Child's Nervous System (2020) 36:1481–1488
https://doi.org/10.1007/s00381-020-04521-w

ORIGINAL ARTICLE

Single-suture craniosynostosis: is there a correlation between preoperative ophthalmological, neuroradiological, and neurocognitive findings?

D. P. R. Chieffo[1] · V. Arcangeli[1] · F. Bianchi[2] · A. Salerni[3] · L. Massimi[2] · P. Frassanito[2] · G. Tamburrini[2]

Received: 16 December 2019 / Accepted: 25 January 2020 / Published online: 1 February 2020

Abstract

Background In spite of literature data stating that children with single-suture craniosynostosis have an increased risk for neuropsychological deficits, no data are present clarifying the potential risk factors.

Methods All children with non-syndromic single-suture craniosynostosis operated on from January 2014 to January 2017 were enrolled. A comprehensive neurocognitive and neuro-ophthalmological evaluation was performed before surgery and 6 months after surgery. A further neurocognitive evaluation was performed 12 months after surgery. All children had a preoperative CT/MR study.

Results One hundred forty-two patients were enrolled; 87 are affected by sagittal craniosynostosis, 38 by trigonocephaly, and 17 by plagiocephaly. A global neurocognitive impairment was documented in 22/87 children with scaphocephaly, 5/38 children with trigonocephaly, and 6/17 children with anterior plagiocephaly. There was a significant relationship between results of the ophthalmological evaluation, global IQ, and CT findings at diagnosis ($r = 0.296$, $p < 0.001$; $r = 0.187$, p 0.05). Though a significant recovery was documented after surgery, a persistence of eye coordination deficits was present at 6 months in 1 out of 3 children with abnormal preoperative exams. A significant correlation was found between pathological CT findings and persistence of below average neuro-ophthalmological and neurocognitive findings 6 months after surgery, as well as between CT findings and neurocognitive scores at the 1 year follow-up ($r = 0.411$; $p < 0.01$).

Conclusion The presence of neuroradiological abnormalities appears to be related to both ophthalmological and neurocognitive deficits at diagnosis. This relationship is maintained in spite of the surgical treatment in children who show the persistence of ophthalmological and neurocognitive deficits during the follow-up.

Keywords Scaphocephaly · Trigonocephaly · Anterior plagiocephaly · Neurocognitive function · Neuro-ophthalmological function · Neuroradiological evaluation

Introduction

Many factors might contribute to the neurological and developmental outcome of children with single-suture craniosynostoses (SSC); these might include the diagnostic subtype (metopic, sagittal, coronal, lambdoid), the eventual presence and duration of raised intracranial pressure (ICP), associated brain abnormalities and their severity, age at surgery, and the child's sociodemographic environment.

Data from the literature [8, 13] suggest that SSC are associated with an increased risk for neuropsychological deficits, which might persist during child growth. When considering the infantile age, a clear, though mild, delay in motor and cognitive functions has been described; behavioral abnormalities, including attention deficit disorders, autism, and hyperactivity, have also been observed. The causes of these disturbances are still not clearly defined [3–5, 8–12, 14, 15].

Speltz et al. [13] suggested a multifactorial pathogenesis: the duration and type of anesthesia, the amount of blood loss, and the eventual occurrence of adverse events have all been claimed to eventually contribute [16].

✉ F. Bianchi
fede0786@hotmail.it

[1] Institute of Pediatric Neurology, Fondazione Policlinico Gemelli IRCCS, Catholic University Medical School, Rome, Italy

[2] Pediatric Neurosurgery, Institute of Neurosurgery, Fondazione Policlinico Gemelli IRCCS, Catholic University Medical School, Rome, Italy

[3] Institute of Ophthalmology, Fondazione Policlinico Gemelli IRCCS, Catholic University Medical School, Rome, Italy

Most of the studies have however focused on the overall intellectual ability without giving information on selective neuropsychological skills. When selective functions are considered, deficits in speech and language, speech reception, and oral–motor-related skills might be present and these include phonological development, visual–spatial skills, and consolidation of learning, memory, and attention.

There are no data in the literature on which might be the risk factors for the development of these deficits. The absence of a clear correlation with age and type of surgical treatment has led to the hypothesis that these deficits may be proper of the child himself and related to a congenital central nervous system dysfunction associated to, but not determined by, the craniosynostosis.

