HELLENIC NEUROSURGERY

June – September 2023. Volume 1, Number 1

Contents

HELLENIC NEUROSURGERY

PUBLISHED FOURTH MONTHLY /
OFFICIAL JOURNAL OF THE HELLENIC NEUROSURGICAL SOCIETY

Address
15 Meandrou Str, 11528 Athens
Tel.: +30 210 7255459
e-mail: hnss@otenet.gr, hnss1966@gmail.com

Instruction To Authors

HELLENIC NEUROSURGERY

Hellenic Neurosurgery is the official journal of the Hellenic Neurosurgical Society. It is published with a frequency of 3 issues per year (every 4 months). It is a peer-reviewed, open-access, which doesn't charge publication fees. The field of interests are clinical and experimental neurosurgery, evolution and history of neurosurgery, and translational research in neurosciences. The official language of the journal is English. The journal accepts the following types of articles: Original studies, Case reports, Review articles, Technical notes, Historical & Socio-economical articles, Letters to the Editor and Book reviews. The journal uses single-blind peer review. All submitted manuscripts are initially assessed by an editor for suitability check. Papers considered suitable for the journal are then sent for review to independent expert reviewers to evaluate the scientific quality and novelty of the manuscript. Submitted manuscripts should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE). Papers are accepted for evaluation on the understanding that they are original and are not under concurrent consideration by another journal.

HOW TO SUBMIT

Manuscripts should be submitted by e-mail to the following address: hnss@otenet.gr, hnss1966@gmail.com Questions about submission should be sent to the Editorial Office to the same e-mail address.

ARTICLE TYPES

This Journal publishes several different article types.

ORIGINAL ARTICLES

Full-length manuscripts on the scope and purpose of the journal will be considered for publication. As a rule, papers should be divided into sections (Introduction, Materials and Methods, Results, Discussion, Conclusion, References), and should not exceed 3.500 words (excluding abstract and keywords, figures, tables, captions and references) with maximum number of 50 references and no more than 8 authors. Original articles can have a maximum of 8 figures or tables.

CASE REPORTS

To be considered for publication, case reports should present rare and unusual cases of interest. Case reports should be divided into sections (Introduction, Case Report, Discussion, References) and should not exceed 1.500 words (excluding abstract and keywords, figures, tables, captions and references). An unstructured abstract not exceeding 150 words must be included. Case reports can have a maximum of 4 figures or tables. Case reports should not have more than 15 references and no more than 4 authors.

Review Articles (including systematic reviews and meta-analyses)

Review articles must not exceed 6.000 words (excluding abstract and keywords, figures, tables, captions and references) with maximum 70 references and no more than 6 authors. Systematic reviews and meta-analyses should follow the guidelines outlined in the PRISMA statement.

TECHNICAL NOTES

Manuscripts on technical notes should have an unstructured Abstract and corresponding sections as needed.

Historical & Socio-economical Articles

Historical or socio-ecomonical articles of neurosurgical interest may be considered for publication. These articles must not exceed 6.000 words (excluding abstract and keywords, figures, tables, captions and references).

LETTERS TO THE EDITOR

Letters to the Editor may be comments from readers related to articles published in the journal over the last 6 months or other topics of interest including unpublished original research. The letter should be no longer than 500 words (excluding keywords, figures, tables, captions and references) with no more than 5 references and maximum 2 authors. No abstract is needed.

BOOK REVIEWS

Reviews of books are invited by the editorial board. The maximum length is 800 words of text (not including references) with maximum 2 authors.

MANUSCRIPT PREPARATION

The submitted manuscript should be accompanied by a cover letter which will include the name, address, and e-mail address of the corresponding author, who is responsible for the communication with co-authors on the progress and final approval of the submitted manuscript. The cover letter should also include a statement that the manuscript is not under consideration elsewhere, and that the corresponding author certifies that all co-authors have seen and approved the submitted manuscript.

TITLE PAGE

The title page should include the Title of the manuscript and the author details. All authors should include their full name and affiliation on the first page of the manuscript. One author should be identified as the corresponding author providing full contact information (Name, title, institution, address, telephone, e-mail). Statement on potential conflicts of interest and sources of support of any form should be included. The role of each contributing author should be also specified.

ABSTRACT

Submitted manuscripts should contain a structured abstract of no more than 250 words with the following headings: objective, material and methods, results, conclusion. An abstract in Greek should be provided. Case reports, Historical, Socio-economical manuscripts and book reviews should have an unstructured abstract and should be maximum 150 words as previously described. For Letters to the Editor no abstract is needed.

KEYWORDS

Please provide 4 to 5 keywords, using American spelling and avoiding general and plural terms and multiple concepts to be used for indexing purposes.

TEXT

Manuscripts should be submitted in Word. Please use normal, plain font (e.g., 12-point Times New Roman, double spaced) with numbered pages. The manuscript should have the following order: main text; acknowledgments; references.

ABBREVIATIONS

Abbreviations should be defined in full when first mention and used thereafter.

REFERENCES

References should be listed in the reference list in order they appear in the text. Within text they should appear in in square brackets, i.e., [1,2], [1,2, 4-8] or [1-3]. List all the authors of the reference. The titles of journals, textbooks, or book chapters should be abbreviated according to the style used in Index Medicus. The journal permits accepted but not yet published articles to be included in the references list as "(in press)".

EXAMPLES OF REFERENCE STYLE:

JOURNAL

Liu W, Ni M, Jia W, Wan W, Tang J. Evidence-based medicine in neurosurgery: an academic publication view. Neurosurg Rev. 2018; 41: 55-65.

BOOK

Author 1; Author 2. Book Title or Title of the chapter and book title, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154–196.

INTERNET SOURCE

Reference should be provided in full, including both the title of the site and the URL, and the date the site was accessed

FIGURES

Figures should be of high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color) and submitted as TIFF or JPEG files. Please ensure that each figure has a caption.

TABLES

Tables should be submitted as editable text (preferable Word) and not as images.

Tables should be placed on a separate page(s) at the end of the text after the reference list. Number tables consecutively in accordance with their appearance in the text

VIDEOS

Videos should be of high quality, no more than 10 minutes and less than 1GB. Accepted video file types is mp4.

PUBLICATION CHARGES

There are no publication charges.

