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Relationship between ocular and computed tomography findings in patients with spina bifida

Onur Temizsoylu[1], Alev Koçkar[2], İbrahim Alataş[3], Hüseyin Canaz[3], Elvan Alper Şengül[2], Erdal Yüzbaşıoğlu[2]

[1]*Department of Ophthalmology, Erzurum Region Training and Research Hospital, Erzurum, Turkey*
[2]*Department of Ophthalmology, İstanbul Bilim University, İstanbul, Turkey*
[3]*Department of Neurosurgery, İstanbul Bilim University, İstanbul, Turkey*

ABSTRACT

Objectives: Spina bifida is one of the most common congenital diseases in Turkey and around the world. Despite the developing diagnostic and therapeutic methods, abnormal ocular characteristicsin spina bifida patients are still quite common. We investigated the ocular characteristics of spina bifida patients with and without hydrocephalus.

Methods: We included 37 patients who were previously referred to the Istanbul Bilim University, Department of Ophthalmology and already had computed tomography (CT) scans. We retrospectively investigated the patients' ophthalmologic findings (refractive errors, strabismus, and optic disc characteristics) and used their recent CT images to measure the Evans ratios (ERs), which indirectly reflect the grade of hydrocephalus. The patients were divided into three groups according to their ERs (ER ≤ 0.3, 0.3-0.5, and ≥ 0.5), and then the ocular characteristics of these groups were compared. In addition, the patients were divided into three groups according to their ages (≤ 1 year, 1-3 years, and ≥ 3 years), and the ERs and rates of refraction defects in these groups were compared.

Results: There was no relationship between specific ocular characteristics and ER or between age and ER. However, refraction errors were observed more frequently as patient age increased.

Conclusions: The degree of hydrocephalus does not affect the ocular characteristics of patients with spina bifida, but emmetropization may be deteriorated in these patients.

Keywords: Spina bifida, ocular findings, computed tomography, emmetropization

Spina bifida is a congenital malformation caused by the embryonic development of a neural tube closure defect, manifesting itself in the form of a split spinal column. It also refers to a neurogenetic disease with a complex aetiology influenced by both genetic and environmental factors [1]. Spina bifida is one of the most common congenital diseases in Turkey and across the world, incidences are 1.04% and 0.31%, respectively [2, 3]. It presents many neurological, urological, and orthopaedic complications, among which ocular manifestations are some of the most common. Patients with spina bifida are at high risk for hydrocephalus and hindbrain herniation, which are characteristic of the Chiari II malformation [4].

Ocular complications induced by hydrocephalus that are frequently seen in patients with spina bifida

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Address for correspondence: *Onur Temizsoylu, MD., Erzurum Region Training and Research Hospital, Department of Ophthalmology, Erzurum, Turkey*
E-mail: onurtemizsoylu@hotmail.com

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include amblyopia, strabismus, anisometropia, optic atrophy, cortical blindness, and nystagmus [5,6]. According to previous studies, optic atrophy is seen in patients with spina bifida at varying rates [7-10]. Several researchers have investigated refractive errors among patients with optic atrophy, hydrocephalus, and spina bifida, independently. However, the existing literature lacks a dedicated comparison of ocular findings against the severity of hydrocephalus, which constitutes the subject matter of the present study.

It has previously been shown that that spina bifida defect closure surgeries performed within 48 hours of birth ensured a decrease in neurological complications, such as muscle paralysis. Based on these determinations, we first measured the extent of hydrocephalus using the Evans ratio (ER) [11, 12]. We predicted that ocular complications might be less common in patients who underwent early surgery and that they would, therefore, experience less ventricular enlargement. To that end, we aimed to compare ocular complications among participating patients, who were grouped according to their ER scores.

METHODS

This study examined 37 patients with spina bifida aged between 0 and 13 years, including 20 males and 17 females, who applied to our outpatient clinic between February 2015 and August 2016. The mean age of the study patients was three years-two months. This research adhered to the tenets set forth in the Declaration of Helsinki and the approval of the local ethics committee was also obtained. Ophthalmologic examinations were analyzed retrospectively, based on their examination files. All ophthalmologic examinations were performed by the same examiner (OT). Visual acuity examinations were excluded, due to the young ages of patients, as well as a lack of patient cooperation. Patients over 13 years old and those who demonstrated isolated ocular pathology (such as congenital glaucoma, congenital cataracts, etc.) were also excluded from the study.

