Research Article **AJOHC (2021) 4:13**

American Journal of Histology and Cytology
(ISSN:2637-5117)

PATHOLOGICAL CHANGES IN THE RATS' EYES AFTER THE ADMINISTRATION OF OIL MACHINERY FLUID THROUGH STEREOTAXIC SURGERY

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ABSTRACT

Purpose: To achieve a relationship between oil machinery fluid (OMF),and the damage this fluid produces in several eye structures. In neuro-oncology patients, we know there are several parasellar tumors; one of them is the craniopharyngiomas that can produce a cystic structure containing an oily material. It has been denominated as an oil machinery fluid (OMF); this fluid has not yet been widely studied. It is a widely held view that it produces toxic effects in the brain and other structures. This paper aims to see the toxicity of the OMF when administered directly in the brain and the changes produced in the rats' eyes.

Methods: 30 Wistar rats were divided into three groups, control, sham and experimental; the oil machinery fluid was obtained directly from human patients during surgery. The oil machinery fluid was administered to the rat thalamus by stereotaxic surgery. The subjects were under observation after the surgery for five weeks and sacrificed once the observation period ended. Finally, immunohistochemistry was performed on tissue recovered from the eyes.

Results: We observed that in the experimental group, there was an increase in glucose levels, the coloration of the eyes changed to a pinkish color, the lenses changed opacity, there were histological changes in the retina, and a reduction of the diameter of the optic nerve in this group in comparison with the control group.

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How to cite this article:
Martha Lilia Tena-Suck, Alma Ortiz-Plata, Joaquín Manjarrez, Wilhelm Moreno, Carmen Rubio. PATHOLOGICAL CHANGES IN THE RATS' EYES AFTER THE ADMINISTRATION OF OIL MACHINERY FLUID THROUGH STEREOTAXIC SURGERY. American Journal of Histology and Cytology, 2021, 4:13.

eSciPub LLC, Houston, TX USA.
Website: https://escipub.com/

Conclusions: All the results observed in this model can be seen in human patients with craniopharyngiomas and diabetes. They are leading us to think that the oil machinery fluid alone can produce ocular changes by damaging several structures by the toxicity created by this fluid.

Keywords: Craniopharyngioma; oil machinery fluid; cyst structures; immunohistochemistry and Eye structures

INTRODUCTION

There are different types of sellar and parasellar tumors; the craniopharyngioma (CP), is the one with the highest mortality of them; this is an embryonic malformation in both sellar and parasellar regions of the brain, its annual incidence goes from 0.5 to 2 cases/million. Being an embryonic malformation, it is most common in children; nonetheless, it can be found in adults. Craniopharyngioma (CP), is an embryonic malformation of the sellar and parasellar regions of the brain; they are considered rare and benign. Its annual incidence goes from 0.5 to 2 cases/million. Being an embryonic malformation, it is most common in children (5% of all tumors), at least half of them are diagnosed in adults. The incidence of this tumor is not affected by race, gender, or geographical localization. [1]

CP produces multiple manifestations; they are slow-growing tumors; therefore, the onset of symptoms can take one or two years and are dependent on location, size, growth pattern, and relationship to adjacent structures, the most frequent presentation is elevated intracranial pressure, endocrine dysfunction, visual disturbances, [2] in children some signs are slow body growth, polyuria/polydipsia, early or late puberty and significant weight gain. [3] About 40–80% of the patients with a suprasellar tumor can produce a constant pressure in the optic chiasm causing partial visual acuity loss and visual field abnormalities, the most common and asymmetric bitemporal hemianopsia. [4] On the other hand, parasellar can produce diplopia and ocular muscle paresis by infiltrating the cavernous sinus. On the statistical side of the visual field defects, it has been reported 60%, decreased visual acuity in 40%, atrophy optic in 14%, and blindness in 3%. Craniopharyngiomas can extend to other areas such as the hypothalamus that´s linked to obesity in CP patients. [5]

There are two histopathological types of CP: Adamantinomatous (AdaCPs), and papillary (PaCPs),[1]; the first one is the most common in adults and is the one that produces the cystic structures containing the oil machinery fluid (OMF). In fact, we know this fluid affects the brain. The mechanism in which the toxicity is done is still not known; we have made experiments to see how damaging can OMF be in the rat´s brain. By applying it in the cerebral cortex producing toxicity in astrocytes and phagocytosis, and having a somatic relationship with obesity, this study aims to mimic the eye damage and increase in obesity reported in human patients with CP by applying OMF to the thalamic supraventricular nucleus (SVN).