ETHICS IN PUBLISHING

STUDIES IN HUMANS

Manuscripts submitted for publication must contain a statement that all human and studies have been approved by the relevant ethics committee/Institutional Review Board, and were therefore carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The approval reference number should be included.

A statement mentioning that the experimental protocol was approved by the Institutional Review Board, and that all subjects gave informed consent should be provided. If case Institutional Review Board approval or patient consent were not obtained, authors must offer an explanation.

STUDIES IN ANIMALS

Manuscripts that report animal experiments must include a statement stating that the study was approved by the Institutional Review Board and that the animal care fulfilled the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (Washington: National Academy Press, 1996).

PATIENT CONSENT

No identifiable protected health information of any person may be included in any manuscript submitted to or published to Hellenic Neurosusgrey unless the information is essential for the published work and the patient has provided written informed consent.

Special attention to images that contain identifiable individual patient characteristics or data head or face characteristics, or where the individual's name or other personal details are mentioned. Special care should be taken when children are concerned.

PLAGIARISM

Plagiarism is scientific misconduct and will be addressed as such. The journal may use plagiarism detection software to screen the submissions. If plagiarism is identified, the Committee on Publication Ethics (COPE) guidelines on plagiarism will be followed. In case of extensive plagiarism, appropriate actions will be taken by the journal.

OTHER

Cases of academic fraud, duplicate and redundant publication will be managed according to COPE Guidelines.

PREVIOUSLY PUBLISHED WORK

The authors are responsible to obtain permission to reproduce any previously published material (i.e. tables, figures), and are responsible for covering any related costs.

Transfer of copyright to the ''Hellenic Neurosurgery'' is a condition of publication.

ACKNOWLEDGMENTS

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be fully provided.

ARTICLE REVISIONS

Submission of a revised manuscript should include a Revision Letter or Cover Letter (with detailed responses to reviewers). Revised Manuscripts should have tracked or highlighted changes including also the revised Figures and/or Tables.

Restarting Hellenic Neurosurgery

George A. Alexiou [1], Parmenion P. Tsitsopoulos [2]

1. Department of Neurosurgery, University of Ioannina, Ioannina, Greece
2. Department of Neurosurgery, Hippokration General Hospital, Aristotle University School of Medicine, Thessaloniki, Greece.

We are delighted to present the first issue of the Hellenic Neurosurgery, the official journal of the Hellenic Neurosurgical Society. The journal restarts after a long pause. The main goal is to index the journal to the main international scientific databases and to achieve a worldwide recognition. The journal will be initially published every 4 months and is peer-reviewed, open-access, without any publication fees. However, this may subject to change depending on the flow of the submissions. The official language of the journal is English. The current issue includes 4 original articles and 2 case reports. The original articles focus on spine and neuro-oncology and the case reports on neurosurgery-related infections and neuro-oncology. All from Greek institutions.

Besides Greek neurosurgeons, we also encourage neurosurgeons from around the globe to submit their research. We also invite colleagues working on related fields to consider Hellenic Neurosurgery for the publication of their work. Finally, we would like to express our sincere gratitude to our contributors, the executive board of the Hellenic Neurosurgical Society and the editorial board of the journal for their support and we hope that the rebirth of Hellenic Neurosurgery will move forward to steady growth to become a high quality journal. This contribution of all is crucial for the success of the journal.

Correspondence:

Alexiou GA, Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece.
Tel.: +30 6948525134
Email: galexiou@uoi.gr

TITLE

Surgical approaches for orbital tumors and pseudotumor. Case series and review of the literature

Georgios Stranjalis[1], Christos Koutsarnakis[1], Pantelis Stavrinou[1], Sotirios Veranis[2], Lampis Stavrinou[3]

[1.] 1st Department of Neurosurgery, University of Athens, Evangelismos Hospital, Athens, Greece
[2.] 251 General Air Force and Reserve Hospital, Athens, Greece
[3.] 2nd Department of Neurosurgery and Neurotraumatology University of Athens, Attikon Hospital, Athens, Greece

KEYWORDS
Orbital tumors, exophthalmos, Spheno-orbital meningiomas, cavernous angioma

ABBREVIATIONS
IG: immunoglobulin, SOM: Sphenorbital meningiomas, CNS: Central Nervous System, MRI: Magnetic Resonance Imaging

ACKNOWLEDGMENTS
To Ms Loufardaki Aggeliki and Mr Spyros Siametis for providing the DICOM imaging of the patients and Surgical Video Editing files

ETHICAL APPROVAL
The study was approved from institutional review board

CORRESPONDENCE
Veranis Sotiris 251 General Air Force and Reserve Hospital, Kanellopoulou Katehaki 3-5, 11525, Athens, Greece, e-mail: veranissotiris@gmail.com

ABSTRACT

Objective: Retrospective analysis of a clinical series of patients that underwent surgical removal of orbital tumors.

Material and Methods: In this article, we present a clinical case series consisting of 30 patients which underwent surgical removal of orbital tumors between 2010 – 2021 in the Neurosurgical Department of "Evangelismos" Hospital.

Results: Preoperative symptoms were exophthalmos in 17 patients, diplopia in 8, visual acuity decline in 6, eyelid edema 1, eye pain in 2 patients. Surgical approach to the lesion was supraorbital in 17 patients, lateral orbitotomy in 12 patients and eye exenteration in 1. Twelve patients were male (40%) and eighteen (60%) female and average age was 46,9 years old. Histological diagnosis was made in 97 % of the specimens (29/30) and these lesions were meningiomas 26% (8/30), inflammatory 10% (3/30), cavernous hemangiomas 13,3% (4/30), neurofibroma 6,67% (2/30), schwannoma 3,3% (1/30), mucocele 6,67% (2/30), solitary fibrous tumor 20% (6/30), melanoma 3,3% (1/30), adenocarcinoma 3,3% (1/30), Histiocytosis Langerhans 3,3% 1/30, non-diagnostic 3,3% (1/30). Postoperative complications occurred in 6 patients (20%), and the most common was transient diplopia.

Conclusion: Surgical excision of orbital tumors could achieve local tumor control with reasonable complication rate and no morbidity.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι όγκοι του κόγχου στον ενήλικο πληθυσμό μπορούν να κατηγοριοποιηθούν με βάση τη θέση και τον ιστολογικό τύπο. Αυτές οι βλάβες μπορεί να είναι είτε καλοήθεις είτε κακοήθεις. Το σηραγγώδες αιμαγγείωμα είναι ο πιο συχνός καλοήθης όγκος των ενηλίκων. Η χειρουργική αφαίρεση είναι η θεραπεία πρώτης εκλογής στις περισσότερες από αυτές τις βλάβες.