The present study has been designed to prospectively and comprehensively evaluate all children affected by single-suture synostosis, before and after surgery, from a neurocognitive, neuro-visual, and neuroradiological point of view, in order to investigate possible predictive factors for children neurocognitive development.

Methods

All children with reasonably non-syndromic single-suture craniosynostosis operated on from January 2014 to January 2017 were enrolled in the study. A comprehensive neurocognitive and neuro-ophthalmological evaluation was performed before surgery (T0), 6 months after surgery (T1), and 12 months after surgery (T2). All children also underwent a preoperative CT/RM study.

Neurocognitive assessment

The five Griffith Mental Development Scales (GMDS) were used to evaluate neurocognitive function: (a) the locomotor sub-scale (scale A) was used to assess gross motor skills, including the ability to balance and to coordinate and control movements; (b) the personal–social (scale B) was used to measure proficiency in the activities of daily living, level of independence, and interaction with other children; (c) the hearing and language (scale c) was used to assess hearing, expressive language, and receptive language; (d) the eye and hand coordination (scale D) was administered to evaluate fine motor skills, manual dexterity, and visual monitoring skills; (e) the performance (scale E) finally was administered to assess the developing ability to reason through tasks including speed of working and precision.

Neuroradiological evaluation

All children included in the study underwent high-resolution head CT scan with 3D reconstructions. Parenchymal sequences were used to evaluate the presence of associated

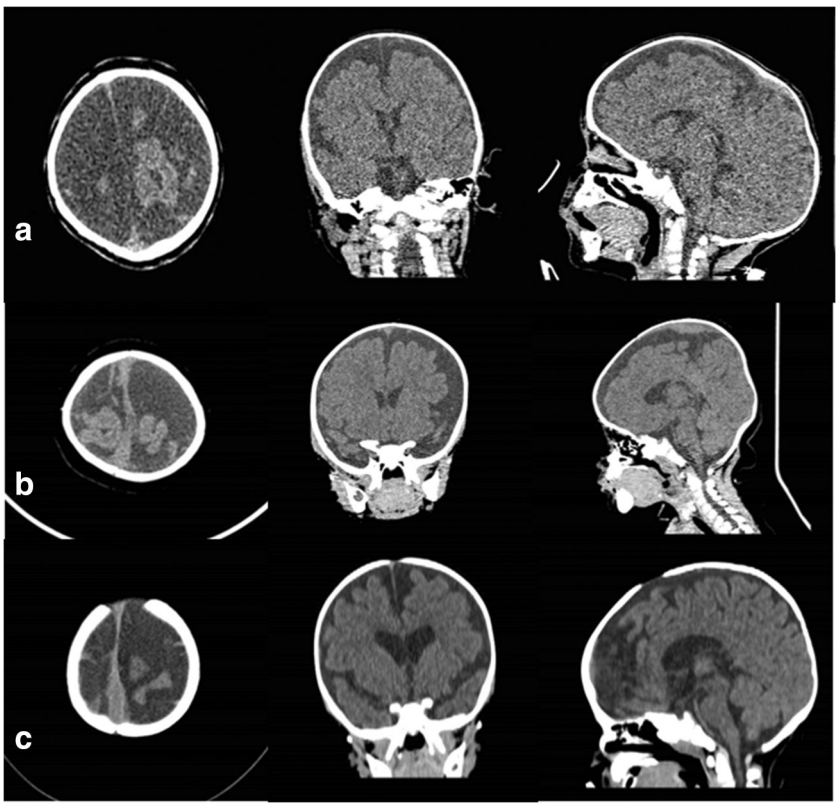

Fig. 1 Widening of the pericerebral subarachnoid spaces in scaphocephaly (**a**), plagiocephaly (**b**), and in trigonocephaly (C)

