions and attention [14]. The most compromised function was sustained attention, impaired in 59% of the patients. To our knowledge, the complex ability to maintain the attention for long periods has not yet been specifically

tested, in children with history of perinatal stroke. Attention is the ability to focus on certain interesting aspects of the environment and to manipulate this information flexibly. In particular, sustained attention is the ability to concentrate on one task for a certain period without switching off. Attention skills are considered a "building block" of higher-level skills (such as memory and reasoning), able to affect gradually other cognitive domains and consequently school achievements and the daytime life of the child. Furthermore, children apparently "normal" and adequate, without neuromotor sequelae or global cognitive impairment, may display sustained attention deficit. Interestingly, the IQ was impaired only in two of our patients in contrast to the widespread neuropsychological involvement.

Our group was too small to evaluate the effect of clinical presentation of stroke on neuropsychological functioning, however qualitatively we observed that all children with a history of presumed perinatal stroke had impaired attention skills and some deficit in other neuropsychological domains; by contrast, only 50% of those presenting acutely in the neonatal period were impaired. When stroke occurs in the perinatal period dysfunction may affect multiple domains, because of the poor specialization of neonatal brain [29]. According to our observation, previous research report a worse neurological outcome in patients with delayed clinical presentation of perinatal stroke [6,30]. Children with left hemisphere lesion had lower scores in language domain compared to children with right hemisphere damage, in line with knowledge on hemisphere specialization. Epilepsy occurred in only two patients of our sample: suggesting occurrence of epilepsy as a possible risk factor for worse neuropsychological outcome.

Concerning the quality of life evaluation, we found that parents perceived a significantly worse quality of life of their sons compared to parents of healthy age-matched peers; this was not the case when comparing stroke children with healthy peers. Indeed, parent/proxy questionnaires are considered the gold standard methods when assessing well-being in children, in particular if they are too young to respond themselves or in presence of cognitive deficits [31]. Our data are in line with studies on other chronic disorders, showing differences in life quality perception between children and their parents, with a better perception of life quality in children [17,32-34].

One other important result of the present study was the observation that cognitive impairment as measured by neuropsychological Cognitive Index was associated to poor parent's perception of their son's life quality. The issue of the effect of neuropsychological deficits on quality of life was not addressed previously, while the literature on neonatal and childhood stroke suggest an effect of neuromotor functioning [16,35,36]. Since severe neuromotor outcome was equally represented in parents with good and poor life quality perception, our data suggest the hypothesis of an impact of neuropsychological impairment on life quality.

The high frequency neuropsychological involvement and its effect on quality of life highlight the importance of early neuropsychological investigation of children with history of perinatal stroke, in order to institute timely rehabilitation programs in patients exhibiting impairments.

Limitations of the present study are the small sample size that precluded full analysis by subgroups and the lack of an ad hoc control group for evaluation of mean group differences in neuropsychological involvement. However, the goal in clinical practice remains the recognition of individual deficits in high-risk populations, rather than group comparisons with healthy control peers. Another limitation was that we were unable to control for the socio-economic status.

Conclusion

This study highlights the wide spectrum of neuropsychological deficits that may affect children having suffered from stroke during the perinatal period. These may be underestimated if not specifically tested but they appear to influence the parent's perception of their son's quality of life. Early detection of such impairments can allow timely implementation of cognitive rehabilitation programs with an inestimable effect on child's future life.

Ethical approval

The clinical management of the patient reported in this paper conformed to the specifications provided by our institutional review board. All investigations were performed according to the recommendations of the ethical committee of our department and after acquiring written permission from the patients' parents.

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