Υλικό και Μέθοδος: Σε αυτό το άρθρο, παρουσιάζουμε αναδρομικά μια σειρά κλινικών περιστατικών αποτελούμενη από 30 ασθενείς που υποβλήθηκαν σε χειρουργική αφαίρεση όγκων του οφθαλμικού κόγχου μεταξύ των ετών 2010 – 2021 στη Νευροχειρουργική Κλινική του Νοσοκομείου «Ευαγγελισμός».

Αποτελέσματα: Προεγχειρητικά τα συμπτώματα ήταν εξόφθαλμος σε 17 ασθενείς, διπλωπία σε 8, μείωση της οπτικής οξύτητας σε 6, οίδημα βλεφάρου σε 1, οφθαλμικό άλγος σε 2 ασθενείς. Η χειρουργική προσέγγιση της βλάβης ήταν υπερκόγχια οστεοτομία σε 17 ασθενείς, η πλάγια κογχοτομή σε 12 ασθενείς και η οφθαλμική εξεντέρωση σε 1. Δώδεκα (40%) ασθενείς ήταν άνδρες και 18 (60%) γυναίκες με μέση ηλικία τα 46, 9 έτη. Η ιστολογική διάγνωση έγινε στο 97% των δειγμάτων (29/30) και αυτοί οι όγκοι ήταν μηνιγγιώματα στο 26% (8/30), φλεγμονώδους αιτιολογίας κατά 10% (3/30), σηραγγώδη αιμαγγειώματα στο 13,3% (4/30), νευροϊνώματα στο 6,67% (2/30), σβάννωμα στο 3,3% (1/30), βλεννοκήλη 6,67% (2/30), μονήρης ινώδης όγκος 20% (6/30), μελάνωμα 3,3% (1/30), αδενοκαρκίνωμα 3,3% (1/30), ιστιοκυττάρωση Langerhans 3,3% (1/30), μη διαγνωστική βιοψία στο 3,3% (1/30). Επιπλοκές προέκυψαν σε 6 ασθενείς (20%) και η πιο συχνή μετεγχειρητική επιπλοκή ήταν η παροδική διπλωπία.

Συμπεράσματα: Η χειρουργική εκτομή όγκων του οφθαλμικού κόγχου επιτυγχάνει έλεγχο της νόσου, με μικρό ποσοστό επιπλοκών και χωρίς νοσηρότητα.

INTRODUCTION

Orbital tumors in the adult population are categorized based on location and histologic type. These lesions may be either benign or malignant. According to Wu et al [1] 64% are benign and 46% are malignant. Cavernous malformations are the most common benign adult orbital tumors. Surgical removal is the first line treatment in most of these lesions. Endoscopic transnasal, transorbital or transmaxillary approaches are emerging minimal invasive techniques [1,14] as opposed to open lateral or supraorbital orbitotomies. Spheno-orbital meningiomas are a separate

entity that is challenging for the Neurosurgeon and require a combination of craniotomy and orbitotomy for surgical excision. [2-6]

PURPOSE

The aim of this study is a retrospective analysis of a clinical series of patient that underwent surgical removal of orbital tumors in the 1st Neurosurgical Department of Evangelismos Hospital and review of relevant literature.

MATERIALS AND METHODS

Retrospective collection of clinical data has been approved from the Head of the 1st Neurosurgical Department of Evangelismos Hospital. Between the years 2010-2021 a total of 30 patient harboring space occupying lesions of the orbit were operated in the 1st Neurosurgical Department of Evangelismos Hospital. Demographic and clinical data are presented in Table 1. All patients have been operated in Evangelismos Hospital by the leading author. Surgical excision of the tumor was the first line of treatment. In all tumors, microsurgical techniques had been used and surgical videos were recorded for further analysis and review purposes.

There were at least one follow up imaging study available before discharging the patient from the hospital to evaluate postoperative result. All the patients included in the study had a regular follow up at the outpatient Neurosurgical clinic of the Evangelismos Hospital.

The scientific council of Evangelismos Hospital has approved the publication of the study.

	AGE	SEX	CLINICAL SYMPTOMS	PATHOLOGY	SURGICAL APPROACH	RESULTS	COMPLICATIONS	FOLLOW UP
1	62	M	Exophthalmos	IG4 FIBROINFLAMMATORY LESION	SUPRAORBITAL	TOTAL EXCISION	DIPLOPIA	NO RECURRENCE
2	62	M	Exophthalmos Diplopia	CAVERNOUS HEMANGIOMA	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
3	31	F	Left Eye Visual Acuity decline 8/10 papilledema	NECROTIC GRANULOMA	LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
4	36	F	Diplopia	NEUROFIBROMA GRADE I	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
5	44	M	Exophthalmos	SOLITARY FIBROUS TUMOR GRADE III	LATERAL ORBITOTOMY SUBTEMPORAL CRANIOTOMY	TOTAL EXCISION	EYELID OEDEMA, TRANSIENT BLURRY VISION	NO RECURRENCE
6	70	M	Exophthalmos, diplopia	MENINGIOMA MIDDLE CRANIAL FOSSA WITH EXTENSION TO THE ORBIT	RIGHT TEMPORAL CRANIOTOMY AND LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
7	69	M	Anterior Cranial fossa abscess complicated left eye exenteration for lacrimal gland tumor	ABSCESS	PTERIONAL CRANIOTOMY PLUS SUPRAORBITAL OSTEOTOMY	SUBTOTAL EXCISION	-	CURED
8	70	F	Exophthalmos Temporal lump	MENINGIOMA MENINGOTHELIAL TYPE GRADE I, MIDDLE FOSSA WITH SUPRAORBITAL EXTENSION	PTERIONAL PLUS SUPRAORBITAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
9	51	F	Exophthalmos, eye pain	SOLITARY FIBROUS TUMOR GRADE III	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
10	62	F	Progression of known tumor during observation period	SOLITARY FIBROUS TUMOR	LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
11	29	F	Loss of vision, exophthalmos	MENINGIOMA MENINGOTHELIAL GRADE I	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
12	55	F	Recurrence of previously excised meningioma	MENINGIOMA MENINGOTHELIAL TYPE GRADE II	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
13	48	M	Eye pain, exophthalmos	ORBITAL EXTENSION OF ADENOCARCINOMA OF THE MAXILLARY SINUS	SUPRAORBITAL	PARTIAL EXCISION	ABSCESS	
14	46	F	Headache, third nerve palsy, loss of vision on the right eye	CAVERNOUS HEMANGIOMA	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
15	17	M	Eyelid edema	HISTIOCYTOSIS LANGERHANS	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
16	43	F	Exophthalmos, blurry vision, diplopia	MELANOMA	PTERIONAL CRANIOTOMY PLUS LATERAL AND SUPRAORBOTAL ORBITOTOMY	TOTAL EXCISION	LATERAL RECTUS PARESIS	NO RECURRENCE
17	55	F	Exophthalmos, diplopia	MENINGIOMA GRADE III	FRONTAL CRANIOTOMY LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
18	34	F	Right eye vision decline	NON-DIAGNOSTIC BIOPSY	LATERAL ORBITOTOMY	SUBTOTAL EXCISION	-	-
19	47	F	Exophthalmos	SCHWANOMMA GRADE I	SUPRAORBITAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
20	49	M	Exophthalmos	CAVERNOUS HEMANGIOMA	LATERAL ORBITOTOMY	TOTAL EXCISION	SUPERIOR RECTUS PARESIS	NO RECURRENCE
21	45	M	Eye pain, diplopia	SOLITARY FIBROUS TUMOR GRADE I	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
22	23	F	Eyelid ptosis, loss of vision	CAVERNOUS HEMANGIOMA	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE