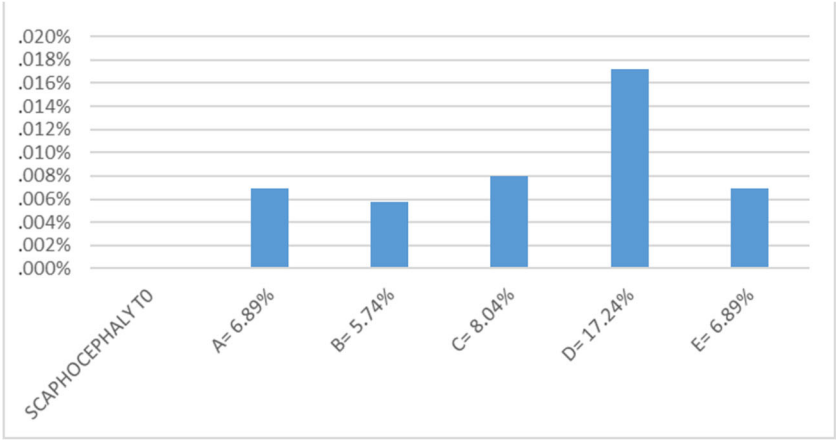

Fig. 2 Neurocognitive evaluation of patients with scaphocephaly at T0. The most frequently compromised scale was the hand and eye coordination scale (D)

anatomical cerebral anomalies; whenever present, an MR examination was performed. CT/MR examinations were evaluated blindly by two different participants to the study.

Neuro-ophthalmological evaluation study

A complete ophthalmological examination was administrated to all patients including the evaluation of the anterior segment, fundus oculi in mydriasis, and refractive examination during cycloplegia. Ocular motility was evaluated in nine gaze positions with lea gratings paddles. Hirschberg and Krimsky tests for near and far were administered in order to study the symmetry of corneal reflexes and the eventual presence of strabismus. In more collaborating children, the cover test for near and far was added too.

Statistical analyses

Univariate and multivariate statistical analysis was performed using the correlation test of Pearson and Spearman. Significance value was set a $p < 0.05$.

Results

One hundred and forty-two patients were enrolled (M = 102; F = 40, mean age 6.19 months, min 2 months/max 10 months): 87 of them were affected by sagittal craniosynostosis (61.26%), 38 by trigonocephaly (26.76%), and 17 by plagiocephaly (11.97%).

Preoperative evaluation

Neuroradiological findings

No brain associated abnormality was documented in 104/142 cases (73.2%). A widening of the pericerebral subarachnoid spaces was present in 39 cases (27.5%) (Fig. 1). Among these 39 cases, in the 74% of them, such CT scan finding was associated with sagittal craniosynostosis, while in 18% of them with trigonocephaly. Only in 2 cases (5%), such a finding was associated with anterior plagiocephaly and 1 case (3%) with anterior brachycephaly. Such a widening was more commonly found in the fronto-parietal vault especially in scaphocephalic patients.

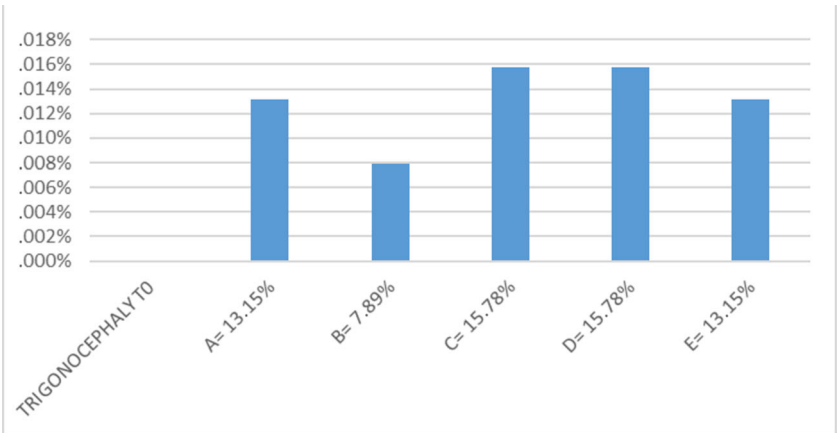

Fig. 3 Neurocognitive evaluation of patients with trigonocephaly at T0. The most frequently compromised scales were the learning and hearing and the hand and eye coordination scale (D)

