Visuoperceptual sequelae in children with hemophilia and intracranial hemorrhage

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Background: The goal of this study was to examine the impact of focal brain injuries on the outcomes of visual perception and visuospatial abilities in Mexican children with hemophilia who have experienced intracranial hemorrhages.
Methods: We assessed ten boys who had hemophilia with intracranial hemorrhage (HIC), six boys who had hemophilia without intracranial hemorrhage (HH), and ten boys without hemophilia (CTL). The Verbal (VIQ), Performance IQs (PIQ), and Full Scale IQs (FSIQ) from the Wechsler Intelligence Scale for Children—Mexican Revision, Visual Perception, and Visuospatial Abilities domains, which are from a neuropsychological assessment battery for Spanish-speaking children (ENI), were employed for our analysis.
Results: The results showed that the HIC group performed in the low-average range on the PIQ and FSIQ, which was lower than the HH group. The HIC group showed low performance on visual perception tests, such as line orientation, fragmented objects, and overlapping figures, compared with their matched controls.
Conclusions: The results suggest that it is not the ability to recognize objects that is impaired in the HIC group, but the ability to identify objects under less favorable conditions. Our findings may have therapeutic and rehabilitative implications for the management of children with hemophilia and early focal brain lesions.

Keywords: Children; visual perception; visuospatial abilities; hemophilia; intracranial hemorrhage

Introduction

There has been great debate in the field of developmental neuropsychology during the last century regarding the concept of brain plasticity in children with early brain injury. Early plasticity theorists have stipulated that a young brain is immature and as a consequence is less susceptible to the impact of cerebral damage (1-4). Conversely, early vulnerability theorists have proposed that brain injury sustained during the developmental window results in significant long-term neuropsychological impairment (5-8). There are many different factors to be considered in this debate. First, plasticity has been demonstrated in both animal models and human studies (9-12). Second, early vulnerability is based on studies that

documented impairments in abilities that are relevant to the acquisition of cognitive processes and skills (7,13-15). Finally, neuropsychological outcomes in both theories are dependent upon different variables such as the type, severity, and age of onset of a lesion, environmental factors, and developmental parameters (10,14,16,17). While there has been a great deal of research to support the contrasting sides of this debate, further exploration is needed to elucidate how early plasticity and early vulnerability theories actually apply in different clinical circumstances. In the field of neuropsychology, brain damage is studied using the nature and severity of the lesion as variables. Generalized brain trauma and focal brain lesions are the two most commonly studied lesions in plasticity and vulnerability theories. In general, when a lesion is generalized, poor

outcomes and global cerebral dysfunction are expected. For example, in traumatic brain injuries where damage is diffused, functional deficits are seen in many cognitive areas, such as attention, memory and learning, psychomotor skills, linguistic abilities, and executive functions (13). In contrast, focal brain lesions are characterized by moderate-to-good outcomes in most cognitive domains, but some deficits have been noted in particular areas (7,18).

The understanding of developmental plasticity and recovery from injury comes from studies of focal brain lesions experienced at particular developmental stages. Furthermore, other cognitive domains are often impaired by early focal brain injury. For example, studies have found that children with early focal lesions manifest difficulties later on in development of higher-level verbal, visual-spatial executive, and information-processing abilities (5,18,19). These findings suggest a variety of factors that interact with focal brain injury to impact specific cognitive outcomes such as attention, memory, and executive functioning, among others.

A growing body of theoretical and empirical work on visual perception areas such as visual recognition, visual organization, and visual interference areas in adults suggests that visual perception may be affected in adulthood after focal brain damage occurs in childhood (20-22). Early trauma or other forms of acquired injury often affect substantial portions of the brain, resulting in damage that could compromise cognitive ability in adulthood. In the specific case of focal brain injury, literature suggests that affected children are at high risk of suffering visual perception and visuospatial deficits, since the development of the neural networks subserving these cognitive functions does not conclude until late adolescence (23). Moreover, the basic neural system that mediates part—whole processing may begin to develop early and continues to undergo significant developmental change for a continued period of time (23-25). Studies addressing specific visual perception and visuospatial abilities in children with focal brain injuries are limited, however.