	AGE	SEX	CLINICAL SYMPTOMS	PATHOLOGY	SURGICAL APPROACH	RESULTS	COMPLICATIONS	FOLLOW UP
23	38	F	Headache, Visual Acuity decline	MENINGIOMA MENINGOTHELIAL TYPE I	SUPRAORBITAL	TOTAL EXCISION	OPTHALMOPLEGIA	NO RECURRENCE
24	56	F	Exophthalmos	MUCOCELE	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
25	40	F	Visual acuity decline, exophthalmos	SOLITARY FIBROUS TUMOR GRADE II	SUPRAORBITAL	TOTAL EXCISION	-	NO RECURRENCE
26	21	M	Tumor recurrence	NEURINOMA	EXENTERATION	TOTAL EXCISION	-	NO RECURRENCE
27	58	M	Exophthalmos	SOLITARY FIBROUS TUMOR STAGE I	LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
28	50	F	Eye pain	MUCOCELE	LATERAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE
29	46	F	Exophthalmos	MENINGIOMA GRADE I	LATERAL ORBITOTOMY	SUBTOTAL EXCISION	-	NO RECURRENCE
30	50	M	Exophthalmos	MENINGIOMA GRADE I	LATEAL ORBITOTOMY	TOTAL EXCISION	-	NO RECURRENCE

Table 1. Demographic and surgical data of the patients that were included in the retrospective study.

RESULTS

Between 2001-2021 a total of 30 patients harboring space occupying lesions of the orbit were operated in the Neurosurgical Department of Evanggelismos hospital. Eleven (40%) patients were male and 16 (60%) female, mean age was 46,7 years. Preoperative symptoms were exophthalmos in 17 patients, diplopia in 8, visual acuity decline in 6, eyelid edema 1, eye pain in 1 patient. Surgical approach to the lesion was supraorbital in 17 patients, lateral orbitotomy in 12 patients and eye exenteration in 1. Subtotal excision occurred in three cases. Histological diagnosis was made in 96% of the specimens (29/30) and these lesions were meningiomas 22% (8/30), inflammatory 11% (3/30), cavernous angiomas 15%(4/30), neurofibroma 7% (2/30), schwanomma 3% (1/30), mucocele 4% (1/30), solitary fibrous tumor 7% (6/30), melanoma 4% (1/30), adenocarcinoma 4% (1/30), Histiocytosis Langerhans 4% 1/30, non-diagnostic 4% (1/30). The most common postoperative complication was transient diplopia in 6 cases. One patient with melanoma received postoperative adjuvant chemotherapy.

CASE PRESENTATION

Case 1

A 47-year-old female patient presented with exophthalmos and eyelid oedema. A well-defined tumor was removed through a supraorbital craniotomy and histology diagnosed Schwanomma grade I. Postoperative MRI showed gross [Figure 1-4] total resection and the aesthetic result was also excellent.

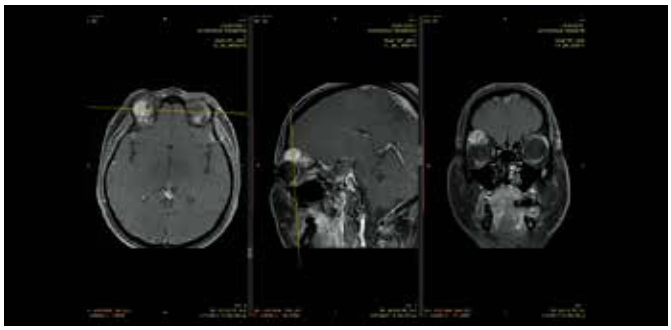

Figure 1. *Preoperative MRI T1 sequence with contrast depicting a right orbital tumor that causes down-migration of the eye (blue arrows).*

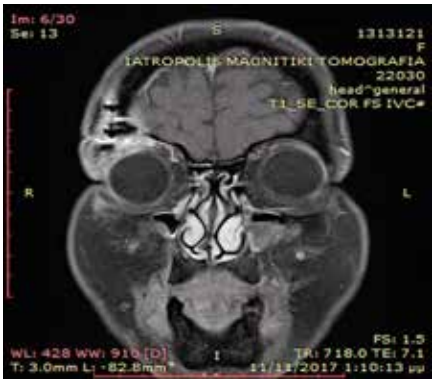

Figure 2. *Postoperative Coronal section of the brain MRI in T1 sequencing with contrast depicting gross total removal of the tumor (yellow arrow).*

