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CLINICAL STUDY

Adaptation of visual cortex to damage of visual pathways in suprasellar tumors before and after gamma knife radiosurgery

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Abstract

Purpose To demonstrate that lesions of the visual pathways due to suprasellar tumors are accompanied by alterations of the visual cortex and to see if these alterations are reversible after treatment of tumors by gamma knife radiosurgery.

Materials and methods In 36 patients with peri-optic tumors and defects of their visual fields and in an age-matched control group, magnetic resonance imaging was performed before and after treatment. T1 weighted images were evaluated by voxel-based morphometry and correlated to the degree of visual field defects.

Results In patients, grey matter density and cortical thickness were reduced in all parts of the occipital cortex, reaching significance ($p < 0.05$) in the left superior and middle occipital gyri, with correlation to visual field defects. Follow-up scans showed further reduction in all occipital areas.

Conclusion As in other peripheral lesions of the optic system, damage of the optic pathways affects the visual cortex. A prospective follow-up study is needed to determine if these alterations are reversible after successful tumor treatment.

Keywords Visual cortex · Neuroplasticity · Suprasellar tumors · Gamma knife radiosurgery

Abbreviations

CC	Correlation coefficient
GKRS	Gamma knife radiosurgery
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MD	Mean diffusivity
AD	Axial diffusivity
RD	Radial diffusivity
HF-SRS	Hypo-fractionated stereotactic radiosurgery
AVP	Anterior visual pathway
SFED	Single fraction equivalent dose
TIV	Total intracranial volume

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Introduction

Long-standing cortical deprivations due to retinal lesions acquired later in life are associated with retinotopic-specific neuronal degeneration of the visual cortex [1]. Reductions of occipital grey matter density have been described in association with retinal visual field defects due to glaucoma and age-related macular degeneration [2–6], Leber's hereditary optic neuropathy [7] and in children and in adults with amblyopia [8].

Although the visual cortex is supposed to retain functional reorganization or plasticity throughout life, this capacity appears to be reduced in older age, mainly in the primary visual area V1 [9]. In optic nerve diseases, there is weak evidence showing that higher-order visual areas undergo plastic changes to optimize visual function [10]. Postoperative increase in grey matter volume in secondary (V2) visual cortex has been reported after unilateral cataract surgery in a group of elderly patients [11], while primary visual cortex seems to lack reorganization [12].

The present study was performed to confirm the hypothesis that suprasellar tumors not only damage the optic nerves, chiasm or tracts, but may as well affect the visual cortex, and—as has been suggested by Prins et al. [3]—to look into the reversibility of these cortical alterations after reduction of tumor size following gamma knife radio-surgery (GKRS).

Materials and methods

This study has been approved by the ethic committee of CEDIMAT and informed consent has been obtained from all patients and volunteers.

Patients and controls

In our database, we retrospectively looked for patients with suprasellar tumors treated by GKRS, who had presented with important defects of their visual fields during ophthalmologic examination. 36 patients were identified. All had received magnetic resonance imaging (MRI) before treatment (Table 1). 19 patients were females and 17 were males with a mean age of 45.1 years (range 11.4–76.7 years). 23 of the tumors were adenomas of the pituitary, nine were meningiomas and four were craniopharyngiomas. 28 patients had been operated before, half of them by an endoscopic transnasal approach. Results were compared to 34 healthy controls without visual problems or pituitary tumors, which had been recruited partially from the general population (24 individuals) and partially from the hospital staff to form an age-matched control group.

In 34 patients, follow-up MRI scans were available for comparison with the pre-operative findings. Of these, 22 patients had a follow-up time of at least 12 months after GKRS.

Ophthalmologic examinations

Examinations included visual field analysis using a Humphrey Field Analyzer, model 745i and a Carl Zeiss Meditec Inc. Dubin/USA, program 30-2. Visual fields were evaluated according to a simple 5-level-scale with 0 for no defect, 1 for a defect of less than 40%, 2 for a defect of 40–60%, 3 for a defect of less and 4 for a defect of more than 90% of a visual hemifield. The score for one side consisted out of the sum of the two corresponding hemifields.

Gamma knife radio-surgery

GKRS was performed on a Leksell Gamma Knife unit (Model 4C, Elekta/Sweden). The treatment was planned on a Leksell GammaPlan workstation (Version 10.1, Elekta/Sweden) by carefully avoiding undue radiation to sensitive structures, especially the optic system, while keeping the coverage index as high as possible (mean: 95.8%).

