Functional Vision Analysis in Patients With CHARGE Syndrome

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Abstract:

Purpose: CHARGE syndrome (CS) is a multiple malformative syndrome in which ocular colobomas cause visual impairment. Data are lacking regarding visual function because classical methods for visual acuity (VA) assessment are often not applicable in patients with CS. We evaluated vision in a pilot study of patients with CS by using a new questionnaire entitled VISIOCHARGE.

Methods: Ophthalmological data including fundus description and VA, when available, were extracted from charts of 83 patients with CS, and VISIOCHARGE was prospectively sent to 55 of them. The answers of the 36 responders (18 males) allowed for calculating 3 scores assessing distance-vision, near-vision, and an "overall ability" score.

Results: Visual acuity measurements were extracted from the charts of 20 of the 36 patients. The mean VA was 20/50. The mean distance-vision score of 0.62 (SD 0.30) and near-vision score of 0.78 (SD 0.23) were correlated with VA in the 20 patients (ρ=0.64, p=0.002 and ρ=0.61, p=0.005, respectively) and were associated with the severity of the colobomatous malformation (p=0.049 and p=0.008, respectively). Severity of the ocular malformation was not associated with overall ability score (p=0.64).

Conclusions: VISIOCHARGE is feasible in patients with CS and may help in the assessment of visual function. The mean VA and the answers to the questionnaire showed relatively good visual skills in these patients in everyday life, even in those with bilateral colobomas, which contrasts with the pessimistic conclusions usually resulting from the initial fundus examination.

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INTRODUCTION

CHARGE syndrome (CS) is a multiple malformative syndrome, with coloboma representing a major feature and diagnostic criterion[1,2]. This ocular anomaly is found in 72% to 95% of patients with CS[3-8] and represents an important cause of disability in affected patients. However, previous studies mainly focused on the anatomical aspects of the ocular manifestation of the syndrome and rarely reported results from visual acuity (VA) and/or visual function assessment. This lack of data is due in part to the difficulty in obtaining a reliable VA value in many patients with CS, as classical ophthalmological evaluation methods are often not applicable because of the multiple sensory deficits and/or cognitive disabilities of such patients. The few series reporting VA in CHARGE syndrome found mean values below 20/60[4-8]. However, in our experience, the parents, relatives and professionals caring for these patients often report good visual skills in everyday life, which contrasts with the often pessimistic conclusions from the ophthalmological examinations, in particular neonatal examinations. This contrast points out the need for a new tool to assess the real visual function in patients with CS regardless of the severity of their sensory, motor and/or cognitive impairments.

In this study, we aimed to develop an original self-administered questionnaire designed for patients with CS (VISIOCHARGE) and we used it to evaluate the functional vision of patients with CS. The other goals were to describe the ocular features of a large series of patients with CS, to analyze the links between the severity of the ocular malformation and practical visual function and to confirm the previously suspected correlation between visual impairment and poor developmental milestones in these children[9,10].

PATIENTS & METHODS

Questionnaire development

The questionnaire, entitled VISIOCHARGE (see Appendix) was built from observations and comments of pediatricians, ophthalmologists and orthoptists used to following up patients with CS. A first version of the questionnaire was randomly sent to 4 families to obtain their comments on its quality, feasibility and understandability. After a review, we adopted a final version of the questionnaire consisting of 30 items in 3 categories: 1) parental evaluation of global vision (2 items), designed to assess parents' feeling about the importance of the visual impairment of their child and its consequences on everyday life; 2) evaluation of distance vision (9 items); and 3) evaluation of near vision (10 items). Additional questions were asked to evaluate the ophthalmological follow-up (4 items), educational level and age of walking acquisition of the patient (5 items). Some free space was available at the end of the document for open answers and comments.