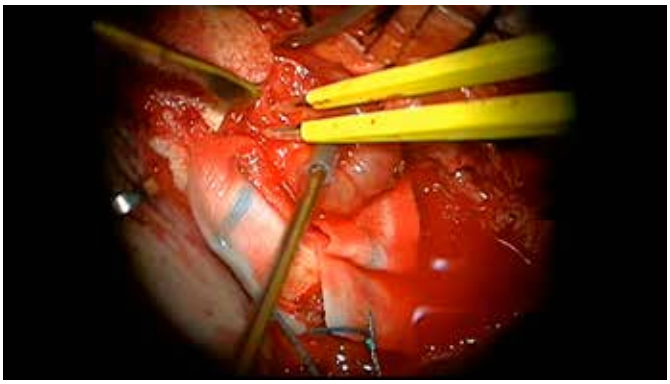

Figure 3. *Intraoperative photo during the last step of coagulation and excision of the schwanomma.*

Figure 4. *Postoperative cosmetic result of the right supraorbital skin incision.*

DISCUSSION

In our study we utilized the lateral and supraorbital approaches to assess orbital pathology. Tumors located in the inferomedial quadrant of the orbit demanded extended approaches and presented difficulties in tumor removal. Wu et al [1] suggested navigational trans maxillary endoscopic approach for inferomedial tumors of the orbit. The maxillary sinus was applied as a surgical corridor to assess the orbital floor and navigation was used to increase accuracy while repairing the orbital floor with biomembrane and titanium mesh reinforcement if it was unnecessary [1]. Yao et all present a review of endoscopically treated orbital tumors. In this review authors suggest that orbital tumors are suitable for endoscopic removal through the ethmoid, maxillary, or sphenoid sinus if they were in the inferior medial quadrant of the orbit and that optic nerve is an anatomic landmark that prevents the lateral extension of these approaches [14].

Sphenorbital meningiomas (SOM) are challenging tumors and they usually require combined cranial and orbital approaches. Agi et al [3] reported 20 patients with SOM meningiomas. Subtotal resection was reported in nine out of 20 patients and complications such as postoperative diplopia 50% and surgical infection 5% were also reported. These results are comparable with the results in our study. Furthermore, they described the Alberta standardized orbital technique which consists of a combined cranial and orbital extension. Before craniotomy they inserted two bridle sutures to the superior rectus and lateral rectus muscles which are used later during the surgery to pull and identify the muscle in respect to the meningioma. In addition to that they used frozen section confirmation to define the borders of meningioma and periorbita, meningioma and muscle interface and meningioma and lacrimal gland [3]. Young et al4 reported a series of 24 patients with SOM. They also noted hyperostosis in one patient as we did observe in our series, and they used fronto-temporal and lateral orbitotomy for surgical excision. They also used extradural clinoidectomy to decompress the optic nerve laterally. Terrier et al [5] reported 130 patients with SOM. Simpson grade I or II achieved in 74.6% of the patients. They suggested that SOM require a long term follow up because of a delayed high rate of recurrence. Hyperostosis is a common feature of SOM according to their findings. Avila et al [2] also reported orbital osteomas related to Gardner's syndrome without meningioma. It is also noteworthy that they observed in six patients (4.6%) that transient hyperpathia of trigeminal nerve postoperatively mostly in V1 and V2 division. Patient treated with carbamazepine and observed for 6 to 9 months. Kong et al6 reported results of endoscopic transorbital superior eyelid surgery for SOM. Although the overall gross total resection rate of these tumors where around 51.2% they suggested that this technique is useful especially if it is combined with lateral orbitotomy. Limiting factors affecting gross total resection were temporal and sub temporal fossa involvement and glomus type of tumor as opposed to the more favorable en plaque SOM. Ore CLD et al [7] defined safe and dangerous zones for bony resection of hyperostosis that is usually related to SOM [7,8]. Safe zones were regarded superior and lateral orbital walls, pterion, zygoma and lateral middle fossa. Dangerous zones that limit resection included orbital rim, medial and inferior orbital walls, sphenoid, and ethmoid sinus walls, intraconal orbit, petrous and sphenoid bones medial to the foramen rotundum, ovale and spinosum and posterior petrous bone around the temporomandibular joint.

Brum et al [9] reported eight cases of solitary fibrous tumor of the orbit and the CNS. They suggested that these are neuropathologically diverse tumors and longer follow up periods are needed to understand their biological behavior.

Calandriello et al [10] in their review of cavernous venous malformation of the orbit, previously called cavernous hemangioma suggested that this is the most common primary orbital lesion of adults. In our study hemangiomas where not the most common tumors and this fact could be explained by a referral bias, because our center is a tertiary Neurosurgical Department, and a variety of more complex tumors are being referred [10].

In our study, we used various methods of reconstructing the cranium and orbit walls. We used titanium plates and titanium mesh combined with a biomaterial to cover any dura or periorbita defect. Weizman et al [11] in their review proposed an algorithm regarding orbital reconstruction after orbital tumor removal. The main points were that exenteration required various flaps to cover the orbit. Furthermore, removal of orbital walls or skull base required reconstruction using titanium mesh and biomaterial. Small defects were treated without reconstruction.

Chen et al [12] in their review of IG-4 related disease describes the lacrimal gland as the most common site of involvement. According to Devron et al [13], orbital inflammatory and lymphoid lesions account for 20% of orbital biopsies.

Orbital schwannoma is a rare tumor which depicts slow growth pattern and complete surgical resection leads to very rare recurrence [15]. The most frequent approaches for these tumors are lateral or superior orbitotomies. Clinical presentation is usually painless non pulsatile ocular proptosis. MRI is the imaging modality of choice to distinguish from cavernous angiomas and meningiomas.

CONCLUSIONS

Orbital tumors are usually benign lesions and surgical treatment is the first line treatment of choice in most cases. In our series depicted results of orbital tumor removal cases using the supraorbital, the lateral orbitotomy approaches combined with pterional approach in some cases of intracranial extension of the tumor. Gross total tumor removal achieved in most cases. We concluded that surgical excision of orbital tumors could achieve local tumor control with reasonable complication rate and no morbidity.