Cerebral hemorrhage in children with hemophilia

One of the most severe and devastating manifestations in patients with clotting disorders is intracranial hemorrhage, which directly affects the central nervous system. Hemophilia is a clotting disease that can cause intracranial hemorrhage due to deficiencies in coagulation factors VIII and IX. Children with hemophilia who have experienced intracranial hemorrhages often received hemorrhages at the time of birth or during the first 2 years of life (26). The literature suggests that children with hemophilia and intracranial hemorrhage show lower performance in visuospatial skills than children from a healthy control group (27,28) and have worse clinical outcomes, especially in the domains of quality of life (29), motor function, visual-motor integration, and behavior (27). Some studies examining neuropsychological outcomes in children with hemophilia who have experienced intracranial hemorrhage have shown a correlation between low visual-motor integration and reduced intelligence, compared with normal controls (27-31). Although some cognitive domains seem to confirm damage in children with hemophilia who have experienced intracranial hemorrhage, the question remains: is there evidence that damage affects visual perception and visuospatial abilities in children with hemophilia and intracranial hemorrhage?

The limited data available that address visual perception and visuospatial abilities in children with hemophilia are not sufficient enough to establish a causal relationship between the illness and these cognitive deficits. Furthermore, because the studies addressing these areas in children with focal brain injuries are limited, conclusions covering these subjects cannot be drawn at this time. The goal of this study is to examine the impact of intracranial hemorrhage on visual perception and visuospatial abilities, as well as outcomes in Mexican children with hemophilia who have experienced intracranial hemorrhage. We hypothesized that children with intracranial hemorrhages will have lower performance in visual perception and visuospatial abilities compared with children with hemophilia who do not have a history of intracranial hemorrhage and to matched controls.

Materials and methods

Participants

The participants in this study were drawn from a larger sample of 118 children with hemophilia from the Children's Hospital at the Mexican Institute of Social Security in Guadalajara, Mexico. The children with hemophilia were identified through records listing all patients with hemophilia A or B who had received treatment at the Hematology/Oncology Department. Children with hemophilia with intracranial hemorrhage (HIC), children with hemophilia without intracranial hemorrhage (HH), and normal controls (CLT) were included in this study.

For the total of children participating in this study, the following inclusion criteria were applied: (I) the ability to complete a cognitive evaluation; (II) age from 5 to 16 years at the time of assessment; and (II) belong to the Mexican Social Security Institute at Guadalajara. The exclusion criteria were (I) psychiatric history of psychotic disorders; (II) positive human immunodeficiency virus status; and (III) living a great distance away from our testing center. The inclusion criteria for the intracranial hemorrhage group was (I) previous cerebral hemorrhage(s) documented by head computed tomography. The inclusion criteria for the hemophilia group was (I) no history of previous cerebral hemorrhage, and (II) a magnetic resonance image conducted within one week prior to the neuropsychological assessment to verify that they did not have evidence of old bleeds or brain injury. Details of the sample and recruitment strategies have been described previously (32). Each child with hemophilia and intracranial hemorrhages was matched case by case with a boy with hemophilia without intracranial hemorrhage and a healthy boy who attended the same classroom, lived in the same neighborhood, was of the same socioeconomic status (SES), and was the closest in date of birth.Previous brain lesions in the HIC group were identified through a review of clinical charts and notes. The lateralization of the lesion and its localization in each of the four lobes (frontal, parietal, temporal, and occipital) were also identified through chart review. In addition, the number of intracranial hemorrhagic events was identified (see *Table 1* for intracranial hemorrhage characteristics).