METHODS

Animals and treatment groups

30 Wistar rats were used, all of them were obtained from the “INNN" vivarium; we used rats weighing 250g, with no other type of interventions. They were housed following the Care and use of laboratory animals guide, housing them separately in a controlled room temperature of 22°C to 24°C, with a light/dark cycle of 12 hrs. food and water were provided ad libitum. We obtained the OMF directly from patients that were undergoing neurosurgery during the CP removal. Once the fluid is in the laboratory, rats were weighed and prepared for the stereotactic surgery to administer the OMF with saline solution in the SVN.

This study is based on Roth 2011 study used to mimic metabolic sequelae of obese craniopharyngioma patients in rodents, adding the complex ophthalmological histopathological disturbances produced by the OMF.

We divided the rats into three groups: a control group (group 1), that underwent a minor surgery only to introduce a catheter. The sham group (group 2) received surgery to introduce a

catheter to administer 500 µl of saline solution in the SVN and an experimental group (group 3), that underwent the same surgery as the sham group to administer 500 µl of OMF directly to the SVN. The exact metabolic measurements were taken in every subject: blood glucose, cholesterol, triglyceride, and weight, were taken for every group before the surgery and after the period of recovery, after the administration of ether anesthesia, a wedge of cortical tissue was excised for further study, part of this tissue was fixed in formaldehyde and embedded in paraffin for light microscopy, whereas the other part was dissected and fixed in 3% glutaraldehyde in phosphate buffer with a pH of 7.4, for one hour, a second fixation was made in a 2% osmium tetroxide in the same buffer from 1.5 to 2 hrs. at 4°C, this the tissue was dehydrated in alcohol and embedded in epon for five weeks after surgery; all animals were sacrificed by intracardiac perfusion at 4% paraformaldehyde in PBS 10M, each eye was fixed in 10% formalin in PBS alcohol and dehydrated so it can be embedded in paraffin.

Studies involving human subjects

Generated Statement: The studies involving human participants were reviewed and approved by the Ethics Committee of the “INNN”. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Glucose level assessment

Plasma glucose levels were determined in tail vein blood samples using the Accu-Check Performa blood glucose meter (Roche Diagnostic, Mannheim, Germany).

Histopathology

Using the tissue mentioned above, four µm sections were stained with hematoxylin-eosin reagent, periodic acid-Schiff (PAS), Masson, and oil red for the routine histopathology analysis. Slides were viewed under a microscope (Imager.Z1; Carl Zeiss Axiolab, Oberkochen, Germany). The changes produced by the OMF in the eyes were studied, we saw denaturation of the lens protein due to the calcium-dependent enzymes leading to lenticular opacity causing cataracts in the subjects, other areas were assessed, such as lens density, in the retina: the external epithelium, presence of vacuolation, ganglion cell layer (GCL), bipolar cells, flakes and canes, both internal and external plexiform layer (IPL/OPL), and limit membrane, in the cornea: the external epithelium, stroma, sclera, internal and external basal membrane, descement and basement membranes, from the optic nerve: the neurofilament fibers and myelin and other degenerative changes in the eyes.

Immunohistochemistry technique

Analysis of Retina, cornea, lens and optic nerve were made by histopathological procedures and immunohistochemical stain. For the immunohistochemical, a 4µm cut was used, the paraffin sections were deparaffinized in xylene and rehydrated through a series of ethanol treatments. Antigen retrieval was accomplished by incubating the sections in 10 mm sodium citrate with a pH of 6.0 that were heated with a steamer. To block the endogenous peroxidase activity, sections were immersed for 30 minutes in a 6% hydrogen peroxide solution diluted with methanol (v/v). After the immersion, they were washed with PBS. The Nonspecific background was blocked using CAS-Block (Zymed), followed by incubation with the primary antibodies at 37ºC for 30 minutes and then at 4ºC overnight. The primary antibodies used were: Glial fibrillary acidic protein (GFAP), (SKU: 040, Biocare, dilution 1:100). Neu-N, neurofilaments (Neuronal Marker (ab104225), | Abcam, dilution 1:100), Myelin basic protein (A0623 Dako, dilution 1:100), DARPP-32 (dopamine- and cyclic adenosine 3′-5′-monophosphate-regulated phosphoprotein, sc-271111, 1:100), Thr 34 (#2302; Cell Signaling Technology, Danvers, MA, USA, dilution 1:100), vimentin (M0725 - Dako – CiteAb, dilution 1:100), Cytokeratin 7 Antibody (M7018-Dako – CiteAb, dilution 1:100), and glut3 (GeneTex, 1:100). A known positive control was included; on the other hand, some sections were incubated with PBS instead of the primary antibody to serve as negative controls. The remainder of the sections were immunostained using the Biocare Kit (San Ramon CA, USA). The final

visualization was carried out by chromogenic detection using a PBS solution containing: diaminobenzidine at 0.1%, diaminobenzidine at 0.06%, dimethyl sulfoxide at 1%, and H_2O_2. After, the sections were immersed in the solution for 5 minutes at 37ºC. Lastly, counterstaining was performed using Harris hematoxylin, positive immunoreactivity of the individual organs was scored from 0 to 3. The scale is as follows: 0, minimal to no reaction; 1, weak; 2, moderate; and 3, strong reaction for the different primary antibodies used.

