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Research Article

Study of Visual Pathway in Strabismic Children through Tractography

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Abstract

Purpose: To identify the morphometric characteristics of the posterior portion of the visual pathway, and estimate the differences between children with essential strabismus and healthy children using Tractography and Voxel-based Morphometry (VBM).

Methods: A prospective, cross-sectional and observational Case-Control study was carried out, in which the morphology of the posterior portion of the visual pathway of 22 patients was analyzed. VBM analysis was performed and the morphology of the Visual tracts was assessed using Tractography. The findings were correlated with the clinical status of patients.

Results: 22 cases were obtained, 11 from the control group and 11 from the case group. The Tractography showed a decrease in interhemispheric, occipito-temporal and occipital axonal connectivity in the group of cases compared to healthy patients. A decrease in the thickness of the *splenium* was evidenced in patients with strabismus. The Tractography VBM showed an average Voxel density of 0.052366 in the control group against 0.045438 of the case group. This shows a 13.23% decrease in Voxel density in comparison to the control group. The standard deviation for the control group was 0.069111 against 0.083697 for the case group.

Conclusions: The study found significant macro and microstructural morphometric alterations in patients with congenital strabismus. A lack of development in the splenium and a decrease in granulometric elements that make up the primary visual pathway, were identified in the case group. Findings suggest that a primary structural alteration could be linked to the origin of congenital strabismus.

Keywords: *Congenital strabismus; Morphometry Based on Voxel (VBM); Splenium; Tractography; Visual pathway; White matter*

Introduction

From the theories of Worth and Chavasse regarding the origin of strabismus, has emerged the question if there is firstly a functional problem or if the primary damage is anatomical. This present research shows that there is a significant anatomical alteration in the visual pathway of children with essential strabismus, which can be demonstrated through the combined study of Tractography, and Voxel analysis in congenital strabismus.

The essential or congenital strabismus refers to early onset pathological ocular deviations, of unknown origin, which are believed to be caused by deficiencies during development [1-3]. This problem affects millions of people and represents the strongest perturbation of the binocular system in humans. It is followed by neurological, cosmetic, psychological, social and epidemiological implications [4,5].

Congenital strabismus is present in 1.3-5.7% of world population [6-8]. Thanks to an improvement in obstetric care, the incidence of this disease changed during the last few years, although the prevalence has not been reduced [9,10]. Even when said improvement in care has positively contributed to decreasing the risk of trauma, asphyxia, and hypoxia, better obstetric care has contributed in increasing the number of premature children that manage to survive. It is estimated that 15% of these children present strabismus before the age of one.

Several factors related to the origin of this disease have been mentioned [2, 11,12]. Genetic predisposition, especially when there is a family history background of the disease [2,13-15]. Or any damage deriving from nutritional, metabolic and perinatal disorders, prematurity, encephalopathy, ventricular hemorrhage, brain abnormalities, neonatal seizures hyperbilirubinemia, neuroinfection, neurodevelopmental disorders, neuronal immaturity and refractive errors are included [16-22].

While the origin of the disease is controversial, the semiology of strabismus allows us to obtain precise measurements through sensory and motor tests that can be easily applied and reproduced. Among the clinical parameters that can be determined one can find are visual acuity, refractive status, the study of versions, muscle hyper and hypo functions, eye deviations, the degree of fusion, and binocular cooperation [23,24].

Even when very important progress has been made in the neuro functional study of strabismus, little has been studied regarding the macro structural alterations and fine morphometric changes of the visual pathway *in vivo* associated with this disease, particularly in children [25-27].

One way to understand the anatomy of the visual pathway is through Tractography [28]. This technique permits the identification of the three-dimensional diffusion of water between the nerve fascicles of white matter (WM) using algebraic tensioners, because water molecules tend to be spherical in their free state, that is, they are isotropic; but they take spheroidal shape when interacting with rigid structures such as WM, and therefore they are anisotropic [29-32].

The anisotropy of water molecules can be measured and computed in order to construct a map of the direction of the axons in the path of a given neuronal tract, as occurs with the visual pathway [33-35]. However, it is different to know the macro structural anatomy of the visual pathway using Tractography, to determining how each segment is constituted in detail through VBM [36-38].

To discern the components of any region of interest of the brain by MRI in children with strabismus, we have used the granulometry or VBM technique [25,36,37].

Through the granulometric technique, the Pixel (picture elements) and Voxel (volume elements) of each image can be calculated by mathematical transformations and openings that determine the values of the volume and density of mentioned elements [37]. The values obtained can be plotted for a better understanding.

Methods

A prospective, cross-sectional and observational case-control study was performed in which tractographies of the visual pathway and the images of 22 children from 7 to 10 years old were analyzed using VBM. All patients agreed to participate in the study with prior informed consent and endorsed by the bioethics committee of the Faculty of Medicine of the Autonomous University of Queretaro.

11 patients with essential strabismus formed the case group and 11 healthy children formed the control group. All patients with strabismus underwent a full examination, and were later classified in accordance with The Committee for the Classification of Eye Movement Abnormalities and Strabismus (CEMAS).