19 patients were treated with single session GKRS with a mean margin dose to the tumor of 15.4 Gy (12 adenomas with mean margin dose of 16.2 Gy, 6 meningiomas with mean margin dose of 14.0 Gy and 1 craniopharyngioma with a margin dose of 14.0 Gy).

According to our institutional protocol, hypo-fractionated GKRS (HF-SRS) was employed in order to reduce the risk for radiation induced optic neuropathy, for all cases when it was technically not possible to limit the maximum point dose to the anterior visual pathway (AVP) to 12 Gy. 17 patients were treated with HF-SRS: 1 treatment with 5 sessions, 13 treatments with 4 sessions, 3 treatments with 3 sessions, separated by 24 h. 3 meningiomas were treated using HF-SRS, with a mean single fraction equivalent dose (SFED) of 10.8 Gy, assuming an alpha/beta ratio of 3.76 Gy [13]. Estimating the alpha/beta ratio to be 4 Gy for both craniopharyngiomas and for pituitary adenomas, 3 craniopharyngiomas were treated with a mean SFED of 11.7 Gy and 11 pituitary adenomas with a mean SFED of 12.9 Gy.

Table 1 Patients and controls, mean and range or standard deviation of gender, age, tumor volume and prescription dose

	n	Gender	Age (years)	Tumor volume (ml)	Dose (Gy)
Patients	36	19 f :17 m	45.1 (11.4–76.7)	6.553 ± 7.407	14.2 ± 4.05
Controls	33	22 f :12 m	43.2 (13.5–71.8)		

Magnetic resonance imaging

Examinations were performed on a 3 T scanner (Achieva, Philips Medical Systems, Best, Netherlands) and included a high resolution 3D MPRAGE sequence: TR/TE 6.8/3.2 ms, TI (TFE prepulse) 900 ms, flip angle 8°, measured voxel size 0.6*0.6*1.0 mm.

Postprocessing of data

Grey matter density was calculated using the computational anatomic toolbox (CAT) 12.1 (http://dbm.neuro.uni-jena.de/cat12/) implemented in the program Statistical Parametric Mapping (SPM 12, http://www.fil.ion.ucl.ac.uk/spm). This program uses high resolution structural 3D MR images and applies voxel-wise statistics to detect regional differences in gray matter density or volumes. In summary, pre-processing involved spatial normalization, gray matter segmentation, non-linear modulation and smoothing with a kernel of $8 \times 8 \times 8$ mm. Volumes were analysed with a two-sample t-test (patients versus volunteers) on a voxel basis, using total intracranial volume and age as covariates to minimize the effect of both parameters. The program allows as well the measurement of cortical thickness by estimation of white matter distance and projection of local maxima onto other gray matter voxels using a neighboring relationship described by the WM distance [14]. Significance was accepted on a 95%-level, corrected for multiple comparison.

Grey matter density values were extracted from both cunei and the pericalcarine cortex on the medial aspect of the occipital lobe and from the superior, middle and inferior occipital gyri on the lateral aspect, as defined by the LONI probabilistic brain atlas (LPBA40) [15] and the neuromorphometrics MRI Brain Atlas (http://www.neuromorphometrics.com), both implemented in CAT12. For extraction of cortical thickness, the DK 40 parcellation atlas was used. Grey matter density and cortical thickness were compared between patients and controls by 2-sample t-test. Within the patient group, grey matter density was correlated to the score of the corresponding visual field and to pre-treatment tumor volume, correcting for age and total intracranial volume by means of partial correlation analysis offered by the statistical package SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). For comparison, density and thickness values were measured in 48 further cortical areas of the LPBA40 atlas situated outside the occipital lobe and compared between patients and volunteers.

Analysis of follow-up scans was performed in the subgroup of those 22 patients with a follow-up time of at least 12 months using the CAT12 functionality for longitudinal data. Here, data were registered to the mean image for each subject by an inverse consistent realignment taking into account deformations between time points. Again, grey matter density were extracted from occipital gyri and cunei, compared between pre- and post-treatment scans by paired *t*-test and correlated to change of tumor volume after GKRS. Effects of delay to follow-up and total intracranial volume were corrected for by introducing these parameters as control variables into the partial correlation analysis performed with SSPS.