RESULTS

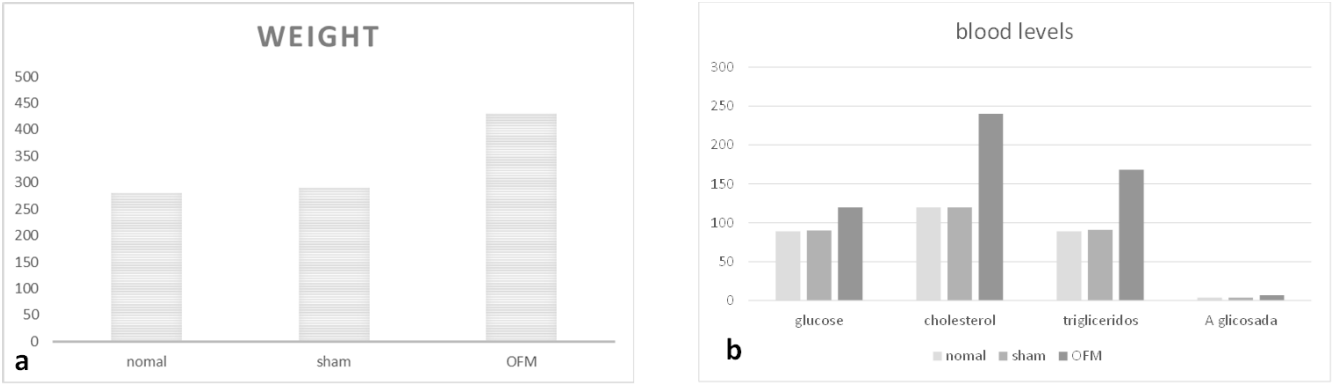

Figure 1 Weight and glucose, cholesterol, triglycerides and glycosylated glucose levels

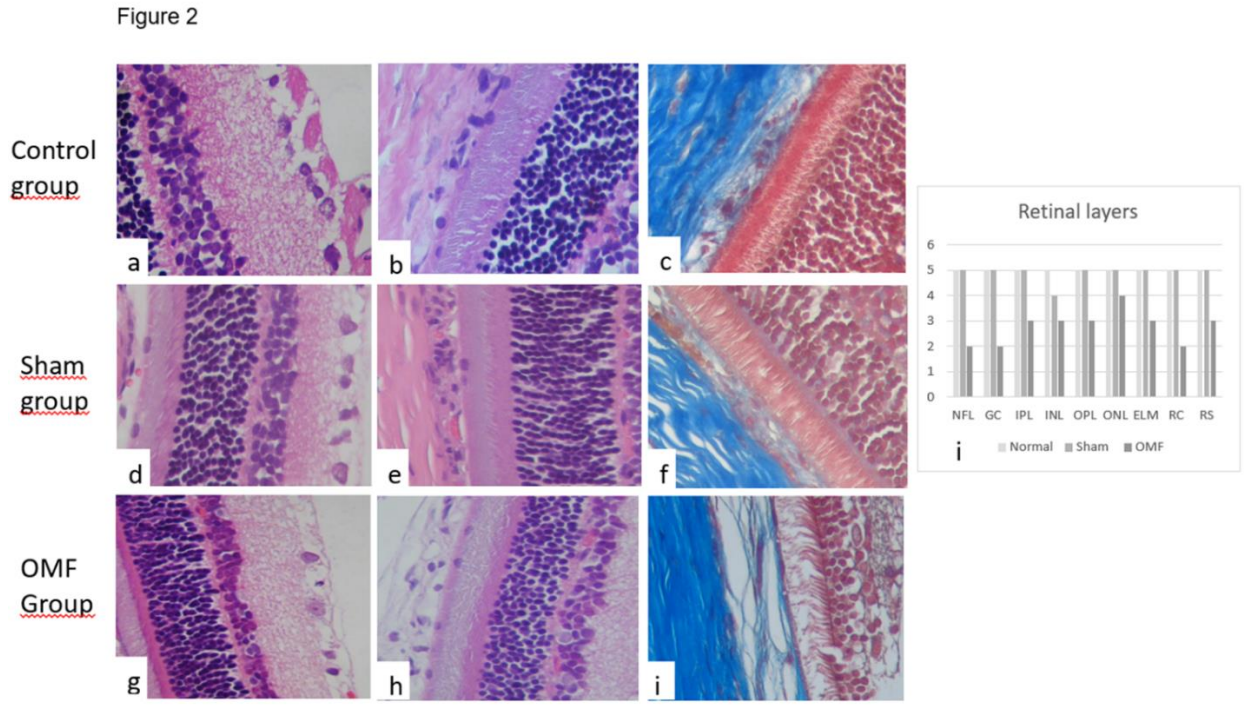

Figure 2 Changes produced by the OMF at the retina a to f, changes in the internal limiting membrane and plexiform layer in 2g, changes in the outer nuclear layer in 2h, 2i. 2j is a relationship of the retina layer.