REFERENCES

1. Wu CH, Ho YY, Liu TL, Wu TY, Cheng HC, Tsai CC. Navigational Transmaxillary Endoscopic Approach for Inferomedial Tumors. Frontiers in Oncology. 2022;12. Accessed July 19, 2022. https://www.frontiersin.org/articles/10.3389/fonc.2022.804070

2. Avila SA, Nguyen G, Wojno T, Kim HJ. Orbital osteomas associated with Gardner's syndrome: a case presentation and review of literature. Orbit. 2022;0(0):1-6. doi:10.1080/01676830.2022.2080231

3. Agi J, Badilla J, Steinke D, Mitha AP, Weis E. The Alberta standardized orbital technique in the management of spheno- orbital meningiomas. European Journal of Ophthalmology. 2021;31(5):2686-26

4. Young J, Mdanat F, Dharmasena A, et al. Combined neurosurgical and orbital intervention for spheno-orbital meningiomas - the Manchester experience. Orbit. 2020;39(4):251-257. doi:10.1080/01676830.2019.1673782

5. Terrier LM, Bernard F, Fournier HD, et al. Spheno-Orbital Meningiomas Surgery: Multicenter Management Study for Complex Extensive Tumors. World Neurosurgery. 2018;112:e145-e156. doi: 10.1016/j.wneu.2017.12.182

6. Kong DS, Kim YH, Hong CK. Optimal indications and limitations of endoscopic transorbital superior eyelid surgery for spheno-orbital meningiomas. Journal of Neurosurgery. 2020;134(5):1472-1479. doi:10.3171/2020.3.JNS20297

7. Ore CLD, Magill ST, Rubio RR, et al. Hyperostosing sphenoid wing meningiomas: surgical outcomes and strategy for bone resection and multidisciplinary orbital reconstruction. Journal of Neurosurgery. 2020;134(3):711-720. doi:10.3171/2019.12.JNS192543

8. Marcus H, Schwindack C, Santarius T, Mannion R, Kirollos R. Image-guided resection of spheno-orbital skull-base meningiomas with predominant intraosseous component. Acta Neurochir. 2013;155(6):981-988. doi:10.1007/s00701-013-1662-8

9. Brum M, Nzwalo H, Oliveira E, et al. Solitary fibrous tumors of the orbit and central nervous system: A case series analysis. Asian Journal of Neurosurgery. 2018;13(2):336. doi:10.4103/ajns.AJNS_111_16

10. Calandriello L, Grimaldi G, Petrone G, et al. Cavernous venous malformation (cavernous hemangioma) of the orbit: Current concepts and a review of the literature. Survey of Ophthalmology. 2017;62(4):393-403. doi: 10.1016/j.survophthal.2017.01.004

11. Weizman N, Horowitz G, Gil Z, Fliss DM. Surgical Management of Tumors Involving the Orbit. JAMA Otolaryngology–Head & Neck Surgery. 2013;139(8):841-846. doi:10.1001/jamaoto.2013.3878

12. Chen LYC, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. Haematologica. 2019;104(3):444-455. doi:10.3324/haematol.2018.205526

13. Char DH. Management of Orbital Tumors. Mayo Clinic Proceedings. 1993;68(11):1081-1096. doi:10.1016/S0025-6196(12)60902-1

14. Yao WC, Bleier BS. Endoscopic management of orbital tumors. Current Opinion in Otolaryngology & Head and Neck Surgery. 2016;24(1):57-62. doi:10.1097/MOO.0000000000000215

15. Imaging characteristics and surgical management of orbital neurilemmomas. Accessed July 19, 2022. http://www.ijo.cn/gjyken/ch/reader/view_abstract.aspx?file_no=20190709&flag=1

TITLE

The Role of Peripheral Blood Natural Killer Cells in Intracranial Neoplasms

Andreas Zigouris [1], George A. Alexiou [1,2], George Vartholomatos [2,3], Christos Exarchos [1], Spyridon Voulgaris [1,]

[1.] Department of Neurosurgery, University Hospital of Ioannina, 45500 Ioannina, Greece
[2.] Neurosurgical Institute, Faculty of Medicine, School of Health Sciences, University of Ioannina, 45110 Ioannina, Greece
[3.] Haematology Laboratory-Unit of Molecular Biology, University Hospital of Ioannina, 45500 Ioannina, Greece

CORRESPONDENCE
Zigouris Andreas, Department of Neurosurgery, University Hospital of Ioannina, Stavrou Niarchou Avenue, 45500 Ioannina, Greece, andzy76@hotmail.com

FUNDING
This research received no external funding

INFORMED CONSENT STATEMENT
Informed consent was obtained from all subjects involved in the study

CONFLICTS OF INTEREST
The authors declare no conflict of interest

ETHICAL APPROVAL FUNDING (NUMBER)
157/26-03-2019

KEYWORDS
NK cells, Tregs, Glioblastoma, Ki-67

ABSTRACT

Objective: Natural killer (NK) cells activity has been examined in several types of cancer and their low activities have been associated with increased risk of cancer. In the present study, we set out to quantify NK cells and other immune cells in peripheral blood of patients with the diagnosis of intracranial tumor and correlate it with tumor type, Ki-67 index and patients' outcome.

Material and Methods: The immune cells were retrospectively quantified in peripheral blood by flow cytometry in 75 patients suspicious for an intracranial tumor that were treated surgically during a three-year period.

Results: Glioma patients had higher percentage of NK cells compared to all other type of brain tumors, however no significant correlation was found. The ratio of CD4/CD8 cells was significant higher in high-grade tumors with higher expression of Ki-67 (p=0.048). A statistical trend (p=0.06) between Ki-67 expression and the ratio of CD3/CD4 was also observed. No significant correlation between NK cell fraction and overall survival in glioblastoma patients was found.

Conclusions: NK cells were found increased in lower-grade malignancies in comparison with high-grade malignancies, indicating a stronger antitumor response.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η δραστηριότητα των NK κυττάρων έχει μελετηθεί σε διάφορους τύπους καρκίνου και η περιορισμένη δραστηριότητά τους έχει συσχετιστεί με αυξημένο κίνδυνο καρκίνου.

Υλικό και Μέθοδος: Με την παρούσα μελέτη έγινε αναδρομικά σε μια περίοδο 3 ετών ποσοτικοποίηση των NK όσο και άλλων ανοσοκυττάρων (Tregs) με κυτταρομετρία ροής στο περιφερικό αίμα 75 ασθενών με ενδοκρανιακό όγκο που υπεβλήθησαν ακολούθως σε χειρουργική εξαίρεση και ακολούθησε ανάλυση της συσχέτισης αυτών των συγκεντρώσεων με τον ιστολογικό τύπο του όγκου, τον δείκτη Ki-67 και την έκβαση των ασθενών.