Study population

All patients with CS followed or seen at least once between January 1, 1990 and December 31, 2016 in the pediatric and/or ophthalmologic departments of Necker-Enfants Malades Hospital and/or La Pitié-Salpétrière Hospital were included. CS diagnosis was established clinically by using the Blake and Verloes criteria[1,2]. When available, their CHD7 mutation status was extracted from medical charts. The VISIOCHARGE questionnaire was sent by mail between January 1 and December 31, 2017 to the most recent address of the patient registered in the hospital database, accompanied by an information letter and a consent form. The patients, or their parents in case of inability to read and/or to understand the questions, were asked to complete the questionnaire and return it by mail to the investigator with a signed consent form. A few days after sending the questionnaire, investigators contacted the patients or their parents by phone call to further explain the aim of the study and answer their

questions. Patients with CS who had died before the beginning of the study were excluded and their parents were not asked for participation. This study was approved by the ethics committee of Necker-Enfants Malades Hospital on October 31, 2016 (authorization number: 2016-VA 24-R1), and adhered to the tenets of the Declaration of Helsinki.

Data collection and outcome measures

The following information was extracted from medical charts of patients: the most recent corrected best binocular VA, the description of fundus of each eye after dilation (presence of chorioretinal and/or optic disk coloboma, involvement of the fovea and/or the optic disk inside the coloboma), and presence of nystagmus, strabismus, and any other anomalies seen during the ophthalmological examination, including ptosis, facial palsy, congenital cataract or retinal detachment.

VA was measured by using the French Monoyer chart and was expressed in decimal, fraction (in feet) and LogMAR units.

On the basis of data from the medical chart, we assigned patients to two groups based on the severity of anatomical lesions. Group A included patients with no coloboma in both eyes or with a coloboma in one or both eyes but at least one eye having a fully preserved optic disk and fovea. Group B included patients with a coloboma involving the optic disk in both eyes, with or without involvement of the fovea.

Answers to each item of the questionnaire were analyzed independently to detail the visual ability. We then calculated three scores by giving a value in points for the different items; the maximum score corresponded to the most difficult or smallest things to see. The three scores calculated were a distance-vision score, a near-vision score, and an overall ability score. The overall ability score combined the answers to six items exploring the ability to perform six tasks: watch TV, move around indoors in a familiar place, move around indoors

in an unknown place, move around outdoors, use a tablet PC, use a smartphone. The scores were expressed as decimals between zero and one.

To simply assess the psychomotor development of patients, the questionnaire asked about the age of walking acquisition, which was verified in medical charts, and the most recently attended educational structure. These educational structures were classified from level 1 to 5, reflecting the communication and cognitive abilities of the patients: 1) in a regular school without any specific assistance; 2) with an assistant dedicated to the child in a regular school; 3) in a specific classroom and/or structure for deaf and/or blind children, without cognitive disabilities; 4) in a structure dedicated to deaf and/or blind children with cognitive impairment but communication abilities; and 5) severe cognitive disabilities without any acquired language and poor learning.

Statistics

Continuous variables were expressed as mean with standard deviation (SD). Because the sample was too small, we could not divide the ophthalmological gravity of patients into more than two groups for analyzing the correlation between anatomic and functional data. We compared groups by Kruskall Wallis, Mann-Whitney and Fisher tests, and used the Spearman for correlations. Significance was considered at two-sided $p < 0.05$.

RESULTS

The database review found 83 patients (46 males) followed in the two centers for typical CS with or without ophthalmological involvement. Among the 83 patients, 10 were deceased and 18 were followed elsewhere. Thus, we sent the VISIOCHARGE questionnaire to 55 patients included in the prospective part of the study. Four questionnaires were returned because of a wrong address, and 15 families received the letter but did not answer or refused to take part in the study. Finally, among the 55 solicited patients, 36 (18 males) with

completed VISIOCHARGE questionnaires were included in the analysis (response rate = 66%). The mean age of responders was 13.8 years (SD 6.9). The demographic, ophthalmological and neurodevelopmental characteristics of the 36 responders were comparable to those of the 83 patients in the whole series (Table 1) allowing for discussion and conclusions. A mutation in *CHD7* was found in 31 children of the 33 investigated patients (94%). The genetics investigation had not been performed for 3 others.

Of the 36 patients, 32 (89%) had at least one ocular coloboma of the posterior segment reported in their medical chart; 4/32 (11%) had presented a unilateral retinal detachment (RD). Overall, 27/36 (75%) patients wore glasses; the mean age at the first optical correction was 4 years (SD 3.7).