As expected, the OMF group showed an increase in weight and elevated levels of glucose, cholesterol, triglycerides, and glycosylated glucose in comparison with the other groups, as observed in Figures 1 (1a and 1b), respectively. Despite these differences in weight, the experimental group was not obese. These were not the only changes observed within the groups; there was a coloration change in the eyes of the OMF group from a light red to light pink in comparison with the other groups in which the eyes stayed in a light red tone seen in

figure 6. We found that the retina, both in the control and sham group, did not show alterations in any of the layers of the cornea, as seen in Figures 2 (fig. 2a, 2b and 2c) for the sham group and (fig. 2d, 2e) and (fig. 2f) for the control group. However, in the OMF group, there was a decrease in several structures such as the internal limiting membrane, the nerve fiber layer, GCL, and the inner plexiform layer (Fig. 2g), as well as in the inner core layer and OPL. There were changes in the outer nuclear layer and the cones and rods layer being thinner in comparison with the control group (Fig. 2h). Using Masson's stain, we observed an intense blue in both the choroid retinal layer and epithelium in both the sham and control group. Whereas in the OMF group, a thin and pale blue can be seen in the same structures (Fig. 2i), the relationship in the retinal layers can be seen in the histogram (Fig. 2j).

Using GFAP, we observed that the internal layer limiting membrane, the nerve fiber layer, GCL, and the inner plexiform layer showed an intensely positive reaction in the sham and control group (Fig. 3a and Fig. 3b), whereas, in the OMF group, it is barely visible or measured, this group had tiny tortuous fibers with branches in the inner and outer nuclear layer (Fig. 3c). The expression of Neuronal nuclear antigen was positive in the GCL and the inner nuclear layer (INL), in the control group (Fig. 3e), slightly positive in the OPL, a lower intensity in the GCL, and negative in the inner and outer nuclear layer in the second group (Fig. 3f), in the OMF group there was a poor expression in the GCL (Fig. 3g). The expression of neurofilaments was positive in all three groups in the nerve fiber layer; in the control (Fig. 3i), and sham group (Fig. 3j), the ganglion cells layer was positive, whereas, in the control and experimental group (Fig. 3k), the internal limiting membrane was positive. In the retinal pigmented skin, we observed positive results in the control (Fig. 3ll), and sham group (Fig. 3m). Instead, the experimental group showed positive results in the linear and fine part of the retinal pigment epithelium (Fig. 3n). We can see these relationships between the different retinal layers and GFAP (Fig. 3d), NeuN (Fig. 3h), and Neurofilaments immunoexpression (Fig. 3i). Visualizing the cornea´s pseudostratified epithelium, there is a thick basement membrane in both the control group (Fig. 4a) and sham group (Fig. 4b); inversely, the OMF group showed a loss in this membrane (Fig. 4c). It can be seen better using the Periodic acid–Schiff (PAS) staining (Figs 4d, 4e, and 4f). Within the stroma, using Masson´s stain, we can observe collagen bands in its core in control (Fig.4g), and sham (Fig. 4h), groups; in contrast with the OMF group, these bands appear to be scattered and lax (Fig.4i). There are less keratinocytes, but the limiting layer and endothelium layer were preserved in all the groups. There are several differences in the vimentin; the control group show scar fibers (Fig. 4j), in the sham group, these are more evident (Fig. 4k), contrariwise the OMF group show dense fibers (Fig. 4l), these contrasts can be seen in the histogram (Fig. 4 ll).

At first glance, the optic nerve appears to be expected in the control (Fig. 5a), and sham (Fig. 5b), groups; having said that it is thinner and narrower in the OMF group (Fig. 5c), going deeper, we observed the Schwann nucleus positive and expected in the control (Fig. 5d), and sham (Fig. 5e), groups, in contrast with the OMF group where there are fragmentations and thinner fibers (Fig. 5f). The calcium-binding cytosolic protein S-100 was positive in some nuclei of the control group (Fig. 5g), presenting a loss of immune nuclear reaction in the sham (Fig.5h), and OMF (Fig. 5i), groups. Neurofilaments of the optic nerve appear to be expected in the control group (Fig. 5j); in the sham group, they appear to be irregular (Fig. 5k), and in the OMF group, they became short and tortuous (Fig. 5i). The neurofilaments in the periorbital muscles were intensely positive in the control group (Fig. 5ll), followed by a decrease of expression in the sham group (Fig. 5m), and, to a lesser degree, in contrast with the OMF group (Fig. 5n). The lens capsule appears to be thick and homogeneous in the control (Fig 6a), and sham (Fig. 6b), group, contrary to the OMF group where it is