Results

Ophthalmologic findings

Examination of visual fields showed bitemporal partial or complete defects in 16 patients and ipsilateral defects in another four patients. 11 patients presented unilateral defects or blindness of one eye, and in five patients, both eyes were severely affected. According to the scaling mentioned above, hemifields of both sides were equally affected: the deficit score was 4.75 ± 1.90 in the left hemifields and 4.42 ± 1.89 in the right hemifields.

All cases were re-examined after GKRS to rule out possible radiation-induced optic neuropathy and other visual impairments. For the 19 cases treated with single session GKRS, 13 cases received ophthalmologic investigations; the other six patients were interviewed. four cases presented reduced vision caused by glaucoma, dry eye or cataracts. In six patients, vision stayed stable and for nine patients improved vision was reported. From the 17 cases treated with HF-SRS, 11 cases received ophthalmologic investigation; the other six patients were interviewed. one reported severely reduced vision after pituitary hemorrhage. In 11 patients vision stayed stable, for five patients improved vision was reported.

MRI, comparison of patients and controls before GKRS

Compared to controls, patients showed a reduction of grey matter density from 3.4 to 9.5% and of cortical thickness from 1.8 to 11.4% in all parts of the occipital lobe, which reached significance ($p < 0.05$) for grey matter density in the left superior and middle occipital gyri and for cortical thickness in the left superior, middle and in inferior occipital gyri, in the right middle occipital gyrus and the right pericalcarine cortex (Table 2). In the right middle occipital gyrus, the reduction of grey matter density of correlated significantly to the degree of defects of the left visual hemifield (coefficient of correlation (CC) 0.342, $p < 0.05$). However, there was no significant correlation between grey matter density and tumor volume before GKRS.

The image map of difference of grey matter density, compared between patients and volunteers, (Fig. 1) presented

Table 2 Grey matter density and cortical thickness of occipital gyri of patients and volunteers and correlation (CC) to defects of corresponding visual hemi-field in patients, corrected for age and total intracranial volume

	Sup occ gyrus L	Sup occ gyrus R	Mid occ gyrus L	Mid occ gyrus R	Inf occ gyrus L	Inf occ gyrus R	Cuneus L	Cuneus R	Pericalc. cortex L	Pericalc. cortex R
36 patients, GM density	3.90 ± 0.73*	4.36 ± 0.81	11.17 ± 2.54*	11.81 ± 2.34	6.38 ± 1.09	6.28 ± 0.96	3.83 ± 0.58	4.41 ± 0.57	3.37 ± 0.67	3.47 ± 0.66
36 Patients, CC of GM density to visual hemifield defect	− 0.207	− 0.342*	− 0.301	− 0.172	− 0.298	− 0.183	0.029	− 0.187	0.131	0.130
36 Patients, cortical thickness	2.23 ± 0.35*	2.28 ± 0.36	2.45 ± 0.63*	2.50 ± 0.53*	2.46 ± 0.43*	2.65 ± 0.40	2.25 ± 0.13	2.26 ± 0.17	2.11 ± 0.17	2.07 ± 0.17*
36 patients, CC of cort. thickness to vis. hemifield defect	− 0.043	− 0.238	− 0.161	− 0.276	− 0.096	− 0.108	− 0.032	0.149	0.136	− 0.050
34 controls, GM density	4.26 ± 0.66*	4.67 ± 0.79	12.24 ± 1.72*	12.39 ± 2.09	6.70 ± 0.95	6.69 ± 0.97	4.07 ± 0.55	4.56 ± 0.58	3.63 ± 0.49	3.69 ± 0.57
34 controls, cortical thickness	2.39 ± 0.20*	2.38 ± 0.26	2.73 ± 0.42*	2.75 ± 0.38	2.68 ± 0.40	2.79 ± 0.32	2.29 ± 0.14	2.30 ± 0.16	2.15 ± 0.21	2.17 ± 0.20*

*Significant difference between patients and volunteers and significant correlation to defect of visual hemifield ($p < 0.05$)

a significant cluster ($p < 0.05$, FWE corrected) of reduced density with a maximum at $x = -11$, $y = -96$ and $z = -3$ in the posterior part of the pericalcarine cortex.