Visual function and its consequences for activities of daily life

Of the 36 patients, only 20 (56%) had VA data available in medical charts. In these patients, the mean VA was 0.42 (20/50, 0.40 LogMAR). When we excluded the only patient without coloboma with a measurable VA, the mean VA stayed similar (0.40 LogMAR). For 26/36 (72%) patients, their parents reported trouble related to the vision of their child; for 11/36 (30%), their child was declared to be “very bothered” by it (Table 2). Nevertheless, 32/36 (89%) patients were able to use electronic devices such as smartphones or digital tablets; 31/36 (86%) were able to watch television, 22/36 (61%) reported an ability to recognize a familiar face at more than 2 m, and 19/36 (53%) were able to read or identify Arial characters of 18 size at a reading distance of 40 cm. The mean distance-vision, near-vision, and overall ability scores were 0.62 (SD 0.30), 0.78 (SD 0.23) and 0.79 (SD 0.25), respectively.

For the 20 patients with a VA measurement, the distance-vision and near-vision scores from the VISIOCHARGE questionnaire were positively correlated with measured VA (ρ=0.64, p=0.002, and ρ=0.61, p=0.005, respectively). Parental evaluation of the global vision of their

child was correlated with the distance-vision and near-vision scores (r_s=0.61, p<0.001, and r_s=0.63, p<0.001, respectively) and with measured VA (r_s=0.68, p<0.001).

Developmental features

In this series, the mean age of walking acquisition was 35.4 months (SD 15.0). The distance-vision score was negatively correlated with age of walking acquisition (ρ=-0.38, p=0.037). Age of walking acquisition was not correlated with parental evaluation of the global vision of their child or near-vision or overall ability score (r_s=-0.22, p=0.23; ρ=0.03, p=0.86; ρ=0.02, p=0.92, respectively). Regarding educational levels, most patients had been schooled in structures of types 2, 3 and 4. The distance-vision, near-vision and overall ability scores were all negatively correlated with educational level (r_s=-0.54, p<0.001; r_s=-0.45, p<0.001; r_s=-0.39, p=0.02, respectively). Educational level was not correlated with parental evaluation of the global vision of their child (r_s=-0.27, p=0.11).

Correlation between anatomic and functional data

Patients in group A (mild anatomical lesions, n=18) were compared to those in group B (severe anatomical lesions, n=17) (Table 3). One patient was excluded from this analysis because of an incomplete description of the fundus. As expected, the mean VA was significantly worse for group B than group A patients: 0.23 (20/80, 0.64 LogMAR) vs 0.88 (20/25, 0.05 LogMAR), p<0.001. Similarly, the mean distance-vision and near-vision scores were significantly lower for group B than group A (0.54 vs 0.71, p=0.049, and 0.69 vs 0.88, p=0.008, respectively). However, the 2 groups did not differ in parental evaluation of the global vision of their child (p=0.07) or in the overall ability score from the questionnaire (0.76 vs 0.83, p=0.64). The two groups did not differ in developmental features. Taken separately, the only two items showing a significant difference between the two groups were those exploring the ability to recognize a familiar face at a given distance (p=0.008) and the smallest size of Arial text readable (p=0.03).

Comments from responders

Ten (28%) patients (or their parents) reported better performance in near vision than distance vision. For 6 (17%) patients, a photophobia was also spontaneously reported in questionnaires. The parents of a young patient reported that at birth, their child had been given a prognosis of severe vision, total blindness, after the first ophthalmological examination because of the severity of the colobomas involving the fovea in both eyes. The VA of this child was actually measured at 0.3 (20/60, 0.48 LogMAR). His distance-vision, near-vision and overall ability scores were 0.70, 0.60 and 1, respectively. One patient spontaneously highlighted a prosopagnosia (difficulty in recognizing faces out of their context).

DISCUSSION

This series is one of the largest to describe the ocular features in CS, and the first to specifically address the question of visual function, showing better visual skills than previously reported. The most recent studies[4,5,7] reported VA under 0.3 (20/60, 0.48 LogMAR) in 58% to 67% of patients with CS for whom VA was measurable, which contrasts with the 30% in our series, closer to the 17% found by Russel-*Eggit et al* (6). However, these comparisons are difficult to interpret because of the very small proportion of patients in each series for whom VA was measurable. With 20 (56%) patients having a measured VA, our study is the first to report such a high proportion of available data. However, the substantial number of missing data is also the main reason that led us to look for another way to explore visual function in this specific population.