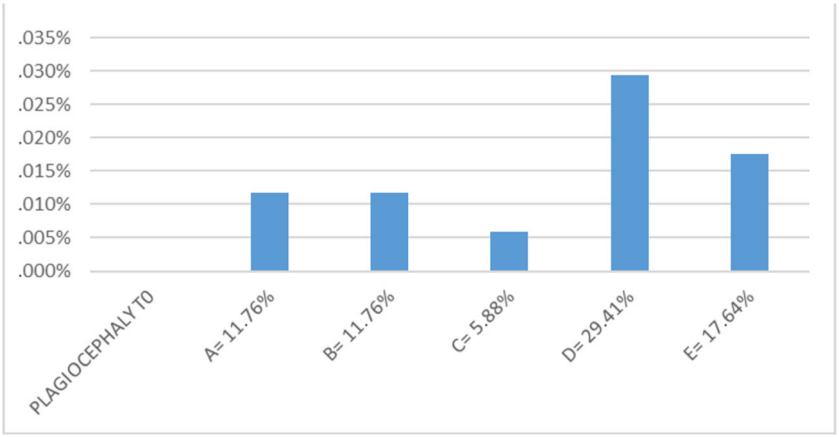

Fig. 4 Neurocognitive evaluation of patients with plagiocephaly at T0. The most frequently compromised scale was the hand and eye coordination scale (D)

A mega cisterna magna was present in 3 patients and a cavum septum was the only abnormality evidenced in the last 2 patients. MR examinations were performed in 44 cases (all the children with an abnormal finding on the CT scan) confirming CT diagnosis without further findings.

Neurocognitive findings

A global neurocognitive impairment was documented at admission in 22/87 children with scaphocephaly (25.28%), 5/38 children with trigonocephaly (13.1%), and 6/17 children with anterior plagiocephaly (35%).

When selective performances were evaluated, 40/142 patients (36.69%) had a drop in one or more scales: these were 22 of the 87 patients with scaphocephaly (22.58%), 12 of the 38 children with trigonocephaly (31.57%), and 6 of the 17 children with plagiocephaly (35%). The most compromised GMDS scale was scale D evaluating the hand–eye coordination. Disturbances of hand–eye coordination were documented in 15/87 (17.2%) children affected by scaphocephaly, 6/38 children (15.7%) affected by trigonocephaly, and 5/17 children (29.4%) affected by plagiocephaly (Figs. 2, 3, and 4).

Neuro-ophthalmological findings

Neuro-ophthalmological abnormalities were found at diagnosis in 69/87 children (79.3%) with sagittal craniosynostosis as the most marked difficulty being represented by an abnormal position of the head (48/69; 71%). A deficit in the elevation of the gaze was documented in (57/69) 84% of these patients. Seventy-five percent (51/69 patients) of these children also showed a pallor of the optic nerves.

Neuro-visual abnormalities were found in 8/17 (47%) of the children with anterior plagiocephaly. In 50% of the cases, this was characterized by dystopia with a consequent secondary torticollis, in 12% by fixed exotropia (1/8), and in 26% of the cases by a disturbance of the gaze elevation. Only in one patient did we observe a pallor of the optic nerves (1/8 = 16%).

Neuro-visual abnormalities were found in 8/38 (21%) of the children with trigonocephaly. In 50% of the cases, this was characterized by dystopia, in 13% by fixed exotropia (1/8) and in 37% of them, we did observe pallor of the optic nerves.

There was a significant relationship between results of the ophthalmological evaluation, global IQ, and CT findings at diagnosis. A higher percentage of children with abnormal CT findings showed visuo-perceptual difficulties and had lower performances at neurocognitive evaluation ($r = 0.296$, $p < 0.001$; $r = 0.187$, p 0.05) (Table 1).

Postoperative evaluation

Neurocognitive evaluation

Postoperative evaluation was completed 6 months after surgery by 109 patients (T1) (mean age 14 months); 63 of them were affected by scaphocephaly, 31 by trigonocephaly, and 15 by anterior plagiocephaly.