From all other 48 cortical areas outside the cortical lobe, which were measured for comparison, only the left posterior cingulated gyrus showed a significant reduction in density in patients before GKRS (− 1.01 units, $p < 0.05$). The mean of grey matter density reduction in all areas outside the occipital lobe was − 0.241 units as compared to a mean of grey matter density reduction in all areas within the occipital lobe of − 0.462 units, and this outside–inside difference was significant ($p < 0.05$).

Differences of cortical thickness between patients and volunteers reached significance as well in the left superior and middle occipital gyrus and the right pericalcarine area ($p < 0.05$). However, patients showed as well significant reductions of cortical thickness in12 areas outside the occipital lobe including the pre- and postcentral gyri, which apparently are unrelated to the visual system. Consequently the parameter "cortical thickness" was excluded from further evaluation.

MRI on follow-up

In all but 2 patients, follow-up MRI scans were available for comparison with pre-operative findings, with an imaging follow-up period of 28.0 months, range 2–72 months, and showed a mean tumor regression of 1.9% per month. Overall tumor control rate was 97.8%, with tumor progression seen in one case only, a pituitary adenoma with intra-tumoral bleeding nearly 18 months after GK treatment.

Follow-up scans after a delay of more than 12 months after GKRS (mean delay 29.5 ± 15.1 months) were available in a subgroup of 22 patients and showed a mean tumor regression of 2.22 ± 2.70 cm^3. Analysis of grey matter density showed a further, but insignificant reduction in all but one occipital area between 1.0% and 2.5%, without significant correlation to reduction of tumor volume (Table 3). The reduction of cortical density at follow-up examination as compared to the scan before GKRS was slightly—but not significantly—higher in areas outside the occipital lobe (mean: − 0.123 units) as than within it (mean: 0.092 units).

Discussion

As hypothesized, occipital grey matter density was reduced in patients with suprasellar tumors and visual field defects due to damage of visual pathways. To our knowledge, this finding has not been reported before and is another argument to treat these growths as soon as possible to prevent this secondary complication. Areas outside the occipital lobe as