All of the participants were screened (via parent or legal guardian interviews) for severe developmental disorders, psychiatric history, and human immunodeficiency virus status. None of the identified participants were in full-time special education, so no one was excluded on the basis of these criteria. SES was determined using the Socioeconomic Stratification of Metropolitan Zone of Guadalajara (33) which rates the observable distinctions of housing, public services, and type of neighborhood into high, middle, low, and marginal socioeconomic levels. Among the participants, the majority were from low or marginal socioeconomic levels. Demographic characteristics of the sample are provided in *Table 2*.

Procedures

This study was approved by the Human Research Ethics Committee of the Children's Hospital and Ethics Committee of the Institute of Neurosciences in Guadalajara,

Mexico. Written, informed consent was obtained from all participants and their parents or legal guardians prior to the study. Testing was completed at a time and location convenient for each family (most commonly in the home) by a trained graduate student in neuropsychology who was blinded to the clinical status of the participants. The families were compensated with a box of groceries for their participation in this phase of the study.

A magnetic resonance imaging (MRI) study was performed for the HIC and HH groups to verify evidence of new bleeds or brain injuries prior to the neuropsychological assessment. All MRI images were independently reviewed by two experienced neuroradiologists who were blind to the clinical status of the participants. *Table 3* includes a list of neuropsychological tests used in the assessment as well as a description of the domains assessed.

Statistical analysis

The data were examined in three different ways. First, the percentages of children performing below average were tabulated for each scale within each group (*Table 4*). Then, Cohen's d (effect size) was calculated to reflect the difference between the means of each pair of groups (HIC-HH, HH-CTL, and HIC-CTL) for each scale (*Tables 5,6*). Lastly, each pair of groups was compared on each of the scales using the Wilcoxon matched-pairs signed-ranks test (*Tables 5,6*) because the data were paired data, not independent observations. The participants were matched across groups. Consequently, when comparisons were made with the HH group, only six participants could be included in the analysis. When the HIC and CTL groups were compared, there were ten participants in each group. It would not have been appropriate to use the chi-square test or Fisher's exact test for two reasons: (I) these tests require independent observations; and (II) these tests require frequency data. Neither of these requirements was met in the current data. Using a statistical test substantially increases the power of paired data, which is especially important in a small sample. Also, Cohen's d was used purely as a descriptive statistic. The assumptions for the parametric, dependent *t*-test did not need to be met because no parametric test was run.

Results

From these 118 children with hemophilia, 102 children could not be recruited for the study due to these study criteria: long geographic distances (n=2), a psychiatric history of

Table 1 Lesion information for children in the intracranial hemorrhage group

Participant	Age at testing (Y/M)	No. of cerebral hemorrhage	Age at the hemorrhagic event (Y/M)	Brain hemisphere affected	Lobe involved	Events of seizure	Actual MRI findings
1	9, 6	1	1, 2	Left	Parietal	No	Integrity of the brainx
		2	6, 0	Left	Parietal	No	
2	12, 3	1	4, 0	Left	Parietal	No	Left ventricular asymmetry
3	9, 4	1	0, 6	Left	Frontal Parietal	No	Arachnoid cyst of the left temporal fossa
4	11, 5	1	0, 4	Left	Parietal	No	Left parietal occipital poroencephalic lesion
		2	0, 6	Left	Parietal	No	
		3	4, 0	Left	Parietal	Yes	
		4	6, 0	Left	Parietal occipital	Yes	
5	9, 5	1	1, 7	Left	Parietal	No	Left periventricular encephalomalacia
		2	3, 0	Left	Parietal	No	
		3	4, 0	Left	Parietal	No	
6	15, 9	1	6, 0	Left	Temporal occipital	No	Left occipital encephalomalacia
7	6, 7	1	0, 3	Left	Parietal	No	Left Sylvian arachnoid cyst
		2	0, 4	Left	Parietal	Yes	
8	10, 3	1	6, 0	Left	Temporal	Yes	Ventricular asymmetry
9	15, 0	1	3, 0	Left	Parietal temporal	No	Bilateral occipital encephalomalacia
10	15, 6	1	6, 0	Right	Parietal	No	Integrity of the brain
		2	7, 0	Right	Parietal	No	

Y/M, year, months; MRI, magnetic resonance image.

