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Research Article

Neurological Implication in Congenital Strabismus

Martín Gallegos-Duarte*[1], Danjela Ibrahimi[1], Jorge Domingo Mendiola-Santibañez[2]

[1]Licenciatura en Optometría, Facultad de Medicina. Universidad Autónoma de Querétaro, México

[2] Facultad de Ingeniería. Universidad Autónoma de Querétaro, México

Abstract

Congenital strabismus is an essentially neurological condition with ophthalmologic, psychological, and social repercussions. In spite of the former its true dimension has not been assayed. This disease affects 3% of the population worldwide and represents the most relevant binocular perturbation in humans. Notwithstanding its importance, the origin of congenital strabismus and its neurological implications have not been completely established. By means of neuroimage studies both functional and morphometric we have found substantial differences in the brains of individuals with strabismus when compared to the asymptomatic population. From a morphometric point of view, we have encountered that in the cerebral cortex of strabismic patients there is a decrease in small-size granulometric elements in the images of the white matter of this cerebral region obtained by the granulometry technique. Studies using RMI spectroscopy indicate that patients with strabismus show a diminution in neuronal volume, as well as signs of neuronal suffering. On the other hand, from a functional perspective, we have discovered important inter-Temporal hipo-coherence when using the Neurometric methodology. Two thirds of the digitized brain mappings obtained from more than 190 patients show cortical dysfunctions such as slowing down of brain waves, paroxysms and eventually some signs of epilepsy, especially in patients presenting "dissociated" ocular movements related to strabismus. SPECT studies have shown metabolic changes associated with strabismus. The outcomes of all these studies indicate that strabismus is not merely a cosmetic issue, rather it is a clinical manifestation of a deeper nature: A cortical problem.

Keywords: *congenital strabismus, cortical alterations, diagnostic methods, origin of strabismus, white matter*

Introduction

Until relatively recently, Congenital Strabismus (CS) was considered to be a disease of unknown origin whose medical implications focused on its cosmetic aspect, on trying to solve the refractive problem and the amblyopia, but the fact that CS is essentially a neurological problem, was left aside.

The little persistence to search in depth on its neurological implications is in part due to the changes on cortical pathways presented in CS, unnoticed in the conventional studies of neuroimaging, so, without knowing its origin, nor the neurological substrate that sets the physio-pathological bases of the disease, the CS was maintained in the list of the congenital diseases, essential or primary [1].

The CS has been considered as "a problem of development", in the best of cases, when it is not only a problem of "immaturity", but from neuroimaging studies, it is now known that there is a cortical connectivity problem in CS [2,3].

In contrast with the lush clinical systematization of the disease, the cortical alterations in the CS have been discovered through sophisticated studies of neuroimaging, which on the present, belong to research [4-6].

Among the morphometric neuroimaging studies that have been used to investigate the cortical alterations that determine the CS are: the analysis Voxel or granulometry of the gray and white cortical matter, the study of cortical thickness using FreeSurfer and Tractography. On the other side, the neurofunctional studies that have been used for research in children with CS include: EEGQ, Neurometric analysis and Digitized Brain Mapping. Last but not least, there have been used neuro-metabolic studies such as the SPECT and Magnetic Resonance Spectroscopy [7-12].

Since the incorporation of these studies regarding research on the CS origin, it comes up the concept of Neuro-Strabismus, this branch of neuroscience which understands the ocular deviation that characterizes the CS, as the manifestation of a primary cortical alteration, explores its ophthalmological, neuro- ophthalmological, perceptual, psychological and/or social implications [13,14].

From this perspective, the ocular deviation sets the loss of the sensory and motor balance which occurs because the cortical integrator fails in its purpose to modulate some oculomotor reflexes anomalies such as the dorsal light reflex, the accommodation, the vergencial and pupil tone, while some sensory phenomena such as the stereopsis, fusion, visual noise, confusion or visual acuity are inhibited [15,16].

Other relevant aspects of the CS are the decrease in the visual-perceptual skills of the patients, which can affect its cognitive process. In addition, some patients showed in their neuro-functional studies a high incidence of paroxysms, anisocoria, and some other disturbances concerning the neurological sphere [17-20].