At T1, 33% of the children with plagiocephaly (5/15), 25.80% of the children with trigonocephaly (8/31), and 17.46% of the patients with scaphocephaly (11/63) showed a

Table 1 The presence of ophthalmological defects at diagnosis (T0) was significantly related to CT abnormalities and GQ compromise in the whole series

			Eye exam T0	CT T0	GQT0
Spearman's rho	Eye exam T0	Correlation coefficient	1.000	0.296**	0.088
		Sig. (2-tailed)		0.000	0.284
		N	149	149	149

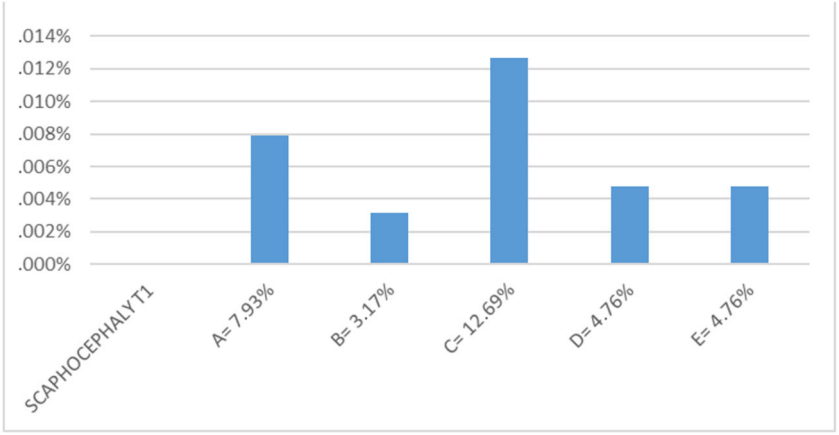

Fig. 5 Percentage of patients with scaphocephaly and cognitive impairment at T1, in selective performance scales. The most frequently compromised scale was the learning and hearing scale (C)

drop in one or more test. The most frequently compromised scale was the language scale (16 cases); children with scaphocephaly more commonly showed pathological results in the language evaluation if compared with the other groups (8/63, 12.6%) (Figs. 5 and 6).

At 1-year follow-up, 50 patients were available for a complete neurocognitive evaluation: seven of them were affected by anterior plagiocephaly, 17 by trigonocephaly, and 26 by scaphocephaly. Overall, 30% of these children (15/50 cases) showed a decrease of cognitive functions with a fall in one or more of the investigated scales.

For children with anterior plagiocephaly, performances in language abilities selectively resulted to be significantly under the average and this happened in 4/7 cases (57%) available at 1-year follow-up.

A similar neurocognitive profile was present in children with sagittal craniosynostosis, 6/26 children (23%) presenting below average scores in language tests.

A wider compromise in multiple scales was found in 5/17 children with trigonocephaly (29%).

A reasonable recovery in language functions was found comparing T0 and T2 scores in the overall population with compromise in neurocognitive abilities at diagnosis, all recovering for a mean of 30% of their initial performance.

When we compared the results of T1 and T2, the rate of the children with scores below average decreased from 52 to 30%.

In this specific subset of children with persistence of general IQ and selective ability compromise, scores did not change significantly ($r = 0.639$; $p > 0.05$). A significant correlation was found between pathological CT findings and persistence of below average scores at the 1-year follow-up ($r = 0.411$; $p < 0.01$).

On the contrary, below average scores at orthoptic and neuro-visual evaluation did not predict difficulties in the psychomotor development ($r = 0.258$).

Neuro-ophthalmological evaluation

A complete evaluation at T1 was available in 76 children (10 children affected by anterior plagiocephaly, 21 children affected by trigonocephaly, and 45 children affected by sagittal craniosynostosis) (Fig. 7). Overall, 21 of these children showed a persistence of visuo-perceptual findings (21/76 = 27%), 9/45 (20%) of the available children were operated on for a sagittal craniosynostosis, 6/21 (28.6%) of the children were operated on for a trigonocephaly, and 6/10 (60%) of the children underwent surgery for an anterior plagiocephaly; ocular torticollis was the main finding in this group (4/6 cases =

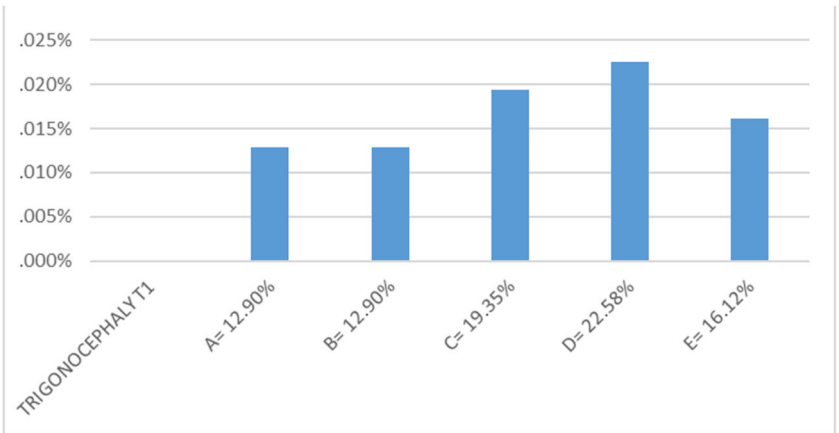

Fig. 6 Percentage of patients with trigonocephaly and cognitive impairment at T1, in selective performance scales. The most frequently compromised scale was the hand and eye coordination scale (D)