Αποτελέσματα: Οι ασθενείς με γλοίωμα είχαν υψηλότερο ποσοστό NK κυττάρων σε σύγκριση με όλους τους άλλους τύπους όγκων εγκεφάλου, ωστόσο δεν βρέθηκε σημαντική συσχέτιση. Η αναλογία των κυττάρων CD4/CD8 ήταν σημαντικά υψηλότερη σε όγκους υψηλού βαθμού με υψηλότερη έκφραση του Ki-67 (p=0,048). Παρατηρήθηκε επίσης μια στατιστική τάση (p=0,06) μεταξύ της έκφρασης Ki-67 και της αναλογίας CD3/CD4. Δεν βρέθηκε σημαντική συσχέτιση μεταξύ του κλάσματος των NK κυττάρων και της συνολικής επιβίωσης σε ασθενείς με γλοιοβλάστωμα.

Συμπεράσματα: Τα φυσικά κυτταροκτόνα κύτταρα βρέθηκαν αυξημένα σε κακοήθειες χαμηλότερου βαθμού σε σύγκριση με κακοήθειες υψηλού βαθμού, υποδεικνύοντας ισχυρότερη αντινεοπλασματική απόκριση.

INTRODUCTION

The central nervous system (CNS) has long been considered an immune-privileged site, since intracerebral injection of an antigen failed to generate a classical immune response [1]. The brain parenchyma, the interstitial fluid and the cerebrospinal fluid (CSF) are isolated from the blood by two barriers: the blood–brain barrier (BBB) and the blood–CSF barrier [2,3]. Despite these barriers, immune cells are detected in the brain parenchyma as well as in the CSF, where memory CD4+ T-cells are predominant, supporting the hypothesis of immune surveillance of the CNS [2,3].

In pathological conditions, the integrity of these barriers can be disturbed, becoming permissive for the entry of inflammatory cells. Among them, NK cells were shown to be recruited to the CNS as a result of several pathological conditions [4-7]. Natural killer (NK) cells are large granular lymphocytes endowed with the inherent capacities to recognize and kill foreign, infected, and malignant cells and to modulate several other aspects of the immune system through rapid production of numerous cytokines and chemokines. NK cells play a critical role in cancer surveillance, and their cytotoxic functions are regulated by a balance between the expression of activating and inhibitory receptors [7,8].

NK cells activity has been examined in several types of cancer and has been found that inhibition of this activity is associated with increased risk of cancer [9-14]. Given the critical role in anticancer immune responses, in the present study, we set out to quantify NK cells and other populations of immune cells in peripheral blood of patients with intracranial tumor diagnosis aiming to find intercorrelations between immune cells populations, to correlate these populations with tumor type, Ki-67 index and patients' clinical outcome and to study the utility of these preoperative assays to count biomarkers.

MATERIALS AND METHODS

NK cells (CD16+CD56+), T cells (CD3+), B cells (CD19+), CD4/CD8 ratio and Tregs (CD4+CD25+Foxp3+) were retrospectively quantified in peripheral blood by flow cytometry in 75 patients suspicious for an intracranial tumor that were treated surgically during a three-year period. The absence of a control group to compare explained from the fact that there is a global standard of the expected normal percentages of subpopulations of lymphocytes that has been determined following the analysis of millions of normal samples. Based on this standard, a control group would be detrimental. In all patients a blood sample was collected prior receiving any treatment. All patients were operated on within a week. The definitive diagnosis was based on pathology evaluation [WHO classification 2016]. The study was approved by the institutional review board (Ethical approval number: 157/26-03-2019).

FLOW CYTOMETRY ANALYSIS

Peripheral blood cells were incubated with monoclonal antibodies that were conjugated to fluorescent dyes. Leukocytes were analysed, (at least 10.000 cells) in a flow cytometer [FACSCalibur (Becton-Dickinson)] using the CellQuest software (Becton-Dickinson). [15,16]. In detail, a combination of fluorescent monoclonal antibodies were introduced into test tubes [mouse anti-HumanCD45 PerCP clone 2D1 (BD Biosciences), mouseanti-Human CD3 PE, clone SK7, (BD Biosciences), anti-Human CD4 FITC /PE clone SK3,(BD Biosciences), anti-Human CD8 PE clone SK1, (BD Biosciences), mouse anti-Human,CD19 FITC clone 4G7, (BD Biosciences), mouse anti-Human CD16 FITC clone 3G8,(BD Biosciences), mouse anti-Human, CD56 PE-CF594, clone B159, (BD Biosciences),mouse, anti-Human,CD25 FITC, clone 2A3, (BD Biosciences)]. All antibodies used have been approved for in vitro diagnostic use (IVD), based on the characterization of binding to a specific epitope.The volumes usedare those recommended by the monoclonal antibody manufacturer (usually 10 or 20 μL). A 100 μL of peripheral blood sample to which anticoagulant (EDTA) has been added to each tube. The mixture was then stirred. Cells were then incubated with themonoclonal antibodies at room temperature for 10 minutes, an incubation time sufficient for efficient binding of the antibodies, as has previously described. Finally, red bloodcells were lysed with an appropriate commercial solution (Versalyse, 500μl, 10 min RT) and analyzed on a flow cytometer. The sample following erythrocyte lysis contains all leukocyte populations, possibly some erythrocytes, platelets, dead cells and debris. The heterogeneity of the sample requires careful distinction of the gating population of leukocytes so that the results of the analysis can accurately determine the immunophenotype of each leukocyte population (See Figure 1 for details). Peripheral blood from healthy individuals has been routinely used as control to evaluate flow cytometry analysis strategy and instrument performance. Briefly, routine instrument performance control is done before each analysis of samples from patients, by using peripheral blood from healthy individuals. Gating of individual cell population as described in Figure 1 is performed to standardize a template, which is then used to quantify cell populations of samples.