By if little, the social and psychological implications of this pathology lead inexorably to one of the most disconcerting aspects of this disease, which is the high incidence of Mental Illness even suicides, which is greater in comparison with the general population [21-23].

Corresponding author: Martín Gallegos-Duarte, Licenciatura en Optometría, Facultad de Medicina. Universidad Autónoma de Querétaro, México, Tel: +52 (442)1118737; Fax: +52 (442)1118737; E-mail: martin_oso@hotmail.com

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On the basis of the foregoing the CS should be considered as something more than a cosmetic issue, patches and glasses. The strabismic patient requires a better support both diagnostic and therapeutic, as well as investigates at depth the neurological implications of this disease that affects 3 % of humanity [24].

Materials/Methods

This Communication is part of a line of research that analyzes the participation of the cerebral cortex in the origin of the CS on the base of various neuroimaging techniques.

By its nature, all studies have been done *in vivo* and using methods of neuroimaging. Each patient underwent a complete neuro-optometric and ophthalmologic examination in order to establish the sensory and motor diagnostic in children who could cooperate with the staff.

All patients were evaluated by the same qualified staff, following a standardized protocol of evaluation, classifying the sensorial, motor and perceptual aspects, establishing the diagnosis of CS on the basis of the "congenital stigma", excluding cases with neurological disease related.

The Protocol established that each cohort was composed of children with proven CS diagnosis, between 7 and 12 years, complete file and a same proportion of boys and girls.

There were randomly realized different neuroimaging studies in different periods of time. The findings of each cohort were analyzed separately, with the purpose of establishing the morphometric and neurofunctional differences of each control and case group such as in the case the Neurometric analysis, comparing with a universally accepted database.

Per protocol, this line of research used only morphometric and neurofunctional methods, always used separately, so that there was no a combined morphometric - functional study of neuroimaging as it occurs with functional RMI.

To analyze the cortical morphology was then used a technique called Granulometric analysis or Voxel analysis. Using this methodology obtained from RMI once separated the gray of the white matter, the pixel (picture elements) and Voxel (volume elements) of each image were filtered and their size, volume and density was calculated and charted for a better understanding. (Figures 1-4)

This same technique was employed additionally to a different cohort to specifically analyze the structure of the visual pathway obtained through Tractography. (Figures 2 and 3)

Granulometric analysis was used for the study of the gray matter (Figure 4) while FreeSurfer analysis was used for the cortical surface. By using separately these methodologies we were able to know the differences that exist in the cortical thickness of a prospective cohort study of 22 patients (Figure 5)

Digitized Brain Mapping was used for the Neurofunctional analysis (Figure 6) while the Neurometric analysis or Neurometry was used for the study of intra- and interhemispheric coherence (Figure 7)

By means of Spectroscopy, the cortical chemical composition of a group of 22 patients with congenital strabismus could be analyzed (Figure 8)

In order to evaluate the Visual-perceptual alteration in Congenital Strabismus (CE), all patients underwent an optometric examination based on the 21 points of (OEP) Optometric Extension Program. A detailed Visual-Perceptual analysis including TVPS (Test of Visual-Perceptual Skills), VMI (Visual-Motor Integration), Memory of MONROE, Directionality of GARDNER, VADS (Visual-Aural Digital Span) and DEM (Development Eye Movement Test) was performed to each one of them. The obtained values were correlated with the type of congenital strabismus (CS) and the alterations found in the Digitized Brain Mapping (DBM).

The most relevant findings as well as their conclusions are cited below.

Results

Morphometric Studies

The first morphometric study used was the Voxel analysis or granulometry of the white substance. This methodology demonstrated for the first time that the CE has an anatomical substrate which introduces very specific changes, consisting in a significant decrease in the fine granulometric elements. (Figure 1 and 4)

Based on these findings, it was decided to investigate using Voxel analysis the Tractography of 11 strabismic patients who were compared with a control group of 11 healthy patients. The study revealed that strabismic patients presented a 15% decrease on granulometric volume, as well as a decrease in the caliber of the splenium. (Figures 2 and 3)

The short and long axons responsible of the intra and inter-hemispheric connectivity form the white matter, for this reason its Morphometric and Functional analysis allowed discover the morphological and physiopathological substrate of the disease.