Table 2 Demographic and clinical information for intracranial hemorrhage, hemophilia, and control participants

Participant	Intracranial hemorrhage group				Hemophilia group				Control group		
	Age (Y/M)	School grade	Type of hemophilia	SES	Age (Y/M)	School grade	Type of hemophilia	SES	Age (Y/M)	School grade	SES
1	9, 6	4th	Severe	Low	9, 1	4th	Mild	Low	9, 5	4th	Low
2	12, 3	5th	Severe	Low	NP	NP	NP	NP	12, 3	6th	Low
3	9, 4	2nd	Severe	Low	9, 7	3th	Moderate	Low	9, 1	2nd	Low
4	11, 5	NS	Severe	Marginal	NP	NP	NP	NP	13, 6	NS	Marginal
5	9, 5	4th	Severe	Low	NP	NP	NP	NP	9, 5	3th	Low
6	15, 9	6th	Severe	Low	15,1	7th	Moderate	Low	15, 2	6th	Low
7	6, 7	1st	Severe	Low	6, 0	1st	Severe	Low	6, 6	1st	Low
8	10, 3	4th	Severe	Low	11, 2	5th	Mild	Low	11, 1	4th	Low
9	15	7th	Severe	Low	15, 3	8th	Mild	Low	14, 7	7th	Low
10	15, 6	6th	Severe	Marginal	NP	NP	NP	NP	15, 3	6th	Marginal

SES, socioeconomic status; Y/M, years, months; NS, no formal schooling; NP, no participant.

Table 3 Neuropsychological measures used to assess global intellectual functioning, visual perception, and visuospatial abilities in the HIC, HH, and CTL groups

Neuropsychological measure	Domains assessed	Description	Tests administered	Scores used in analysis
WISC-MR (34)	VIQ, PIQ, FSIQ	Measures general cognitive/ intellectual functioning	VIQ: information, similarities, arithmetic, vocabulary, comprehension, digit span; PIQ: picture completion, picture concepts, block design, object assembly, mazes, claves	IQ
ENI (35)				
Visual perception	Visual recognition	This domain assesses the high-level perceptual analysis of a visual stimulus and the matching of that perceptual description to a stored visual representation in memory	Facial expression of emotions test: contains basic categories of emotions, such as happiness, sadness, anger, and fear; Line orientation: estimates the angular relationship between line segments by visually matching angles and lines	Number of correct answers
	Visual organization	The visual interference domain assesses the way that a child organizes the elements of his/ her visual field into objects	Integration of objects: different objects segmented; Closure figures: occlusion contours are being tested; Blurred figures: deciphering unusual, blurred views	Number of correct answers
	Visual interference	This domain requires the subject to analyze the figure-ground relationship, in order to differentiate the figure from the interfering element	Overlapping figure: the patients are asked to name as many of the overlapping line-drawn objects presented in one page as possible	Number of correct answers
Visuospatial abilities	Spatial orientation	This domain is based on visual-vestibular interaction, which provides the subjects with visual cues about vertical orientation in a three-dimensional coordinate system	Left-right comprehension: subject's comprehension of left-right orientation; Left-right expression: subject's expression of left-right orientation; Different angles figures: comprehension of objects in different angles; Coordinate maps: using a coordinate system to describe the position of each subject	Number of correct answers

WISC-MR, Wechsler Intelligence Scale for Children-Mexican Revision; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FSIQ, full-scale intelligence quotient; ENI, Evaluación Neuropsicológica Infantil.