In the ophthalmological field, some examination methods exist to assess visual function in non-verbal children who are very young or have intellectual impairment. Among them, the preferential looking procedures[11] (Cardiff Acuity Test, Teller Acuity Test), optokinetic nystagmus assessment, and visual evoked potentials are the most commonly used. However,

these tools are not widely available in routine care and may not be suitable for some patients with CS because of cognitive disabilities reducing their attention or some ophthalmological features such as oculomotor palsies or nystagmus, commonly found in this population.

Questionnaires assessing functional vision in the pediatric field are being increasingly used to assess the consequences of the visual impairment on quality of life. We reviewed seven available questionnaires[12-18] but none were suitable for patients with CS because the questions implied an absence of sensory, motor or cognitive disabilities besides the visual impairment (Table 4). We found two questionnaires designed for children with disabilities[19,20]. However, one was not appropriate for regular self-administered evaluation, because some items seemed equivocal, whereas the other was specifically aimed at children with severe cognitive disabilities, which is not a systematic feature of patients with CS. Thus, we aimed to develop an original questionnaire, suitable for every patient, regardless of the age or any motor and/or cognitive disability. VISIOCHARGE not only proved is feasibility in a heterogenous population of patients with CS, but also demonstrated that most of the patients with CS were able to perform similar tasks as other children. Most of the patients were not very bothered by their visual impairment, especially in tasks involving near vision. The main difficulties reported were in distance vision and outdoor activities.

VISIOCHARGE could reflect visual function because the distance-vision and near-vision scores were well correlated with VA, when available. To confirm these results, this questionnaire should be tested in other diseases featuring impaired visual function in children with or without associated disabilities. Indeed, the main limitation of this study is that this questionnaire has not been rigorously validated yet. Now that we have proven the questionnaire's feasibility on a pilot population, its use in a much larger population is possible, and its validation by evaluating its metrological qualities has to be done. Another important limitation of the study is the risk of subjectivity, unavoidable with self-administered questionnaires and perhaps more so when a relative performs it. However,

because we wanted to assess visual skills in everyday life, we cannot totally suppress this subjectivity.

With a total of 83 charts reviewed, our series is the largest to detail the ocular features in CS. As previously described, the most frequent feature is chorio-retinal coloboma, found in 83% of our patients, close to the 82%, 79% and 90% of Russel-Eggit *et al.*, Tellier *et al*. and Strömland *et al.*, respectively[6-8]. Retinal detachment was found in 4,4% of colobomatous eyes, in the low average of previously published data about RD complicating colobomas, suggesting that CS may not be a risk factor for RD.

The correlation between anatomy and function is incomplete. Although VA and distance-vision and near-vision scores were better in children with peripheral colobomas than those with colobomatous lesions involving both the optic nerve and/or macula, the results from our questionnaire did not find any difference between these patients in overall ability score and parental evaluation of their global vision. This lack of correlation may be due in part to a potential failure of our questionnaire to reveal a difference. However, these results confirm the general impression of parents and caregivers that children with CS and large colobomas can develop some surprising compensatory strategies, allowing them to use their remaining vision, either central or peripheral. Another explanation for the lack of anatomic and functional correlation is the difficulty for ophthalmologists to assess macular anatomy by fundus examination alone, as it was previously shown[21]. Thus, as suggested by Nishina *et al*., it seems crucial not to predict poor vision in a neonate with CS and bilateral coloboma because our experience showed that some of these children can later show correct visual function[5].

Our series also confirmed the previously suspected association between visual function and some developmental parameters[9,10] independent of other manifestations of the syndrome. Late acquisition of walking has been found negatively correlated with distance-vision score, and educational level has also been correlated with all visual function scores. This

observation reinforces the promotion of regular and rigorous ophthalmological care for every patient with CS, regardless of the severity of the ocular malformation, to assure the best visual prognosis as well as good general development.