To further study this anatomic substratum we decided to analyze the cortical thickness of a group of patients with CE through FreeSurfer. This technique uses a set of automated tools for the reconstruction of the cerebral cortical surface based on structural imaging of magnetic resonance; as well as the overlay data of functional magnetic resonance on the reconstructed surfaces which is known as the most reliable existing technique to measure the cortical thickness in subjects alive. The cortical surface of 11 children with CE was analyzed using this methodology, which was then compared with a group of 11 healthy children. The results show that there are substantial changes between one group and another, especially in temporal and frontal lobes. (Figure 5)

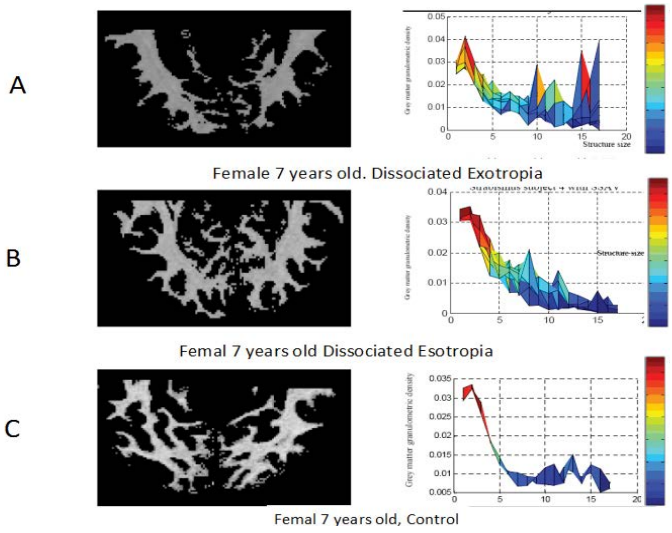

Figure 1: Indicated with the letter "A" is observed a predominance of large components of the white matter in the posterior portion of the brain of a 7-year-oldgirlwith diagnosis of dissociated exotropia. In the Middle, marked with the letter "B" shows a predominance of medium and large components of the white matter in the posterior portion of the brain of another girl of 7 years old with strabismus. In this case it's a dissociated strabismus in esotropia. Finally, below, indicated with the letter "C" is observed a predominance of small components of the white matter in the posterior portion of the brain of another 7-year-oldgirlbutwithout strabismus. This is the normal pattern.

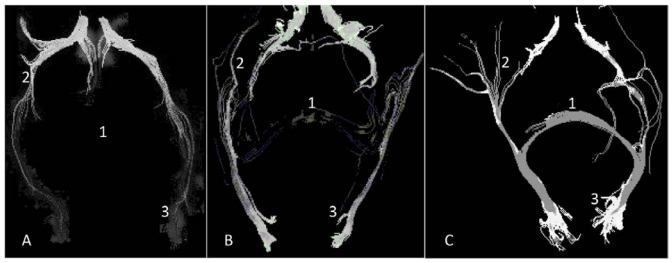

Figure 2: A decrease in the interhemispheric axonal connectivity (1) Occipito-Temporal (2) and occipital (3) was found in the Case Group (A and B), compared to healthy patients (C).

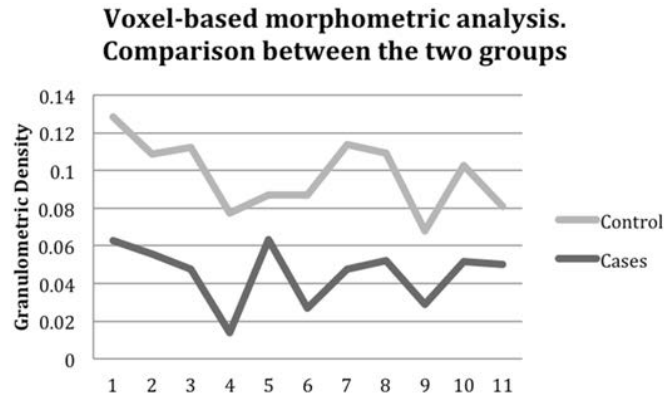

Figure 3: Morphometric analysis based on Voxel (VBM) identified a decrease in the granulometric density of the posterior visual pathway in all children with congenital strabismus compared to the control group. An increased granulometric density was always present in the right hemisphere compared to the left across the analyzed sample, both in the case and the control group.