First, all patients were subjected to refraction measurements by a 2 win hand-held auto refractometer (Adaptica, Padua, Italy) following the application of 1% cyclopentolate eye drops every 15 minutes, i.e. three applications spanning 45 minutes in total. As suggested by the manufacturer, measurements were recorded only when the reliability index was over 5 (maximum 9). Measurement precision was set as 0.25 diopter for power and 5 degrees for the axis. In the case of patients who did not allow for measurement due to cooperation issues, refraction was assessed by manual retinoscopy. In order to rule out normal-ranged refractive errors, which are seen in the first years of life in most patients, cycloplegic refraction measurements for the patients aged 3 years and below were adjusted in accordance with the relevant table in Guidelines for Refractive Correction in Infants and Young Children, published by the American Academy of Ophthalmology in 2012. Patients with eyes that needed refractive correction were considered to have the refractive disorder. In contrast, a refractive defect was not noted down for that did not require refractive correction [13]. For children over three years of age, we followed the methodology adopted by previous studies (Biglan [5], Caines *et al*. [9]). In other words, refractive error was defined as: hypermetropia ≥ 3D, myopia ≥ 1D, and astigmatism ≥ 1D (Fig. 1).

Following refraction measurements, strabismus examinations were conducted. To begin, a Hirschberg test was performed by shining a light in the subject's corneas from fifty centimetres away, at eye level. Any reflex landing on the temporal of the cornea was recorded as esotropia, and any reflex landing on the nasal of the cornea was recorded as exotropia. Then the cover-uncover and alternate cover tests were performed on the patients. During these strabismus examinations, the presence or absence of fixation and nystagmus was also noted. For patients in whom cyclopentolate did not ensure a sufficient level of dilatation, an additional 0.05% tropicamide eye drop was applied, and dilatation was achieved.

Eyelid, conjunctiva, anterior-posterior chamber, and fundus examinations were then conducted using a biomicroscope in the patients who cooperated, whereas those same examinations were completed using a binocular indirect ophthalmoscope (Welch-Allyn, Model: WA 12500) in the patients aged below 3, as well as those who did not cooperate. In the fundus examinations, 90D lenses were employed for the biomicroscope, while 20D lenses were used for thebinocular indirect ophthalmoscope.