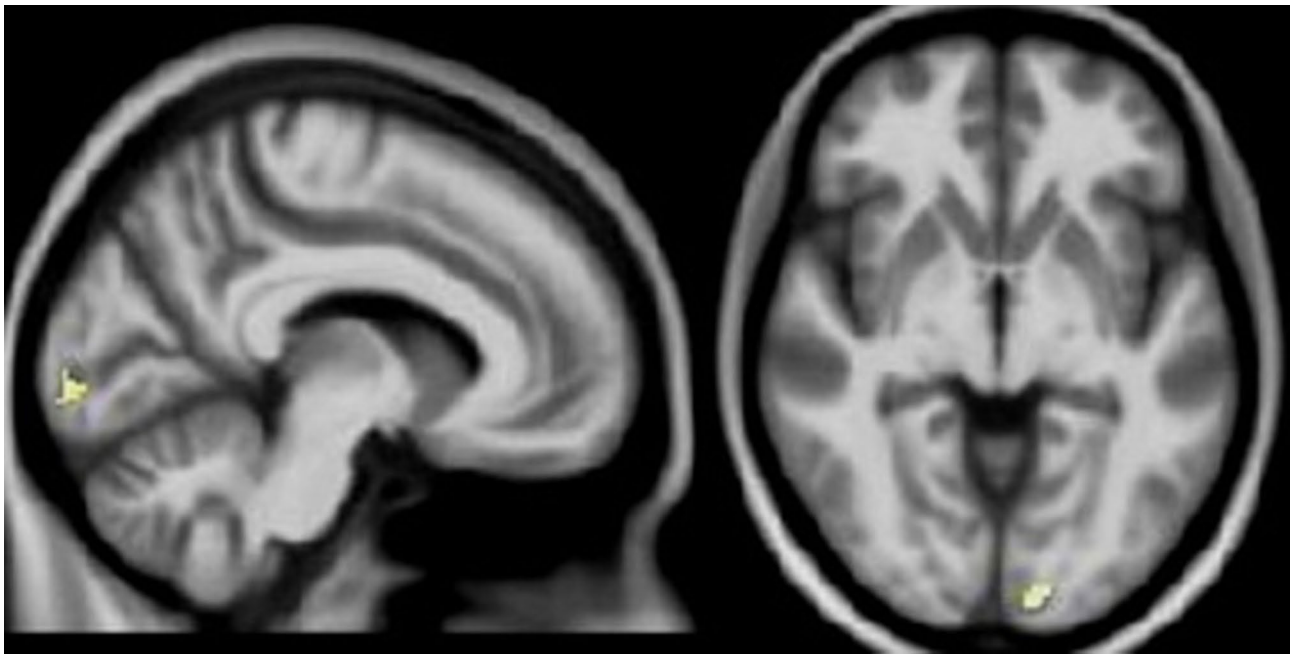

Fig. 1 Analysis of grey matter density. Significant reduction around posterior part of pericalcarine cortex in patients as compared to controls, corrected for patients' age and total intracranial volume. $p < 0.05$, FEW corrected

well showed slight, but insignificant reduction of grey matter density and were affected significantly less than those related to visual functions. The only area where grey matter density was reduced in a similar as within the occipital lobe, was the left posterior cingulated cortex, which has to be shown to be involved in processing of motion stimuli [16].

The reason for the reduction in cortical density in these instances is still a matter of debate. In patients with visual pathway affection, there is accumulating imaging evidence of trans-synaptic degeneration of the visual cortex [10]. In Leber's optic nerve neuropathy, damage to the posterior parts of the visual pathways was demonstrated and attributed to trans-synaptic degeneration secondary to neuroaxonal damage in the retina and optic nerve or to local mitochondrial dysfunction [6].

A significant reduction in grey matter within the posterior region of the occipital cortex has also been demonstrated in adult macular degeneration by VBM to analysis [1]. A negative correlation between volume and severity of visual defects could be demonstrated [17]. However, in contrast to grey matter density, cortical thickness was no reduced or only affected in the V2 area, but not in V1 [3, 18]. Authors speculated that cortical changes in adult macular degeneration could be relatively subtle and might be missed by one of these methods of analysis.

Additionally, the observed neuroanatomical changes in adult macular degeneration might not only be explained by functional deprivation due to the visual field defect, but also to an associated neurodegenerative processes, because more wide-spread atrophic changes have been observed in this condition [2, 19]. In our patients however, we did not see any clinical or imaging signs of degenerative cerebral disease, and all evaluations of the present study were corrected for patients' age to minimize the effect of normal aging.

Kitajima et al. [20] found that the calcarine fissure was increased in width in retinitis pigmentosa patients, notably within anterior and middle regions that normally represent peripheral vision [21]. This corresponds well with the progression of visual deprivation in this disease, which starts in the peripheral visual field and progresses inwards towards the fovea. The fact that we did not observe any retinotopic reduction of grey matter density is easily explained by the inhomogeneity of visual field defects among patients in our study.

The reduction of cortical thickness however was confined to areas related to visual processing and thus appeared to be specifically related to the damage of the visual pathways. The fact, the lesions of the visual pathways can primarily be regarded a white matter lesions, may explain the unexpected finding of a more wide-spread reduction of cortical thickness in patients before GKRS, which was significant in 12 cortical areas outside the occipital lobe. Changes in packing and myelination of subcortical fibers might affect classification of grey-white matter boundaries and influence measurement of cortical thickness in a different way than measurement of cortical density [22]. The wide-spread reduction of cortical thickness patients were showing outside the occipital lobe, could thus be an expression of a general brain affection in

Table 3 Change of grey matter density of occipital gyri, after a delay to FU of more than 12 months, corrected for TIV, as well as correlation (CC) to reduction of tumor volume, corrected for TIV and for delay to follow-up

22 patients, delay to FU > 12 months	Sup occ gyrus L	Sup occ gyrus R	Mid occ gyrus L	Mid occ gyrus R	Inf occ gyrus L	Inf occ gyrus R	Cuneus L	Cuneus R	Pericalc. cortex L	Pericalc. Cortex R
GM density before GKSRS	3.99 ± 0.59	4.46 ± 0.89	11.37 ± 1.67	12.02 ± 2.26	5.72 ± 0.77	5.93 ± 0.99	3.565 ± 0.54	3.80 ± 0.67	3.20 ± 0.63	2.97 ± 0.76
GM density after GKSRS	3.95 ± 0.64	4.41 ± 0.93	11.23 ± 1.97	11.88 ± 2.28	5.62 ± 0.88	5.81 ± 1.12	3.58 ± 0.67	3.75 ± 0.72	3.12 ± 0.72	2.94 ± 0.73
CC of GM density change to change of Tu volume	− 0.006	− 0.093	− 0.163	− 0.153	0.335	0.246	0.144	− 0.147	0.091	0.163

Changes of grey matter density and of CCs were not significant

patients with tumors of the sellar region, who had been operated before in more than two-thirds of cases. Memory deficits have been described in this condition even before operation and/or radiation [23]. Because the focus of the present study was confined to the visual system and the study was conducted in a retrospective way, reasons for the changes of cortical thickness remain speculative.