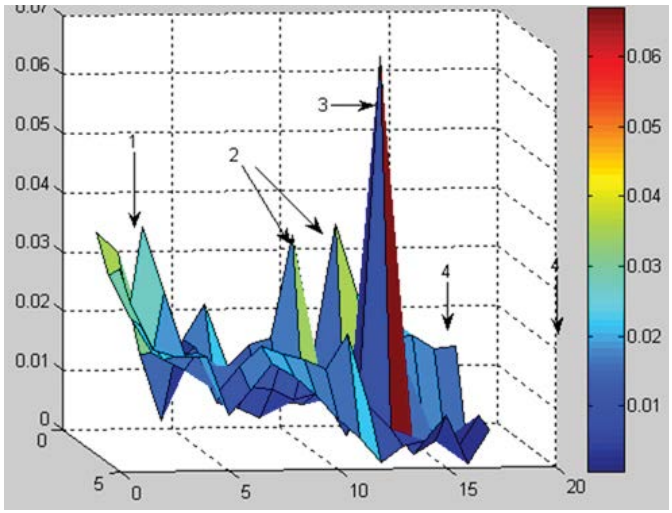

Figure 4: 3D graphics display the granulometric pattern of the gray substance of 11 patients with congenital strabismus. There is a large amount of large and medium items (arrows 2 and 3; openings 7 to 14) with a relative decline of the small items (arrow 1; openings 1 to 6). The distribution of all elements is characteristically irregular.

Neuro-Functional Studies

In a study through Digitized Brain Mapping was found that: Two thirds of the Digitized Brain Mappings obtained from 193 patients show cortical dysfunctions such as slowing down of brain waves, paroxysms and eventually some signs of epilepsy, especially in patients presenting "dissociated" ocular movements related to strabismus. (Figure 6)

In another recent study the intra and inter-hemispheric coherencies of 63 patients with CE were analyzed, finding that there is a relationship of hypo-coherence and hypo-function of the temporal lobes in 66% of the sample. (Figure 7)

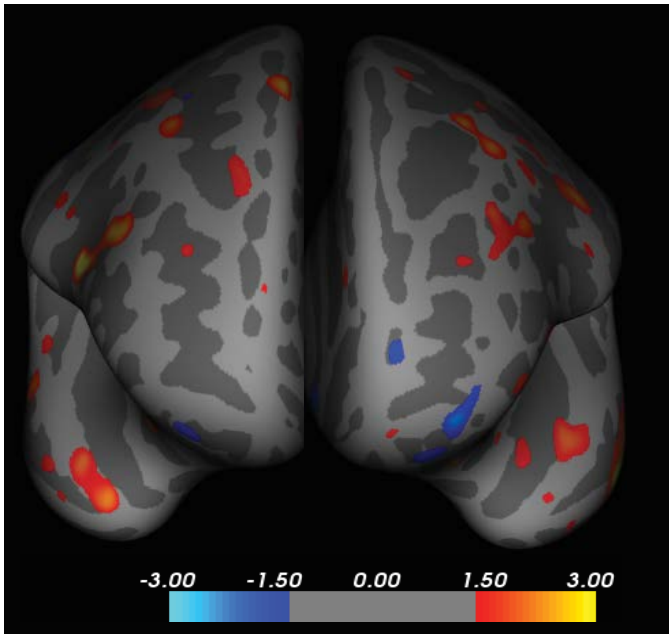

Figure 5: Brain images obtained by FreeSurfer that shows the differences in cortical thickness between 11 brains for the control group and 11 brains of patients with strabismus. The image shows an increase of cortical thickness in the temporal and parietal lobe of right hemisphere-in yellow and orange color- possibly relating to the suppression of visual noise. It also shows a decrease of cortical thickness - in blue color- probably related with low cortical activity front left and difficulties in visual perception. The colorimetric scale indicates the cortical thickness in values of -3.00 to 3.00

Coherence analysis permits the understanding of how the brain is interconnected and represents a correlation coefficient of frequency bands. This coherence analysis is determined by the activity of the fibers of short and longs interhemispheric interconnected pathways contained in the white matter of the brain. Coherence measures the correlation between simultaneous signals of QEEG and expresses the capacity of neuro-electrical connectivity among different brain regions.