Based on the results of our patients' latest follow-

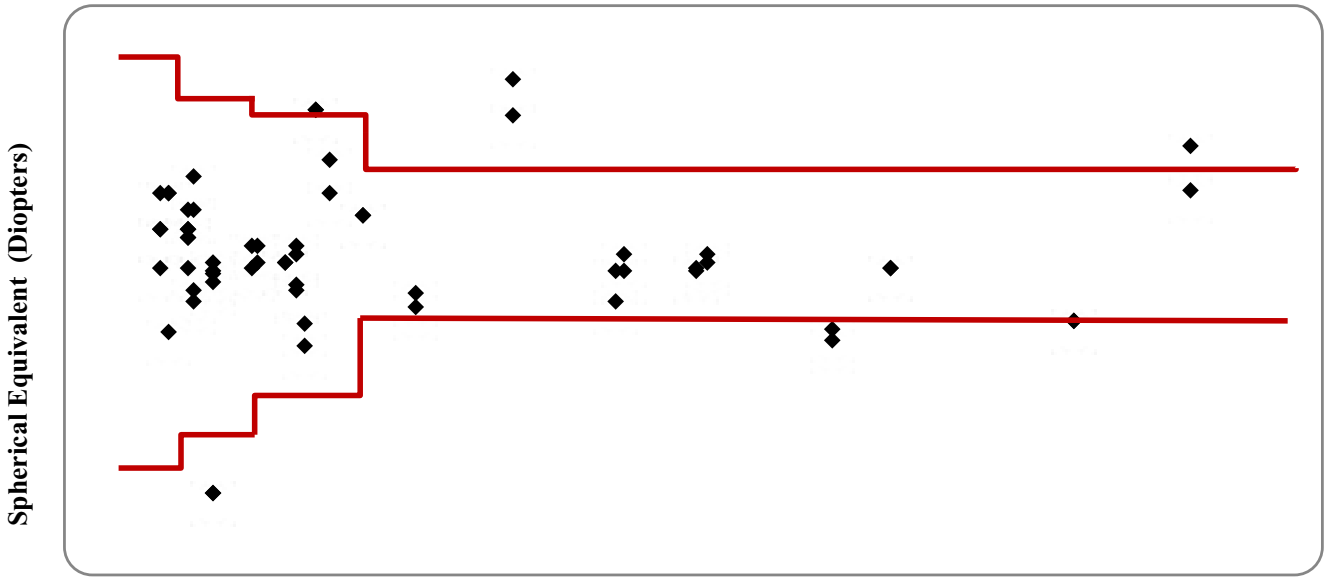

Fig. 1. Spherical equivalent values of patients' eyes refraction measurements. The red line shows the cut-off values which we used for refraction defect. This figure does not include astigmatic refractive errors.

up computed tomography (CT) scans, anterior-posterior optic canal diameters and ERs were calculated. The Somatom Sensation 16 (Siemens, Forchheim, Germany) CT scanner was used to scan all patients. Radiological values used for that purpose were as follows: kilovolt (peak): 100 kV; milliampere-second: 150 mas; section thickness: 0.67 mm; interslice distance: 0.4 mm. In order to determine ERs, a review was held of CT scans after they were retrospectively assessed by a neurosurgery consultant. In the axial plane, the distance between the external walls of both lateral ventricles was measured where anterior horns were found to be the largest in size. Next, that distance was divided by the distance between internal tabula of the cranium, to obtain the ER. An ER $\geq$ 0.3 was considered to indicate the existence of hydrocephalus. The patients were then divided into three groups, based on their ERs: < 0.3, 0.3-0.5, and > 0.5.

Statistical Analysis

In accordance with the purposes of this study, the links between categorical variables were investigated using a Chi-square test (nonparametric test). Cohen's d values were calculated to determine effect size in an independent sample t-test: d values measuring 0-02 indicated a minimal effect, those close to 0.5 represented a moderate effect, and those $\geq$ 0.8 demonstrated a significant effect.

RESULTS

No refraction measurement could be performed on six patients, out of 37 in total, due to a lack of cooperation. According to measurements taken from the 61 eyes of the remaining 31 patients, a refractive defect was found in 19 (31%). Furthermore, 6 (31%) of these eyes featured hypermetropia, 2 (10%) from myopia, 11 (57%) from isolated astigmatism, and 3 (15%) from hypermetropia + astigmatism.

In addition to refraction measurements, CT scans for the 37 patients included in the study were reviewed with the purpose of calculating ERs. However, an ER could not be calculated for one patient, due to an arachnoid cyst. When the remaining 36 patients were divided into groups by calculated ERs, the following results were obtained: ER $\leq$ 0.3 in 8 patients, ER < 0.5 in 20 patients, and ER $\geq$ 0.5 in 8 patients. Upon comparing 59 eyes from 30 patients for whom both refraction measurements and ER calculations were practicable, no statistically significant relationship was found (χ^2=.71, p > 0.05).

Furthermore, all patients included in the study were subjected to fundus examinations, and all patients demonstrated a normal appearance of the retina. Among these findings, only optic disc findings were used for fundus examination. Among the patients, 5 (13%) were found to have bilateral optic atrophy, 1 (2%) to have optic discs with obscure boundaries, and 1 (2%) to show signs of optic disc oedema. For statistical analysis purposes, all patients demonstrating any optic disc symptoms, which are mentioned above, were placed in the "positive optic disc symptom" group. No statistically significant correlation was found between the ER and the presence of optic disc symptoms (χ^2= 3.60, $p > 0.05$). However, a significant relationship was detected between the presence of optic disc symptoms and the presence of refractive error (χ^2= 5.85, $p < 0.05$). This result indicates that patients with optic disc symptoms tended to experience refractive defects less frequently.