psychotic disorders (n=17), human immunodeficiency virus positive status (n=11), not currently belonging to the Mexican Social Security Institute (n=59), or refusal to participate in the neuropsychological examination (n=13). The remaining 16 boys with hemophilia were selected for our study. Only 10 children with hemophilia who had experienced intracranial hemorrhages (HIC group) were identified; their ages ranged between 6 and 15 years (X=11.10; SD =3.10). In order to have much

better control of the variables, authors decided to pair the ten HIC children with HH children. Due to the specific characteristics of the HIC group, it was difficult to find ten children with hemophilia without intracranial hemorrhage (HH group) with the same criteria. We paired the HIC group with six children with hemophilia but without intracranial hemorrhages between 6 and 15 years old (X=10.83; SD =3.60). A control group of 10 healthy children between 6 and 15 years old (X=11.30; SD =3.02)

Table 4 Percentages of children performing below average in the hemophilia with intracranial hemorrhage (HIC), hemophilia without intracranial hemorrhage (HH), and control (CTL) groups

Variables	HIC (n=10) (%)	HH (n=6) (%)	CTL (n=10) (%)
Intellectual function			
WISC-MR			
Verbal IQ	70.0	50.0	50.0
Performance IQ	70.0	0	20.0
Full IQ	60.0	33.0	60.0
Visual perception			
Visual recognition			
Facial expression of emotions	50.0	16.7	30.0
Line orientation	60.0	33.3	50.0
Visual organization			
Fragmented objects	70.0	66.7	40.0
Closure figures	80.0	83.3	80.0
Blurred figures	10.0	0.0	10.0
Visual interference			
Overlapping figure test	50.0	16.7	20.0
Visuospatial abilities			
Spatial orientation			
Left-right comprehension	100.0	100.0	90.0
Left-right expression	90.0	100.0	100.0
Figures with different angles	50.0	50.0	30.0
Coordinate maps	10.0	16.7	10.0

WISC-MR, Wechsler Intelligence Scale for Children-Mexican Revision.

was also included in this study.

All patients with hemophilia included in this study were diagnosed with hemophilia A. The severity of the hemophilia in the sample was as follows: 68.7% of children with hemophilia had severe hemophilia (defined as <1% clotting factor), 12.6% had moderate hemophilia (1% to 5% clotting factor), and 18.7% had mild hemophilia (>5% clotting factor).

The percentage of children performing below average was highest in the HIC group for five of the scales (PIQ, overlapping figures, and facial expression of emotions, fragmented objects, and line orientation). When comparing

the HH and CTL groups, the percentage was higher for the HH group than the CTL group on five scales (fragmented objects, closure figures, left-right comprehension, different angle figures, and coordinate maps), lower on four other scales (facial expressions of emotions, line orientation, blurred figures, and overlapping figures), and equal on one scale (left-right expression) (see *Table 4*).

In the comparison of the HIC and HH groups, the largest Cohen's d (d=0.2 as a small effect size, d=0.5 as a medium effect size, and d =0.8 as a large effect size) were found for the WISC-MR: Full IQ (d=−1.38) and Performance IQ (d=−1.35). The ENI showed the largest Cohen's d in visual interference area for overlapping figures (d=−1.09); the next largest were in the area of visual organization for blurred figures (d=−0.91) and closure figures (d=0.85). For the comparison of the HH and CTL groups, the WISC-MR showed the largest Cohen's d for Full IQ (d=1.27), and the next largest was for Performance IQ (d=−0.87). In the ENI subscales, the Cohen's ds were generally quite small, the largest being found in the visual organization area for blurred figures (d=0.80) (see *Table 5*). In the comparison of the HIC and CTL groups, the largest Cohen's d was found in the visual organization area for fragmented objects (d=−0.71), followed by the visual recognition area for line orientation (d=−0.59) and visual interference area for overlapping figures (d=−0.55). Nearly all ds were in the expected and the CTL group (see *Table 6*).