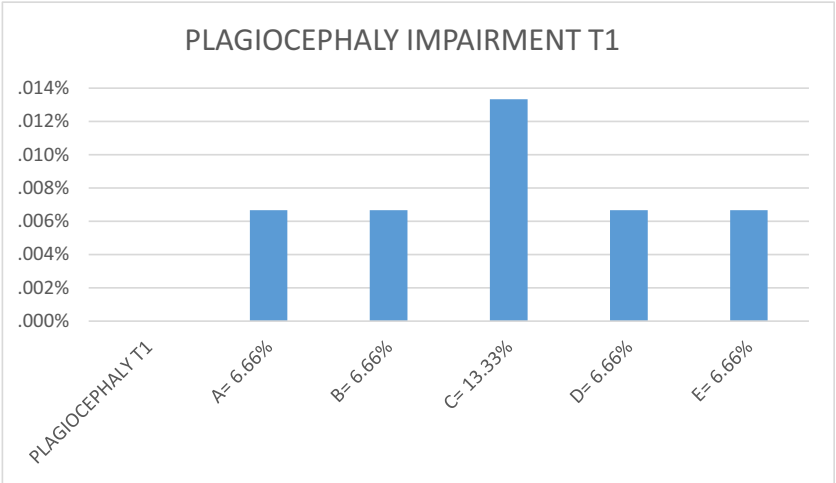

Fig. 7 The mean of patients with plagiocephaly at T1. The most compromised scale is learning and hearing scale (C)

66.6%); 2/6 children still show a gaze elevation deficit (2/6 = 33%).

Three of the nine patients with sagittal synostosis (3/9 = 33%) had a deficit of gaze elevation, one out of the nine (1/9 = 11%) showed an ocular torticollis, and three of nine showed the presence of an exotropia (3/9 children = 33%). Two of the three children of this last group also had the persistence of a pallor of the optic nerve (2/9 = 23%). Overall, we found a significant correlation between the presence of pathological ophthalmological findings at T1 and pathological results in the locomotor scale ($r = 0.265$*, p 0.05) (Table 2).

One of the six patients with trigonocephaly (1/6 = 16%) had a deficit of gaze elevation; 1 child (1/6 children = 16%) showed the presence of an exotropia. Two of the three children of this last group also had the persistence of a pallor of the optic nerve (4/6 = 68%).

Four of the six patients with plagiocephaly (4/6 = 68%) showed an ocular torticollis, one out of the six (1/6 = 16%) had a deficit of gaze elevation, and one of six showed the presence of an exotropia (1/6 children = 16%).

Overall, we found a significant reduction of the number of children with neuro-visual deficits 6 months after surgery. The overall percentage of these patients was lowered from 64% (71/111 children) to 27% (21/76 children). The presence of pathological results at the ophthalmological evaluations was significantly related to the presence of pathological results in the global Q evaluations (Table 3).

Discussion

The present study was selectively performed on a homogeneous series of monosutural non-syndromic craniosynostosis analyzing neurocognitive and neuro-visual functions before and 6 months after surgical treatment. An additional neurocognitive evaluation was performed at 1 year.

Overall, at the latest follow-up, cognitive retardation was present in 4% and global cognitive functions were borderline in 13% of the cases; 6% of the children showed autistic traits.

At diagnosis, the hand and eye coordination scale was the most commonly compromised scale in children with sagittal craniosynostosis, whereas the most compromised scales in patients with trigonocephaly were the learning and hearing scale (C) and the hand and eye coordination scale (D); similarly to children with sagittal craniosynostosis, children with anterior plagiocephaly had more frequent pathological results in the hand and eye coordination scale (D).