For the next series of comparisons, patients were broken into a group according to age: 10 (27%) patients were aged one year or below, 16 (43%) patients were aged between 1 and 3 years, and 11 (29%) patients were above the age of 3 years. As noted previously, the mean age of all subjects was calculated as three years and two months. When examining the distribution of ERs by age groups, it was found that they were distributed normally ($p > 0.05$). To compare ERs by age groups, a one-way analysis of variance (ANOVA) was performed According to the results of this analysis, ERs did not to vary with age groups ($p > 0.05$). In fact, the ERs of patients in different age groups were quite close to one another (Table 1).

Additionally, refractive defect and age were found to be statistically significantly correlated (χ^2=13.25, $p < 0.05$) (Table 2). Specifically, as a patient gets older, the refractive defect is more likely to emerge. Meanwhile, a correlation analysis of spherical equivalents of refraction values of the patients revealed a considerably weak correlation among those values (r = 0.01). This indicates that spherical equivalents of refractions tend to remain unchanged by age.

Lastly, 19 (51%) patients were found to have strabismus. Of these, 16 (84%) cases were esotropia, 2 (10%) were exophoria, and 1 (5%) was esophoria. An examination of the relationship between ERs and strabismus revealed no statistically significant connection (χ2=320, $p > 0.05$) (Table 3).

Table 1. The relationship between Evans ratio and refraction defect

	Refraction Defect		Total	χ^2	*p* value
	Negative	Positive			
Evans Ratio					
≤ 0.30	7	5	12	0.71	0.70
0.31-0.49	25	10	35		
≥ 0.50	8	4	12		
Total	40	19	59		

Table 2. The relationship between refraction defect and age groups

	Refraction Defect		Total	χ^2	*p* value
	Negative	Positive			
Age group					
≤12 months	16	1	17	13.25	**< 0.01**
12-36 months	18	6	24		
≥36 months	8	12	20		
Total	42	19	61		

Table 3. The relationship between strabismus and Evans Ratio groups

	Strabismus		Total	χ^2	*p* value
	Negative	Positive			
Evans Ratio					
≤ 0.30	3	5	8	3.20	0.20
0.31-0.49	12	8	20		
≥ 0.50	2	6	8		
Toplam	17	19	36		

DISCUSSION

Despite technological advances in radiologic imaging systems, the ER, developed in 1942 by William Evans, remains a significant indicator in clinical settings to determine ventricular expansion [14-18]. In their study on patients with meningomyelocele, Stein *et al*. found the prevalence of hydrocephalus to be 80%, which is in keeping with the present study, as we calculated the rate as 77.7% [19].

The existing literature contains many studies on ocular manifestations in patients with hydrocephalus; however, ocular manifestations in spina bifida patients with hydrocephalus have attracted the attention of very few researchers. Refractiveerrors in newborns generally display normal distribution with a wider range, which is also referred to as Gaussian distribution [20]. Since the emmetropization process occurs over the course of years, the average spherical equivalent of this distribution decreases with reduced standard deviation (SD); as such, the distribution tends to be concentrated in a specific interval.

As the present study did not involve a control group consisting of subjects without spina bifida, we were not able to compare the refractive defects of our patients to a normal population. However, other researchers have included such populations in their investigations. For instance, in their study on Swedish children, Caines *et al*. [9] found that 81% of patients with meningomyelocele demonstrated significant refractive error, which is 10.3 times greater than the prevalence of refractive error among normal Swedish children. In a different study on 3,568 primary school children in Turkey, Toygar *et al*. [21] calculated a refraction error prevalence of 10.7%. Based on cycloplegic refraction scores for our subjects, 32.2% of them were found to have refractive error. Although, according to the present study, the prevalence of refractive error among those with spina bifida is 3 times greater, we are of the opinion that extended series are required considering the size of sample and patient age covered by this study. In comparison, Lennerstrand and Gallo [22] found the rate of refractive error to be 54%. We suggest that the difference between this study and ours was caused by the narrow age range and criteria that we adopted for refractive error. The present study could establish no statistically significant difference between the prevalence of refractive error across the patient groups with spina bifida, i.e. those without hydrocephalus, with moderate hydrocephalus (ER: 0.3-0.5), and with severe hydrocephalus (ER ≥ 0.5).