diminished (Fig. 6c). There were no visible changes in the external epithelium layer for the control (Fig 6a) and sham (Fig. 6b) group; oppositely, the basal layer of this epithelium had hypercellular and hyperchromatic cells in the OMF group (Fig. 6c). Using PAS staining, the control (Fig. 6d),and sham (Fig. 6e),group have a homogeneous basal membrane; then again, the OMF group shows an irregular and thinner membrane (Fig. 6f). The crystalline fibers are reddish and homogeneous as expected in the control group (Fig.6g); discreetly irregular and reddish in the sham group (Fig. 6h); the OMF group showed the most differences with them losing the reddish color for a blue one. Thus, becoming irregular and alternating within areas that can suggest gaps or clear spaces (Fig. 6i). The expression of Glut3 is homogenous in the control (Fig. 6j), and sham (Fig. 6k),group; in contrast, the OMF group showed fewer cells and light spaces (Fig. 6l).

Figure 3

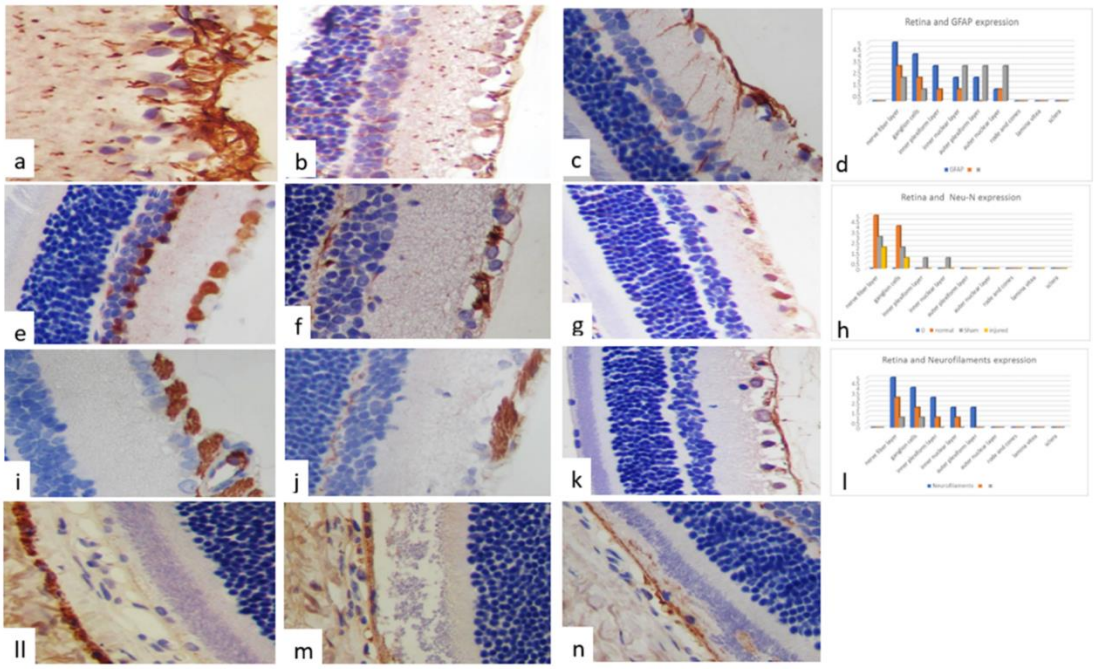

Figure 3 Changes in the retina seen with GFAP

Figure 4

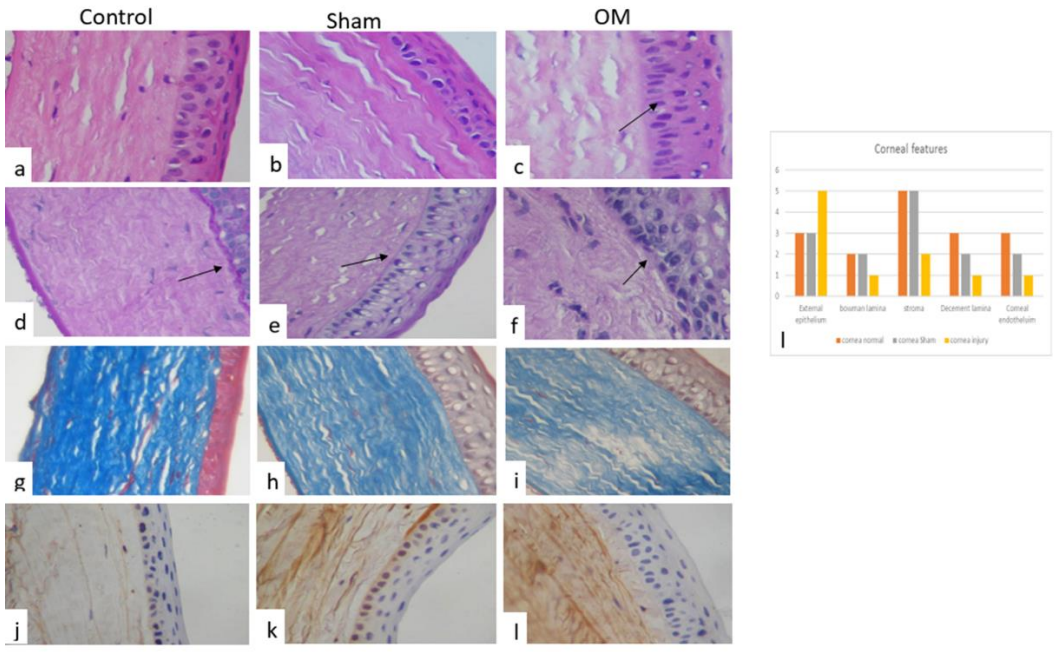

Figure 4 Different changes produced at the cornea

Figure 5

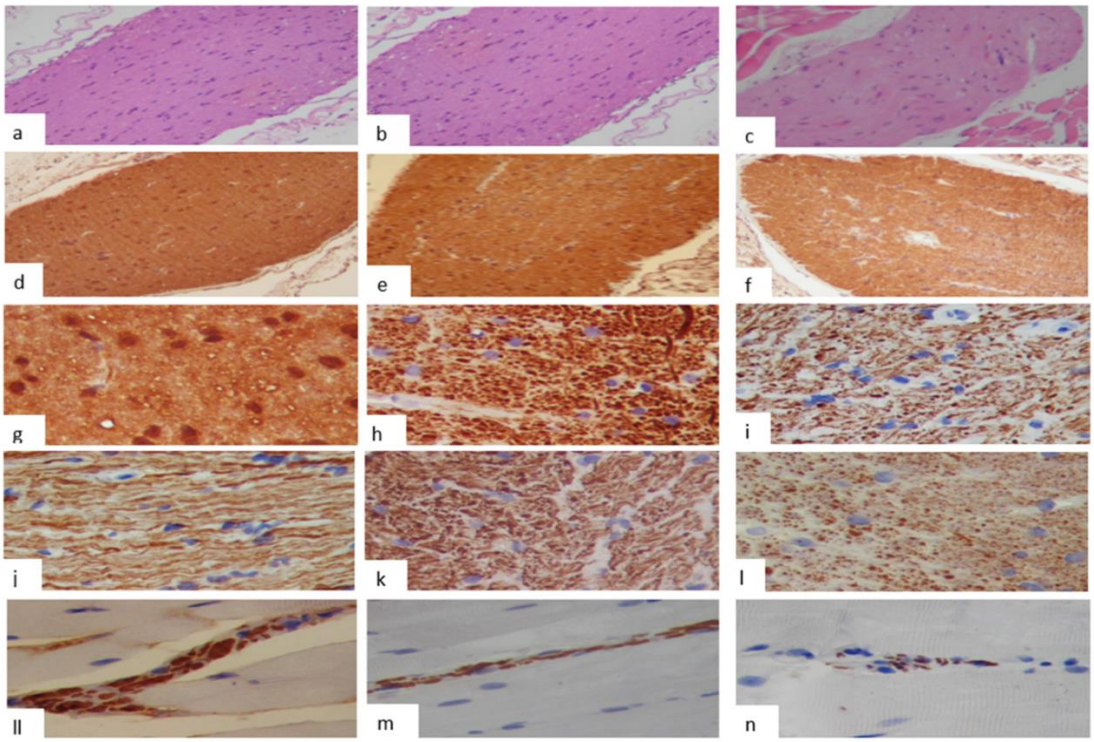

Figure 5 Changes produced in the optic nerve

Figure 6

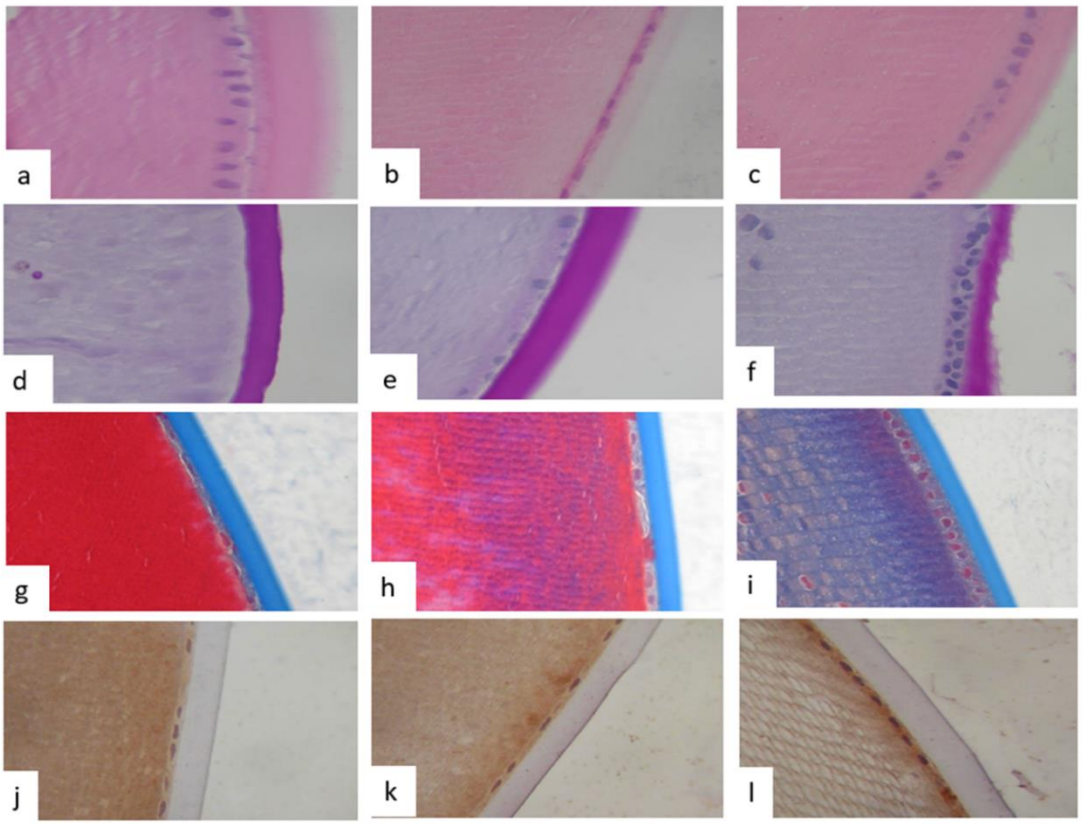