Table 2 Pathological results at the ophthalmological evaluation at T1 were significantly related to pathological results in the locomotor scale, in patients with scaphocephaly ($r = 0.265$*, p 0.05)

			Eye exam T1 scapho	Scale D T1 scapho
Spearman's rho	Eye exam T1 scapho	Correlation coefficient	1.000	0.295*
		Sig. (2-tailed)		0.019
	Scale D T1 Scapho	Correlation Coefficient	0.295*	1.000
		Sig. (2-tailed)	0.019	
		N		

*Correlation was significant at the 0.05 level (2-tailed)

Table 3 The presence of pathological results in the global *Q* evaluations of the whole series at T1 was significantly related with the presence of pathological results at the ophthalmological evaluations

			GQ T1	Eye exam T1
Spearman's rho	GQ T1	Correlation coefficient		0.142
		Sig. (2-tailed)		0.129

At 6 months, the most compromised scale in patients with scaphocephaly was the learning and hearing scale (C), whereas patients with trigonocephaly showed more frequent pathological values in the hand and eye coordination scale (D), and children with plagiocephaly more frequently had below average results in the learning and hearing scale (C) (Table 4).

Interestingly, patients who showed difficulties in ocular motility and vision showed greater difficulties in locomotor skills, a factor that confirms that visual perception skills of children improve as their gross motor skills improve. In this context, a dynamic system of self-organization has been previously described [7], where perception and action appear to be strictly related. Glencross and Piek [6] hypothesized that the distinction between sensorial processes and motor functioning might be an artificial dichotomy, constituting most probably a circular phenomenon (perception– action–perception) where structures operate parallel to each other, with interactions at increasing levels of complexity.

A further interesting result of our study was represented by the significant relation between neuroradiological alterations on CT at diagnosis and alterations in visuospatial skills and global developmental scales. This result actually confirms that even the once considered para-physiological findings of increased representation of pericerebral spaces represents in reality the visible sign of a chronic disturbance of brain function (most probably the sign of chronically increased intracranial pressure), conditioning the correct integration of the cerebral circuits involved in complex cognitive functions, visible at a selective evaluation of the same. Previous studies of brain morphology in cases of sagittal and unicoronal synostosis have demonstrated that changes in brain structure might be found not only in regions of the brain adjacent to the fused suture but also at distance and at the level of subcortical regions [1].

Early detection and selective rehabilitative treatment should represent a mainstay in the follow-up of these children. In the present experience, a selective neurorehabilitation program allowed to obtain a significant improvement of visuospatial and locomotor skills already at 1 year. Such a program is of utmost importance taking into account that surgery alone is not always enough to prevent long-term neurocognitive imbalance [4].

Language and learning scores which were more frequently compromised in children with scaphocephaly and trigonocephaly required a longer rehabilitation program which lead to a homogeneous improvement only visible at 6–7 years of age (T3).

Some clues persist and relate to children who did not show the expected improvement in spite of a dedicated neurorehabilitation program.

Aldridge et al. documented in this context that, in spite of the surgical correction of the skull shape in children with craniosynostoses, the brain might follow a growth pattern similar to that observed in patients untreated for their disease indicating the possibility, in this specific subset of children, of an at least partially independent growth pathway of the skull and the brain [2].

Conclusion

Our paper, to the best of our knowledge, is the first one addressing specifically each one of the specific scales of neurocognitive development as well as neuro-ophthalmological and neuro-visual findings in single-suture craniosynostosis. Furthermore, it shows a link between CT scan anomalies, namely the widening of the pericerebral space, with cognitive and ocular alterations, underlining the importance of multidisciplinary evaluation and treatment for single-suture craniosynostosis. Such a relationship is also maintained in spite of the surgical treatment in children who

Table 4 Correlation

			Eye exam T1 scapho	Scale D T1 scapho
Spearman's rho	Eye exam T1 scapho	Correlation coefficient	1.000	0.295*
		Sig. (2-tailed)		0.019
	Scale D T1 scapho	Correlation coefficient	0.295*	1.000
		Sig. (2-tailed)	0.019	.
		N		

*Correlation was significant at the 0.05 level (2-tailed)

show the persistence of ophthalmological and neurocognitive deficits during the follow-up. Further studies are warranted in order to understand even more such a complex pathology.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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