The fact that correlation analysis of spherical equivalents of refraction values against patient age revealed no correlation between age and refractive disorder is indicative of the failed emmetropization process in this group of patients. Similarly, a comparison among age groups, i.e. 0-1, 1-3, and > 3, revealed a statistically significant increase in refractive errors by age, which is also indicative of failed emmetropization. The emmetropization process is affected by many factors, notably genetic and environmental. One of these factors is poor accommodation. For example, Schaeffel *et al*. [23] showed that pupillary response was greater in chicks with damaged accommodation due to defocused lenses.

No study has been conducted thus far to evaluate the emmetropization process in patients with spina

bifida. However, various studies have found the prevalence of refractive error to be as high as 76% in patients with cerebral palsy involving cerebral damage [24]. For instance, McCelland *et al*. [25] showed that these patients suffered from both a higher prevalence of refractive error and a lower accommodation response, as compared to those without cerebral disease. A refractive correction with the help of added plus bifocal lenses at near was shown to be helpful for near reflex [26, 27]. This also highlights the importance of accommodation in emmetropization, because in patients with Down's syndrome, impaired accommodation gave rise to emmetropization failure, even in the absence of any cerebral damage [28, 29].

Additional studies are required to assess accommodation in patients with spina bifida, investigating both the cause of emmetropization disorder and the necessity of employing added plus bifocal lenses for treatment purposes. It is hypothesized that, in addition to impaired accommodation, the transmission of visual signals to the brain would affect emmetropization. Troilo and Wallman [30] showed that chick eyes were made functionally myopic and hypermetropic with lenses adjusted their axial extension, re-approaching emmetropia once lens administration ceased. The same emmetropization process was observed in eyes after the optic nerve was cut [30]. In the present study, patients whose fundus examination revealed atrophy in the optic disc, obscure boundaries, or papilledema did not demonstrate a higher prevalence of refractive error than those in the other patient group; in fact, it was found to be significantly lower. In the same study by Troilo and Wallman [30], refractive error in eyes with cut optic nerves became more prevalent in a reversed manner in the subsequent period. This finding indicates that the emmetropization process involves a feedback mechanism [30]. From this point of view, a prospective investigation on our study group may shed light on the emmetropization process in patients with optic disc symptoms.

In the present study, 51% of patients with spina bifida were found to have strabismus. For context, in a study on 298 patients with spina bifida in 1990, Biglan [5] estimated a strabismus prevalence of 61%. Other studies suggested 42-52% prevalence rates among spina bifida patients [6, 9]. The findings revealed by the current work are in harmony with those of previous studies. For instance, studies on healthy Turkish children indicate that the prevalence of strabismus ranges between 3% and 6.5% [31-33]. It can therefore be argued that strabismus among those with spina bifida has become 7 to 17 times more prevalent in Turkish society. However, no statistically significant relationship could be established between ER and strabismus prevalence. In short, these results show that strabismus is common among patients with spina bifida; however, the prevalence of strabismus remains unchanged concerning the presence of hydrocephalus or its severity.

Finally, in Gaston's 1991 study [6], the prevalence of optic atrophy was found to be 17%. In comparison, the present study found five subjects (13%) with optic atrophy, although no statistically significant relationship was detected between ER and optic disc manifestation. Despite ever-advancing medical technology, this prevalence remains high. Therefore, the present authors suggest that early diagnosis and treatment should more actively be pursued in patients with spina bifida. Limitations of this study include an insufficient number of subjects across groups, as well as a lack of differentiation when interpreting CT results, especially in terms of whether the ER calculations were obtained pre- or post-V-P shunting. In the present study, we sought to investigate the genesis of ocular manifestations in patients with spina bifida in an effort to pave the way for future applications aimed at patients' ocular rehabilitation.

CONCLUSION

According to the results of our study, patients with spina bifida were found to have a higher prevalence of ocular manifestations as compared to the normal population, in keeping with previous studies. However, we found that the severity of hydrocephalus had no impact on the prevalence of ocular manifestations. Furthermore, a comparison among different age groups of patients revealed a higher prevalence of the refractive disorder in older age groups, which might be suggestive of the failed emmetropization process in this group of patients.

Authorship declaration

All authors listed meet the authorship criteria

according to the latest guidelines of the Internaional Committe of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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