Inclusion criteria did not allow the presence of amblyopia or any significant refractive errors, anisometropia, neurological problems, or any other condition other than strabismus.

All patients underwent a study of Tractography through MRI and anisotropy was measured to identify the nerve paths of the visual pathway. The single skull images of MRI were obtained using a Signa HD 1.5T GE MRI with Coil Head NV/Neck_A, 8 channel- equipment, under the following sequence for Tractography: spin echo/EPI, DTI 25 b-value 1000 s/mm 2, repetition time of 9000m 127.7m echo time, field of view (fOV) 24 x 24 cm; sequential axial parallel slices, thickness of the cut (slice thickness) 3mm with no space between slices (0.0 interval), with square matrix of 128, made in 1 (one) single NEX.

The images of the posterior portion of the visual pathway were analyzed and ranked based on the thickness, and the ramifications and distribution of the nerve weft of the interhemispheric portion (splenium), the occipito-temporal and occipital portion. Each segment was assigned with a qualitative value of normality vs. abnormality based on an anatomical pattern [29,39]. Under this criterion all tractographic images of the sample were rated and compared.

Subsequently, the tractographic images obtained by MRI were processed and subjected to VBM or granulometric analysis, using the following technique: the visual pathway was distinguished from brain slices by changing the saturation toward red and applying a threshold. Once the visual pathway was separated, a mask was obtained regarding the original image in order to regain the exact intensities and convert them to a scale of gray. A granulometry was applied to this image [40]. Obtaining a chart depicting the volume density of internal structures that compose the visual pathway.

Thanks to this technique it is possible to determine both, the granulometric density and volume of the visual pathway in each individual. In the end, the results obtained by the control and case groups were statistically compared.

Results

22 studies were obtained, 11 of the control group and 11 of the case group. The control group consisted of 7 girls and 4 boys with an average age of 8.3 years and the case group consisted of 8 girls and 3 boys with an average age of 8.1 years.

The VBM analysis showed significant differences between groups. The case group had a 13% lower granulometric density than the control group (Table 1, Figure 1).

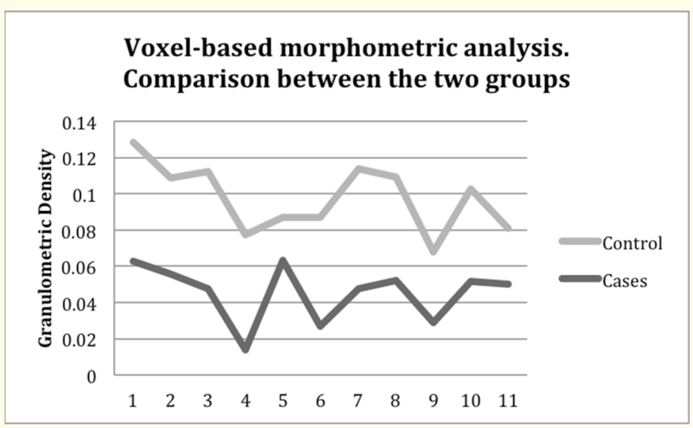

Figure 1

Morphometric analysis based on Voxel (VBM) identified a decrease in the granulometric density of the posterior visual pathway in all children with congenital strabismus compared to the control group. An increased granulometric density was always present in the right hemisphere compared to the left across the analyzed sample, both in the case and the control group.

Tractography allowed identifying the components of the posterior portion of the visual pathway, that is, the dorsal portion of the optic chiasm, wherein a decrease of *splenium* in strabismus patients is observed. The three segments of the posterior portion of the visual pathway that were analyzed using Tractography showed normality in all control group subjects, whereas in the case group, abnormality was found in 8 patients, who evidenced a lower thickness and lower amount of branching in the interhemispheric and/or interhemispheric paths than healthy subjects (Figure 2).

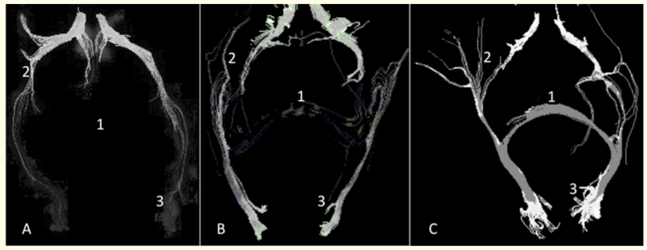

Figure 2

A decrease in interhemispheric axonal connectivity or *splenium* (1) occipito-temporal (2) and occipital (3) was found in the group of strabismic patients (A and B), compared to healthy patients (C).

The VBM of Tractography showed an average granulometric density of 0.052366 in the control group, against just 0.045438 in the case group (Table 2). This means that the group of patients with strabismus had a density of 13% lower than healthy subjects (Table 1).