For the Wilcoxon matched-pairs signed-ranks tests, P was set at 0.05 to allow for maximum sensitivity in this small sample. These tests produced significant differences for two scales in the comparison between HIC and HH, no scales in the comparison between HH and CTL, and two scales in the comparison between HIC and CTL. HIC and HH differed significantly on PIQ, FSIQ, overlapping figures, and blurred figures. These differences reflected poorer performance by the HIC group. HIC and CTL differed significantly on PIQ, FSIQ, integration of objects, and line orientation. Again, the differences reflected poorer performance by the HIC group (see *Tables 5,6*).

Discussion

This study examined the impact of focal brain injury on visual perception and visuospatial abilities in Mexican children with hemophilia who had intracranial hemorrhages. We hypothesized that children with hemophilia who experienced intracranial hemorrhage would have lower

Table 5 Comparison of visual perception and visuospatial abilities between matched children who have hemophilia with intracranial hemorrhage (HIC) and hemophilia without intracranial hemorrhage (HH), and between matched children with hemophilia without intracranial hemorrhage (HH) and the control (CTL) group

Variables	HIC (n=6)		HH (n=6)		CTL (n=6)		Effect size	
	M	SD	M	SD	M	SD	HIC-HH	HH-CTL
Intellectual function								
WISC-MR								
Verbal IQ	86.17	20.88	93.00	22.57	94.33	20.33	−0.45	−0.12
Performance IQ	87.33	16.02	101.83	10.38	102.83	8.40	−1.35*	−0.12
Full IQ	85.17	19.77	97.67	16.00	98.67	13.92	−1.38*	−0.21
Visual perception								
Visual recognition								
Facial expression of emotions	6.33	1.21	6.67	1.03	6.00	1.10	−0.27	0.49
Line orientation	4.83	0.75	5.33	1.75	5.33	0.52	−0.25	0.00
Visual organization								
Fragmented objects	2.00	1.26	2.67	1.37	3.00	0.89	−0.32	−0.27
Closure figures	2.83	1.17	2.00	0.89	2.50	1.05	0.85	−0.41
Blurred figures	8.17	0.98	9.17	0.75	8.00	1.79	−0.91*	0.80
Visual interference								
Overlapping figure test	10.33	3.14	11.83	3.71	10.83	1.47	−1.09*	0.30
Visuospatial abilities								
Spatial orientation								
Left-right comprehension	1.17	0.98	1.67	1.63	1.17	1.17	−0.30	0.25
Left-right expression	2.17	2.04	2.33	1.97	2.50	1.97	−0.41	−0.41
Figures with different angles	5.33	2.42	5.33	2.42	5.33	2.34	0.00	0.00
Coordinate maps	6.67	2.80	7.67	0.82	7.83	0.41	−0.32	−0.17

*, $P<0.05$. WISC-MR, Wechsler Intelligence Scale for Children-Mexican Revision.

performance in visual perception and visuospatial abilities than children with hemophilia who did not experience intracranial hemorrhage and their matched controls. The results were as predicted in the visual perception area, the HIC group showed low performance on visual perception tests, such as line orientation, fragmented objects, and overlapping figures, compared with their matched controls. However, visuospatial abilities were not significantly different among the three groups.

Effects of intracranial hemorrhage

This study found that children with hemophilia and intracranial hemorrhage showed PIQ and FSIQ scores in the low-to-average range. This result is consistent with results reported by previous studies which used the same methodology (age at lesion, age at testing, and number of strokes) and IQ materials (21,22). These studies have shown that children who had experienced focal brain injury achieved IQ scores in the low-average to average range (21,22). Moreover, earlier brain lesions are associated with lower intellectual quotient and intellectual quotient deterioration over time (21). Our research supported these findings and found that early brain damage influences cognitive outcomes in children with hemophilia who have suffered intracranial hemorrhage. Additionally, members of the HIC group showed difficulties with visual perception areas, such as visual recognition, visual organization, and visual interference tasks, compared with their matched controls. Visual recognition tasks are used to assess visual perception, and in these tasks, the child must have the ability to interpret facial expressions and other nonverbal cues. This ability plays an important role in the development and maintenance of intimate human relationships (36).