Assessment of visual function in patients with CS may be challenging because VA measurements are often not possible in these patients. We present encouraging preliminary results with an original questionnaire, specifically designed for children with visual impairment and associated sensory, motor and/or cognitive disabilities. The relatively good visual skills of the patients in this series contrast with the often-pessimistic conclusions from initial ophthalmological examinations. Ophthalmologists should not give a poor visual prognosis to parents of a newborn recently diagnosed with CS and bilateral coloboma. They should encourage parents to stimulate their child with lights and colored objects as much as possible to foster the developmental of their social brain and visual cortex.

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Tables

Table 1: Comparison of the 36 responders to the VISIOCHARGE questionnaire and the total number of CHARGE syndrome patients followed in our center

	Charts reviewed n=83	VISIOCHARGE responders n=36	p
Sex, n patients (%)			0.69
Male	46 (55)	18 (50)	
Female	37 (45)	18 (50)	
Ocular features, n patients (%)			
Posterior coloboma	69 (83)	32 (89)	0.58
- unilateral	14 (17)	7 (19)	
- bilateral	55 (66)	25 (69)	
Iris coloboma	12 (14)	7 (19)	0.59
- unilateral	6 (7)	3 (8)	
- bilateral	6 (7)	4 (11)	
Microphtalmos	28 (34)	15 (42)	0.41
- unilateral	25 (30)	13 (36)	
- bilateral	3 (4)	2 (6)	
Ptosis	14 (17)	7 (19)	0.80
Nystagmus	24 (29)	11 (31)	1
Facial palsy	24 (29)	10 (28)	1
Congenital cataract	4 (5)	1 (3)	1
- unilateral	3 (4)	1 (3)	
- bilateral	1 (1)	0	
Retinal detachment	6 (7)	4 (11)	0.49
- unilateral	6 (7)	4 (11)	
- bilateral	0	0	
Severity of the coloboma*			0.55
Group A, n patients (%)	42 (51)	18 (50)	
Group B, n patients (%)	36 (43)	17 (47)	
Unclassified	5 (6)	1 (3)	
Age of walking (months)			
Mean (SD)	36.9 (15.7)	35.4 (15.0)	0.66
Min–max	19–78	19–78	
Visual acuity (decimal):			
Mean	0.41	0.42	0.97
Unmeasurable	48 (58)	16 (44)	

*Group A, patients with no coloboma in both eyes or with coloboma in one or both eyes but at least one eye having a fully preserved optic disk and fovea; Group B, patients with coloboma involving the optic disk in both eyes, with or without involvement of the fovea.

Table 2: Answers for the VISIOCHARGE questionnaire for the 36 children

Global vision	Parental evaluation of the global vision of their child, n (%)	
	Normal, or abnormal but without inconvenience	10 (28)
	Slightly bothered by his/her visual impairment	7 (19)
	Moderately bothered by his/her visual impairment	8 (22)
	Very bothered by his/her visual impairment	11 (31)
Distance vision	My child can watch TV, n (%), IDK*	31 (86), 0
	If yes, the TV is placed at a distance of: n (%)	
	> 2 m	7/31 (23)
	50 cm to 2 m	17/31 (54)
	< 50 cm	7/31 (23)
	My child can recognize a familiar face at a maximum distance of: n (%)	
	> 10 m	9 (25)
	2 m to 10 m	13 (36)
	< 2 m	12 (33)
	IDK	2 (6)
	When looking at the sky, my child can see:	
	The moon, at night, n (%), IDK*	19 (53), 9
	A plane, at daytime, n (%), IDK*	19 (53), 5
	The visual impairment of my child bothers him/her in moving:	
	Indoor, in a familiar place, n (%), IDK*	3 (8), 4
	Indoor, in an unknown place, n (%), IDK*	9 (25), 5
	Outdoor, n (%), IDK*	19 (53), 2
	Distance vision score, mean (SD)	0.62 (0.30)
Near vision	My child can use a tablet PC, n (%), IDK*	32 (89), 0
	If yes, he uses it:	
	In "normal" conditions	28/32 (88)
	With specific adjustments (e.g., character magnification)	4/32 (12)
	My child can use a smartphone, n (%), IDK*	32 (89), 1
	My child can read a text (or identify drawings) of a minimum size of (at a distance of 40 cm): n (%)	
	Arial 8	12 (33)
	Arial 10	4 (11)
	Arial 18	3 (8)
	Arial 28	4 (11)
	Arial 48	6 (17)
	> Arial 48	2 (6)
	My child cannot perform this test	5 (14)
	During lunch time, my child can see on the table in front of him/her: n (%)	
	A grain of rice	29 (81)
	An olive	35 (97)
	An apricot/plum/strawberry	35 (97)
	An apple/orange	36 (100)
	My child is able to see and catch a strand of hair, n (%), IDK*	22 (61), 2
	Near vision score, mean (SD)	0,78 (0.23)
	Overall ability score (TV, motion, smartphone, tablet PC), mean (SD)	0,79 (0.25)