Voxel-Based Morphometry Density in Each Hemisphere		
Control Group	**Case Group**	**Percentage Difference**
Left Hemisphere 0.051105	Left Hemisphere 0.044600	13%
Right Hemisphere 0.053628	Right Hemisphere 0.046276	14%
Average = 0.0523665	Average = 0.045438	13%
N = 11	N = 11	N = 22

***Table 1:** The average of Voxel-based Morphometry (VBM) density of right cerebral hemispheres was always greater with respect to the left side in all patients analyzed. The average VBM density in children with strabismus was 13% lower than in healthy children.*

Granulometries of the two groups were compared statistically. The analysis of variance showed 0.004776 for the control group and 0.007005 and for the case group and Student's t was significantly less than t0 (t < t0), being α = 0.005. (Table 2)

Analysis of Comparison of Granulometric Measurements	
Control	**Cases**
N = 11	N = 11
Average 0.052366	Average 0.045438
Variance 0.004776	Variance 0.007005
Standard deviation 0.069111	Standard deviation 0.083697
Student of reference: t0 = 0.946757 Degree of confidence, α = 0.90 Calculated Student of data: t = 0.125734 Degree of confidence, 1-α/2 = 0.05 Degrees of freedom = 438 Conclusion: Reject Null hypothesis, H0: the means are not equal	

***Table 2:** The table shows the differences that exist between the Voxel-based Morphometry density of group of cases (0.045438) compared with the group of healthy children (0.052366).*

Discussion

Although many factors have been associated with congenital strabismus, its origin is unknown. Until now, the uncertainty whether the origin of strabismus was a primary structural damage, or the disease was due to a functional impairment has prevailed [41].

Even when there have been studies focused on the cerebral cortex and its white matter related to strabismus, these have been performed *in vitro* and experimented in animals. Neuroimaging studies in children exist, but basically focused on understanding the neurosensory disturbances of the disease; what hasn't been done is an *in vivo* study in a homogeneous group of children with congenital strabismus and compared to healthy children, with the purpose to assess the visual pathway.

The reason why children between 7 and 10 years old were selected is that the final development of the visual system takes place at this age, so it is expected that each child has a complete development and maturation of each one of the structures and functions of the visual system. The present study demonstrates that the underlying origin of the disease is a primary structural damage, which affects the WM that forms the tracts of the visual pathway.

These findings are consistent with earlier studies regarding WM changes in the cerebral cortex where the granulometric technique has been used for studying congenital strabismus [25,36]. But it is the first time that this combined methodology is used, by means of which, it has been made clear an accurate structural damage in the later portions of the visual pathway in children with strabismus.

This is very relevant, since from these findings it can be inferred that the structural damage to the visual pathway may be due to an early injury. This damage may be pre-established genetically as lability mode in the WM, that is, due to a genetic damage; or perhaps the damage can be triggered by a lesional acquired damage, which may be due to hypoxia or asphyxia.

In any case, even the disease is triggered by a genetic or lesional damage; such damage should be of a sufficient magnitude so as to alter the quality and/or quantity of the WM of the visual pathway in early stages of development. If so, the damage of WM would determine the early ocular deviation that characterizes congenital strabismus, the dilemma now is to know from which point, the decrease in the granulometric density would encourage disease. This study may contribute to prevent strabismus in susceptible families, who should take additional steps and double perinatal care.

In this study, the macro-structural Tractographic analysis and Voxel micro-structural analysis were combined to examine the posterior portion of the visual pathway from the posterior portion of the optic chiasm to the striate cortex, and to correlate these findings with the clinical status of the patients.

The study showed evidence of structural damage that occurs in the visual pathway of patients with strabismus. The morphometric changes of the sample could be identified and measured accurately, regardless of what caused the injury to the WM.

From a macro-structural point of view, in patients with strabismus, the most significant finding is the insufficient structuring of the *splenium*, which is a very important way of interhemispheric visual communication [29,39]. (Figure 2)

However, the problem of interhemispheric interconnection is not the only problem that children with strabismus presented. It was found that where there is a poor interconnection of occipito-temporal pathway, a significant decrease of the branches and of the thickness of the posterior portions of the visual pathway was also observed, all of which may explain why most of these patients are unable to have stereopsis, or, present deficits in other visual-perception skills (Figure 2).

To summarize, the study reveals that there is a significant connectivity problem associated to the first and second visual pathways in children with congenital strabismus. This is important to note because these findings haven't been previously described and we believe that this study may shed light for a better understanding of the origin of congenital strabismus, which affects millions of people worldwide.

Moreover, the micro-structural analysis through VBM of three-dimensional images revealed that a lower rate of granulometric density is statistically correlated with strabismus, suggesting the existence of a lower neuronal connectivity in the posterior visual pathway.

Harmonizing a disease like strabismus that can be objectively and clinically measured, through neuroimaging studies with high spatial resolution such as tractography and combined Voxel analysis, allows us to probe the exact nature of strabismus, to identify and describe the structure of nerve conduction pathways involved in the disease. This can be used not only to learn about the origin, prognosis and the best therapeutic possible, but to better understand how a damaged 'in parallel' network of neuro-information works and how the brain, which is the central integrator, compensates for this anomaly.

Conclusions

Finally, we believe that based on these findings it is plausible to claim that in the origin of strabismus there is a primary anatomic abnormality background. This study clarifies that the anatomy of the visual tract in children with strabismus is different from that of healthy children with solid anatomical evidence.

The former opens the possibility to apply this knowledge to other neurological diseases and its possible application in artificial communication systems working in parallel.

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