Figure 6 Changes in the lens capsule and epithelium

DISCUSSION

The present study confirms the metabolic changes in the retina, lens, and optic nerve. Thus, producing alteration and abnormalities, such as cataracts, seen in the diabetic state produced by the injection of streptozotocin (STZ, 25 mg/kg). The pathology's treatment and progression significantly impact the CP prognosis due to

the consequent hypothalamic alterations like hypothalamic obesity. [6,7] The emphasis was given to the most common animal obesity models in research; this includes monogenic models in the leptin pathway, polygenic diet-dependent models, or mechanical intervention (e.g., chemical lesion of the ventromedial hypothalamus). Recent insight into molecular genetics, treatment strategies, risk factors, and outcomes associated with hypothalamic obesity have provided novel therapeutic perspectives in this area. The hypothalamus has been recognized as a crucial area for energy balance, the ventromedial nucleus (VMN), and the paraventricular nucleus (PVN), are identified as “satiety” centers; this was seen in brain lesion experiments, provoking an injury in these areas causes hyperphagia and obesity, on the other hand, electrolytic stimulation produces a reduction of food intake. [7] The main objective of this paper is to analyze the effects of the OMF fluid as a neurotoxic agent capable of injuring the hypothalamus. [8] On the one hand, Roth et al., [7] described these features, including excessive weight gain due to increased adiposity, food intake also, producing hyperinsulinemia and hyperleptinemia. This experimental model mimics the metabolic abnormalities presented by obese CP patients. [7] On the other hand, in the model, proposed we observed: weight gain, not enough for obesity; also, there was an increase in cholesterol and glucose. Lastly, we observed that the exposure to OMF produced lens opacity, change to a lighter pink color, and visual disturbance. Provided a visual disturbance, the rats could not identify the food pellets and hit the cage walls.

A cataract is defined as a clouding of the clear lens of the eye. Specifically, it is an opacification of the eye lens, interfering with the transmission of light to the retina. Cataracts develop by injury in the tissue; also, they can be caused by diabetes, medications, and aging. The aforementioned is caused by alterations in the structure and chemical processes in the retina colloids. [9] As mentioned before, cataracts can be produced as a diabetes complication. [9] Nonetheless, retinopathy is the most common eye pathology in diabetes; however, cataracts have a higher complexity.