Table 6 Comparison of visual perception, visual organization, visual interference, and spatial orientation between matched children who have hemophilia with intracranial hemorrhage (HIC) and the control (CTL) group

Variables	HIC (n=10)		CTL (n=10)		Effect size
	M	SD	M	SD	HIC-CTL
Intellectual function					
WISC-MR					
Verbal IQ	81.67	18.96	85.40	24.80	0.60
Performance IQ	88.11	17.72	99.20	10.80	−0.87*
Full IQ	83.22	17.87	91.80	17.30	−1.27*
Visual perception					
Visual recognition					
Facial expression of emotions	5.70	1.70	6.20	1.14	−0.30
Line orientation	4.30	1.89	5.30	0.48	−0.59*
Visual organization					
Fragmented objects	1.90	1.37	3.10	0.88	−0.71*
Closure figures	2.50	1.08	2.70	0.95	−0.14
Blurred figures	7.90	1.66	8.30	1.57	−0.18
Visual Interference					
Overlapping figure test	10.30	3.53	12.30	2.26	−0.55
Visuospatial abilities					
Spatial orientation					
Left-right comprehension	1.20	1.14	1.40	1.07	−0.13
Left-right expression	1.90	1.73	2.00	1.83	−0.11
Figures with different angles	5.20	2.86	5.80	2.15	−0.18
Coordinate maps	7.20	2.20	7.60	0.97	−0.18

WISC-MR, Wechsler Intelligence Scale for Children-Mexican Revision.

In our study, the HIC group performed significantly worse than the control group on the line orientation task. The majority of children in the HIC group scored below average in this task compared with the HH and CTL groups. Previous research supports our findings and has also found that individuals who have experienced brain damage (37,38) or genetic disorders such as neurofibromatosistype-1 (39) and

Turner syndrome (40) typically have significant difficulties with this line orientation task. Face recognition tasks did not show significant variances between the three groups; however, the HIC group performed below average on this task. In the case of visual organization, the HIC group's performance was lower than the HH group's performance in the integration of objects and blurred figures. These tasks primarily focus on visual recognition of objects from partial or degraded images resulting from viewing objects from different viewpoints, which often causes features of the object to be blocked, cut up, or altered (41). One purpose for the use of these tests is to identify the possibility of object recognition breakdowns, which may cause individuals to lose stored knowledge about objects. Without stored knowledge, object recognition cannot occur. Finally, the HIC group demonstrated low performance on the visual interference task compared with the HH and CTL groups. On this task, the HIC group had significant difficulty with identifying parts of the visually presented object and understanding how the parts combined to form a unified whole.

Overall, the results of the present study revealed differences between the HIC and HH groups for PIQ and FIQ and some visual perception tasks. However, no differences were found between the HH and CTL groups. In other words, the differences that were found in this study were exclusively related to intracranial hemorrhage. This finding is consistent with the literature, as different studies have found lower neuropsychological performance in children with hemophilia who presented a history of intracranial hemorrhage (27-29,42).

Effects of hemophilia

One unexpected finding of our study was that performance was not significantly different between the HH and CTL groups. This result is not consistent with the literature due to the potential negative impact of hemophilia on academic and cognitive functioning suggested by previous studies (43,44). The similar performance of the HH and CTL groups further indicates that these groups are not likely to be carrying out tasks in different manners or using different strategies to recognize objects. In this sample, both the HH and CTL groups were matched on SES, and members of both the HH and CTL groups grew up in low-SES environments. Apart from other cultural contexts, support from family is particularly important for Mexicans with chronic illnesses such as hemophilia. In this regard, parents and families are protective of their children, and

this protection increases during times of illness. Ultimately, protective factors such as these may have influenced the performance of those in the HH group on these tasks.