In this study it was found that there was a relationship of hypo-coherence between the inter Occipito-Temporal, Parieto-Temporal and inter-Temporal conectivity. It was also showed a decrease on the connectivity of the neighboring areas toward the temporal lobes.

Neuro-Metabolic Studies

In order to know the chemical composition of the cerebral cortex, spectroscopy has been used. This study allows knowing some aspects that have to do with both, the neuronal volume as to identify the presence of lactate, which let you know if there has been neuronal suffering.

Studies using RMI Spectroscopy (1H-NMRS) indicate that patients with dissociated strabismus exhibit a diminution of N-acetyl-aspartate which indicates that there is a decrease in neuronal volume, as well as increase of Lactate, indicative sign of neuronal suffering. (Figure 8)

Visual-Perceptual Skill Analysis

As far as their visual-perceptual skills, figure 9 show the divergence in age encountered in different type of strabismus.

Patient with exotropia (XT) had the poorest motor ocular-motor performance while dissociated strabismus (DS) patients performed badly during TVPS analysis. Congenital strabismus patients performed almost the same during VMI and TVPS analysis.

Regarding the rest of Visual-Perceptual analysis, the greatest deviation at the Memory of MONROE test was found in dissociated strabismus (DS) with a divergence of 3 years and 9 months from the

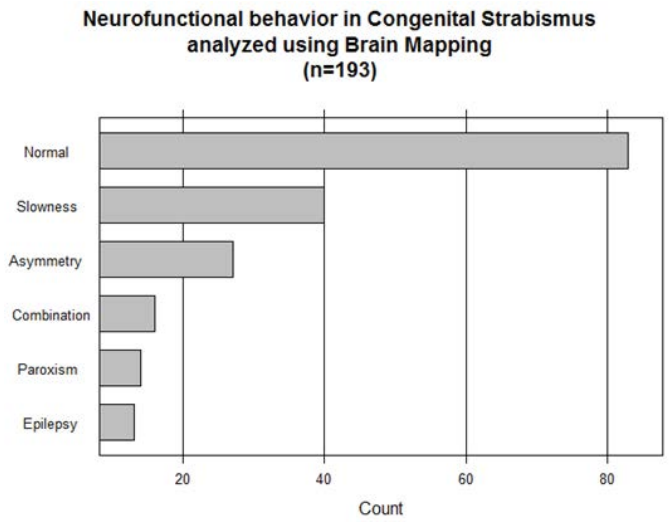

Figure 6: Of the 193 Brain Mappings made in patients with congenital strabismus, 80 were normal and 113 abnormal. 40% of the patients with abnormal brain mapping presented slowdown of brain waves, 27% problems of asymmetry, 16% a combination of the above, 14% paroxysms and 13% epilepsy.

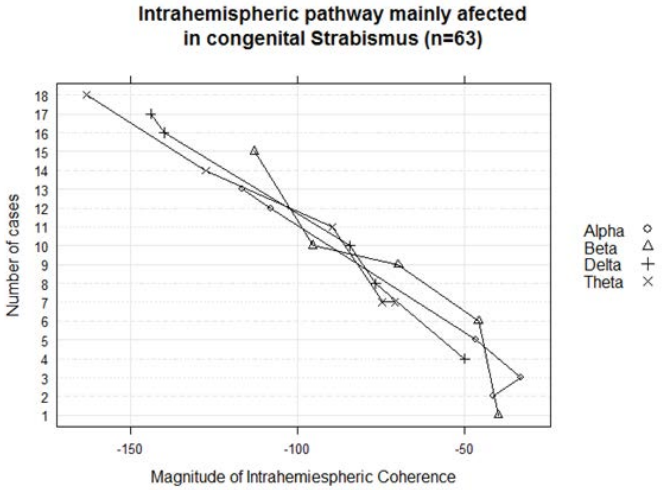

Figure 7: Behavior of intrahemispheric coherencies in congenital strabismus. The lines show the magnitude of the hypocoherence of the four brain waves. The abscissa show the range of accumulated hypocoherence by brain wave, while the orders show the number of cases that presented the alteration in a sample of 63 patients. The trend was evident: hypocoherence brain wave prevailed in whole sample.