Lens opacity has been detected in clinical and experimental models of diabetes due to an increase of intracellular accumulation of sugar alcohol and morphological changes, thus, producing swelling, rounding of nuclei, and vacuole formation in the peripheral lens. [9] Furthermore, the opacity of the lens could be due to oxidative stress or superoxide ion produced by diabetic patients [10]; this opacity can be seen in experimental models by hypercholesterolemia. [11] For instance, the experimental models showed that there is oxidative stress in the retinal tissues, thus, causing an insufficient supply of nutrients to target structures such as the optic nerve, head, lens, and retina. Accordingly, increasing glutamate levels, thus initiating retinal neuronal cell death. [12] Just as important, we observed hydropic degeneration on lenticular fibers was detected histologically. Subsequently, forming large cysts filled with amorphous material, foam cells in the lens epithelium, invading the lens's nuclear part, causing lysis in the lens fibers, producing an epithelial cell high density, and forming the prospective nuclear cataract. [13] In the OMF fluid group, we observed greater MDA expression and DARP-32 in the retinal ganglion and pigmented epithelial cells. Also, a loss of immunoexpression of Neu-N and neurofilaments were reported in the OMF group.

Likewise, there are reports of retinal arteries stiffness, enhancing retinal ischemia, and arterial thrombosis in atherosclerotic patients. [9] In fact, we observed crucial vascular dilatation in the OMF group compared to the other two groups. In addition, photoreceptors, neurons, and Müller cells (glia), contribute to the removal and metabolization of glutamate in the retina. Also, in our experimental model, we observed a high GFAP immunoexpression in defense against oxidative and nitrosamine stress. The aforementioned is due to the production of glutathione and the production of substrates for neuronal metabolism. [10] Lastly, the OMF group showed a higher MDA and GFAP expression in Müller cells in comparison with the other groups.

In order to observe secondary changes in patients with CP, the tumor size and location are crucial. [14] To be specific, there can be a delayed visual deterioration; it can be attributed to secondary empty sella syndrome or by a downward herniation of the optic nerve and chiasm. In fact, the pathophysiological basis of this condition is still a matter of debate. [15] As an example of the importance of location and tumor size, retro chiasmal tumors are commonly associated with hydrocephalus, producing an increase in the intracranial pressure (i.e., papilledema, double horizontal vision). Furthermore, the retro chiasmal tumor compresses the floor of the third ventricle, leading to an obstruction of the cerebrospinal fluid through Monroe´s foramen. [16] In addition, there is a displacement and stretching of the chiasm away from the optic nerve, eventually causing vascular deprivation in the nerves and damage in the nerve fibers. [16]

So far, no experimental or clinical models explain the histological changes in the craniopharyngioma patients' eyes. In contrast, in our experimental model, we observed thinning of the optic nerve compared to the other groups. In addition, we saw a smaller nerve and less expression of GFAP, myelin, S-100, and neurofilaments. Furthermore, we carried out an experimental model of supposed obesity in rats to demonstrate that OMF can have extravasation by rupture or pressure. Afterward, if OMF arrives at the thalamus, it can produce metabolic alterations and degenerative changes in CP patients. On the one hand, we observed that rats could have metabolic changes with increased cholesterol, triglycerides, blood glucose, and weight gain without considering significant obesity. On the other hand, there are changes in the lens opacity and histological alterations in the cornea, retina, and optic nerve. Lastly, the changes mentioned above can be seen in experimental models of diabetes. [10]

In diabetic patients, chronic hyperglycemia leads to microvascular and macrovascular circulatory impairment, overproduction of reactive oxygen species, and inducing insulin resistance. [17] In fact, diabetic retinopathy may be the most common diabetic implication and is a leading cause of visual impairment and blindness in CP patients. Lastly, the ocular damage observed in CP patients with OMF is produced by this fluid and not by compression as it has been considered. Nonetheless, tumor growth cannot be ruled out in some patients. In addition, an increase in size can compress the optic nerve and chiasm, producing damage by itself or by the extravasation of the OMF. Thus, directly affecting the structures mentioned before. Therefore, new studies are required to demonstrate and or prevent eye damage to patients, and the studies should consider both patients with CP and experimental models.

Conflict of interest statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors have no conflict of interest.

Authors' contributions

Joaquín Manjarrez was in charge of surgical procedures, Alma Ortiz-Plata and Francisca Fernández-Valverde care and sacrifice of rats, Martha Lilia Tena-Suck wrote the manuscript; Carmen Rubio and Wilhelm Moreno critically revised it.

All authors read and approved the final manuscript.

Acknowledgment

The use of the Confocal microscope was thanks to the "CONACYT", México, grant number 300461.

Competing Interests

The authors declare no conflict of interest.

Availability of data and materials

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Funding

The authors received no specific funding for this work.

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