* IDK: I don't know

Table 3: Comparison of visual and developmental features by severity of the colobomatous malformation: Group A and B patients

	Group A* (n=18)	Group B* (n=17)	p
Age (years), mean (SD)	13.1 (6.8)	14.7 (7.3)	0.50
Parental evaluation of the overall vision of their child, n (%)			0.07
Normal, or abnormal but without inconvenience	8 (44)	2 (12)	
Slightly bothered by his/her visual impairment	2 (11)	5 (29)	
Moderately bothered by his/her visual impairment	5 (28)	3 (18)	
Very bothered by his/her visual impairment	3 (17)	7 (41)	
Visual acuity (LogMar), mean (SD)	0.05 (0.10)	0.64 (0.28)	**<0.001**
Distance-vision score, mean (SD)	0.71 (0.31)	0.54 (0.27)	**0.049**
Near-vision score, mean (SD)	0.88 (0.20)	0.69 (0.22)	**0.008**
Overall ability score, mean (SD)	0.83 (0.20)	0.76 (0.30)	0.64
Age of walking (months), mean (SD)	34.7 (15.9)	36.2 (15.1)	0.79

*Group A, no coloboma in both eyes or with a coloboma in one or both eyes but at least one eye having a fully preserved optic disk and fovea; Group B, a coloboma involving the optic disk in both eyes, with or without involvement of the fovea.

Table 4: Comparison of existing questionnaires evaluating visual function and visual disability in children

	Age range (years)	Target children	Person interviewed	No. of items	Evaluated parameters
VAS[a]	2–18	Children with visual impairment with no other sensorial, physical or cognitive disability	Parents	16	Visual acuity, visual field, color vision
CVFQ[b]	≤ 7	Children with visual impairment with or without developmental delay	Parents	40	Personal, social and familial impact of visual disability
CVAQC[c]	5–18	Children with acquired spoken language and no sensorial, physical or cognitive disability	Child	25	Ability to complete tasks requiring vision
IVI_C[d]	8–18	Children with visual impairment with acquired spoken language and no other sensorial, physical or cognitive disability	Child	24	Personal, social and scholar impact of visual disability
LVP_FVQ II[e]	8–18	Children in developing countries with acquired spoken language and no sensorial, physical or cognitive disability	Child	23	Grading of visual impairment
FVQ_CYP[f]	10–15	Children with acquired spoken language and no sensorial, physical or cognitive disability	Child	36	Ability to complete tasks requiring vision
PreViAs[g]	≤ 2	Babies, except premature infants, without a "major" adverse medical history or developmental delay	Parents	30	Reactions of the infant to visual stimulations

[a]Visual Ability Score (Katsumi *et al.*, 1998)
[b]Children's Visual Function Questionnaire (Felius *et al.*, 2004)
[c]Cardiff Visual Ability Questionnaire for Children (Khadka *et al*., 2010)
[d]Impact of Vision Impairment for Children (Cochrane *et al*., 2011)
[e]L.V. Prasad – Functional Vision Questionnaire (Gothwal *et al*., 2012)
[f]Functional Vision Questionnaire for Children and Young People (Tadic *et al*., 2013)
[g]Preverbal Visual Assessment questionnaire (Pueyo *et al*., 2014)

Appendix: The VISIOCHARGE Questionnaire (translated from its original French version)

Appendix - Questionnaire