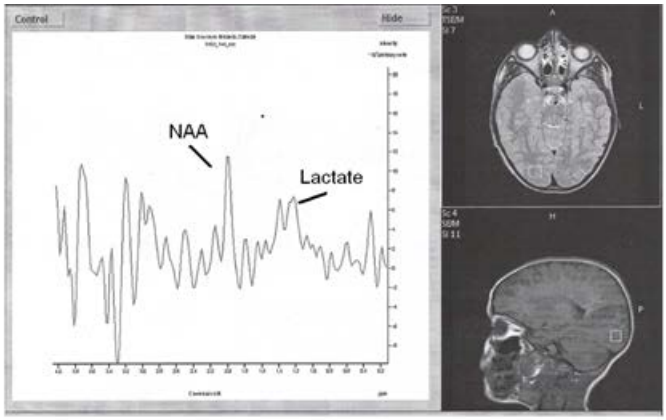

Figure 8: Spectroscopy (1H-NMRS) performed in a 4 year-old girl with Congenital Strabismus showing high lactate levels (4 units) and decressed N-acetyl-aspartate concentration (12 units). The white square in the axial and sagital projections shows theexactlocationwherethe1H-NMRS simple was taken from. The study suggests that there is a decrease in cortical white matter in the Congenital Strabismus.

expected age. As far as Eye Movements test, Types 2 (oculomotor dysfunction) and 4 (deficiencies in automaticity and oculomotor skills) were the most frequented in whole sample. Patients with CE presented greater directionality problems, reaching only 17.7%. Both visual and aural pathways showed deficiencies in all three categories of strabismus.

The study also showed that the most affected cortical areas in the whole sample were P4T6 (Parietal-Temporal of right hemisphere) and FP1FP2 (Frontal-Parietal of left and right hemisphere respectively) with a predominance of Delta wave at P4T6 and Theta at FP1FP2. (Figure 9)

Discussion

Based on the results we believe that strabismus leads to a severe neurological alteration of the integrator network, demonstrated by neuroimaging studies, and when being treated produces very favorable neuro-adaptive changes very for the patient.

The neurofunctional and morphometric findings of these investigations are consistent with the fact that the white matter is affected, perhaps due to the fact that this structure formed by the axons of neuronal interconnection is more delicate than the gray substance to asphyxia, hypoxia and prematurity, situation that occurs in many strabismic patients.

From these studies it can be said that the congenital strabismus should no longer be considered as a disease of unknown origin. The analysis of its structure and function shows that there is a primary cortical damage that occurs mainly in the white matter, which causes a reduction of the capacity of the cortical integrator to modulate some oculomotor reflexes, which are exacerbated, while some sensory and visuo-perceptual abilities are inhibited; this sensory–motor and perceptual imbalance is what characterizes this disease.

However and against all logic, some publications insist on the one hand that the origin of CS is still unknown and on the other the disease continues to be treated in many parts of the world as a motor problem in the best of cases, or even as something merely aesthetic. The neuroimaging studies, which are very punctual point the cortical damage, happened in these children who should be treated in a multidisciplinary and integrative way.

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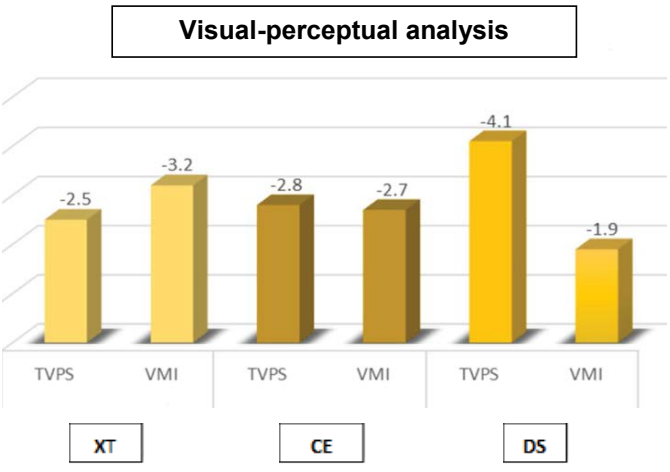

Figure 9: divergence in age of visual- perceptual skills (TVPS) and visual-motor integration (VMI) at patient with exotropia (XT), congenital esotropia (CE) and dissociated strabismus (DS).

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