As far as the follow-up findings of our study are concerned, results of the present study are not in favor of recuperation. In the ideal case, GKRS induces tumor regression, the less severely compressed parts of the optic pathways might regain some function and increased sensory input could reverse cortical atrophy. An important prerequisite for cortical "recovery" is a preserved neuronal plasticity. Indeed, studies on brain plasticity in adult humans related to extensive training have reported increases in grey matter volume [24, 25], that may be explained by axonal sprouting or increased spine density in those structures critical for a certain skill or task performance [26].

Moreover, imaging results with determination of magnetization transfer ratio results suggested that one mechanism for this reorganization may be related to increased myelination of intracortical neurons or of fibers conveying information to and from remote locations [27]. The circuitry underlying the association field includes a plexus of long range horizontal connections formed by cortical pyramidal cells. These connections undergo rapid and exuberant sprouting and pruning in response to change of sensory input, which can account for the topographic reorganization following retinal lesions [28].

Follow-up reports about imaging of the occipital cortex after treatment of lesions of the retina and/or optic pathways are rare: A voxel-based morphometry study after cataract surgery revealed a regional expansion of grey matter volume in the area V2 contralateral to the operated eye during the 6-week period after surgery [11]. The authors concluded that activity-dependent cortical plasticity was preserved in the ageing visual cortex and might have been triggered by restoration of impaired vision. However, grey matter changes correlated more with improved parity of visual acuity between the two eyes than with improved vision of the operated eye, and the question which neurobiological mechanism drives structural plasticity in V2, remained open.

In our study however, there was no increase in grey matter density. Unfortunately, visual field controls after GKRS were not available in most of our patients, and reliable relations between the clinical course and development of alterations of the visual cortex cannot be drawn. However, the fact that during clinical follow-up of the subgroup of 22 patients, in whom follow-up scans were analyzed at least 12 months after GKRS, 39% of patients reported an improvement and another 47% no further deterioration of their vision after

GKRS, might support a less pessimistic view at least in the clinical sense.

Conclusion

As in other peripheral lesions of the optic system, damage of the optic nerves, chiasm and tracts due to compression by suprasellar tumors affects the visual cortex and induces a reduction of grey matter density which—in contrast to some clinical recuperation—does not recuperate after successful GKRS. However, a follow-up study in a prospective design including only patients without previous operations, which might have injured these structures in an irreversible way, together with consecutive ophthalmologic examinations after GKRS including assessments of visual fields is needed to confirm this conclusion or show under which conditions exceptional recuperations of the visual cortex are possible. In addition, the unexpected finding of a more general affection of cortical thickness in patients with pituitary tumors could be looked into more closely in order to identify and possibly prevent any predisposing factors.

Author contributions Conception and design: Peter Stoeter, Herwin Speckter. Data collection: Jose Bido, Remberto Escoto, Cesar Gonzalez, Giancarlo Hernandez, Jairo Oviedo, Diones Rivera, Luis Suazo, Santiago Valenzuela, Peter Stoeter, Herwin Speckter. Data analysis and interpretation: Jose Bido, Remberto Escoto, Bernd Foerster, Cesar Gonzalez, Giancarlo Hernandez, Jairo Oviedo, Diones Rivera, Luis Suazo, Santiago Valenzuela, Herwin Speckter, Peter Stoeter. Manuscript writing: Peter Stoeter, Herwin Speckter, Remberto Escoto. Final approval of manuscript: Jose Bido, Remberto Escoto, Bernd Foerster, Giancarlo Hernandez, Jairo Oviedo, Diones Rivera, Luis Suazo, Santiago Valenzuela, Cesar Gonzalez, Peter Stoeter, Herwin Speckter.

Compliance with ethical standards

Conflict of interest All authors declares that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has been approved by the ethic committee of CEDIMAT (CEI-290).

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

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