In this context, it is important to mention that the severity of hemophilia is an important variable to be analyzed. Our study included 11 participants with severe hemophilia (10 participants in the HIC group and 1 in the HH group), 3 participants with mild hemophilia (belonging to the HH group), and 2 participants with moderate hemophilia (belonging to the HH group). In order to analyze this variable, we would need a greater sample size to group them according to severity. Although the literature has stated that patients with severe hemophilia suffer complications such as bleeding episodes and such bleeding can affect the central nervous system (27-29,42), different studies have suggested that hemophilia severity is not significantly related to neuropsychological outcomes (45,46).

Visuospatial abilities

In our study, the three groups did not show statistically different performance in terms of visuospatial abilities. It appears that all three groups showed difficulties in this area, as the majority of the participants had below-average abilities in left-right comprehension and expression tasks. It is important to highlight that children typically apply these terms to their own bodies correctly around seven years of age, in addition to applying them to another person facing them (47). The use and determination of a person's position with reference to right and left wording evolves as age increases, and the steps in verbal use of right and left terms are well known. The evolution of mental representation is not age dependent; however, the evolution is dependent on cognitive development. In part, this is because we know that development is gradual and cannot take place from 1 year to the next (48). Although left-right comprehension and expression are dependent on cognitive development rather than being age dependent, this process may be delayed due to environmental factors, such as lower SES level, deferred school years, and chronic illness.

Clinical implications

Our findings have important clinical implications for the use of neuropsychological assessments in high-risk children with hemophilia and children with hemophilia

who have experienced intracranial hemorrhage. The impacts of problems with visual perception and visuospatial functioning on the everyday lives of children emphasize the importance of early detection of visual functioning difficulties and relevant interventions for these children. Therefore, it is not possible to know the potential academic impact of visual perception and visual spatial deficits in children with hemophilia. However, the importance of visual perception and visuospatial abilities to academic achievement in such areas as reading and math is well established in children without chronic illness (49). As a result, it is likely that children with hemophilia who have histories of intracranial hemorrhage and visual perception and/or visuospatial difficulties are at risk for academic challenges. Among neuropsychology studies, hemophilia is a genetic disorder that is not well understood. Studies of patients with hemophilia have mainly focused on outcomes associated with HIV status, behavior, and social interactions. The majority of those results were derived from the Hemophilia Growth and Development Study (50). We are not aware of any studies that have examined visual perception and visuospatial abilities in children with hemophilia, which makes this topic of greater interest and provides an opportunity for future explorations in this area.

Limitations and future directions

A variety of potential limitations should be considered when interpreting the results of our study. The small sample size in each group limited the power of the group comparisons to detect the effects of intracranial hemorrhage. Next, the participants in this study varied substantially in age. Finally, given the wide variation in lesion locations and numbers of intracranial hemorrhages, a large sample would provide more rigorous results of the moderating influences of these factors. In future studies, it would prove beneficial to examine visual perception and visuospatial abilities in a group of children with hemophilia who had intracranial hemorrhages within a smaller age range in order to consider more precise questions regarding the effects of development on visual perception and visuospatial performance.

While unanswered questions remain for future research efforts, hematology practices can now incorporate routine screening via regular neuropsychological assessments of the visual perception and visuospatial abilities discussed in this work. Specifically, neuropsychologists working

within hematology clinics can recognize the importance of neuropsychological evaluations that include visual perception (visual recognition, visual organization, and visual interference) and visuospatial abilities (visual construction, visuospatial orientation, and spatial visualization). This study can serve as a pilot study for the remainder of patients with hemophilia in Latin America, in order to ascertain whether Mexican patients with hemophilia display specific cultural characteristics that must be taken into account, especially when considering the impact of hemophilia on individual development.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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