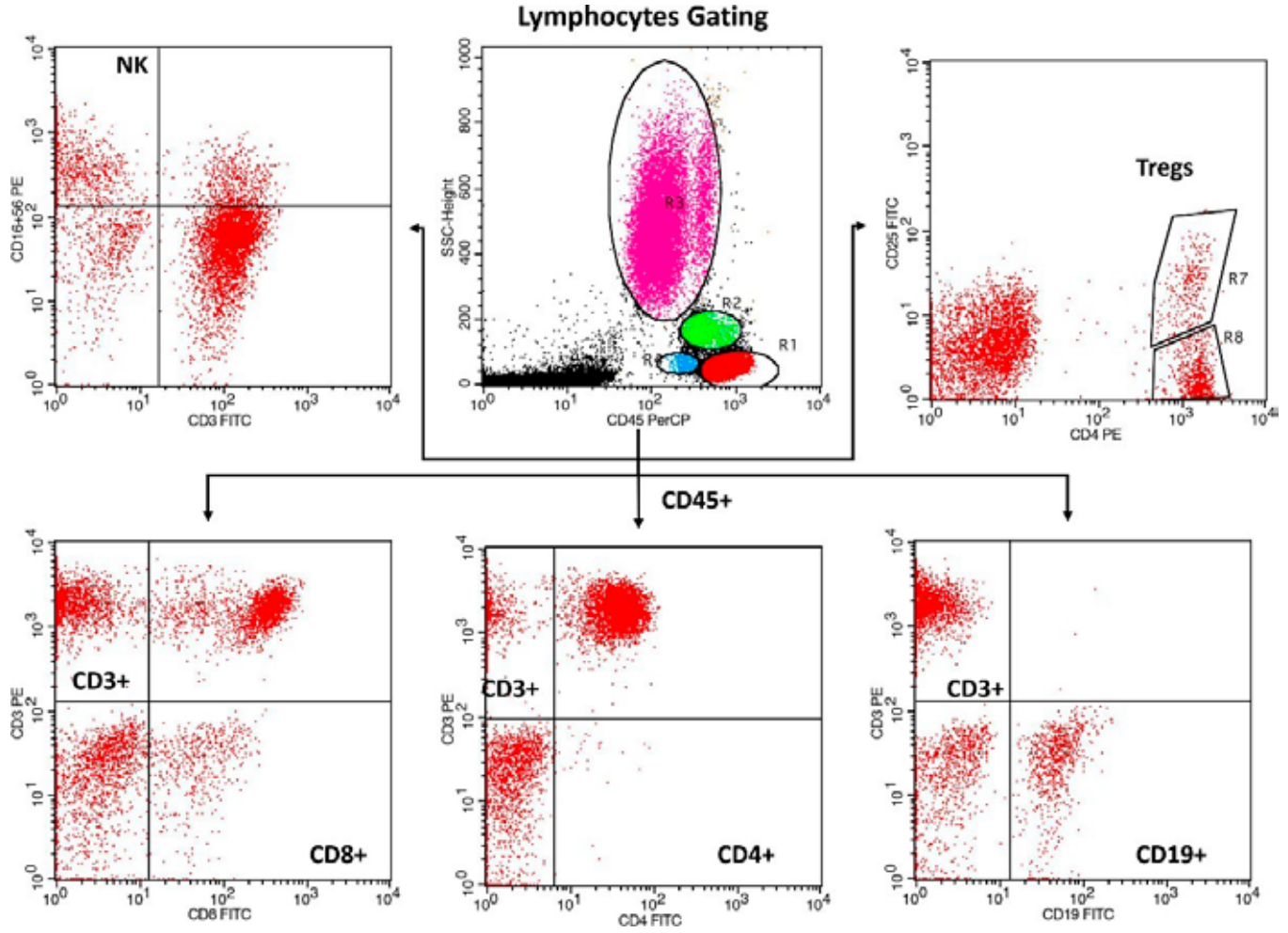

Figure 1. Gating strategy for lymphocyte subpoulations. Lymphocytes were gated using SSC and CD45 expression. On the lymphocyte gate, the different subpopulations were quantified using the specific markers for T Cells (CD3+), cytotoxic T cells (CD3+CD8+), helper T cells (CD3+CD4+) and Regulatory T (Tregs) cells (CD3+CD4+CD25+), as well as Natural Killer (NK) cells (CD3+CD16+CD56+).

STATISTICAL ANALYSIS

Continuous data were expressed as mean ± standard deviation. The correlation between the expression of each antibody and tumor grade were compared using the two-sided, non-parametric Mann-Whitney U test. Correlation between Ki-67 and antibody expression was analyzed using Spearman rho test. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Our analyzed population included 35 males and 40 females with a mean age 54 ± 24,17 years (range: 21-79 years). Of those, 36 patients suffered from glioblastoma, 6 from recurrent glioblastoma, 7 from solitary metastasis, 20 from meningioma Grade I, 3 from meningioma Grade II, III, and 3 from low-grade glioma (Table 1). The flow cytometry results are also summarized in Table 1. Cell populations were quantified by flow cytometry, using a CD45+ gate as described in Figure 1.

The mean percentage of NK cells was 13.2% (range: 2-57%). The correlation between NK cells and tumor type and NK cells in glioblastoma compared with other tumor types was not significant (p=0.18, p=0.24 respectively). No significant correlation has been detected between NK cells and the grade of glioma malignancy (p=0.22). Glioma (low grade, glioblastoma) patients had higher percentage of NK cells compared to all other type of brain tumors, however the increase was not statistically significant.

The total amount of T-cells (CD3+) in peripheral blood was not correlated between glioblastoma patients and patients with other tumor types (p=0,32), a fact that was also verified for the ratio between CD3+/CD4+ cells, B-cells (CD19+) and the ratio CD3+/CD8+(with p=0.26, p=0.76, p=0.93 respectively).

The CD8+ population included mainly T-cytotoxic cells and secondary NK and dendritic cells. The CD4+ population included T-helper cells. The correlation between CD3+, CD19+, NK cells and Ki-67 was also not statistically significant (p=0,25, p=0,85 and p=0,18 respectively). No significant correlation was also recorded for the ratios CD3/CD8 and the presence of CD4+CD25+ cells (p=0,24 and p=0,19 respectively).

An interesting finding was that the ratio of CD4/CD8 was significant higher in high-grade tumors with higher expression of Ki-67 (p=0,048) and for the correlation between Ki-67 and the ratio of CD3/CD4 there was a statistical trend, near statistical significance cut-off (p=0.06).

During a mean follow-up period of 3 years, 69,2% of glioblastoma patients died. One patient harboring a meningioma Grade I died because of post-operative meningitis and all patients with low grade glioma were alive. No significant correlation between NK cells levels and overall survival in glioblastoma patients was found.

	M	F	AGE	CD3	CD19	NKC	CD3 / CD4	CD3 / CD8	CD4/CD8	Tregs	Ki-67
GBM	17	19	64,19 ± 9,35	63,32 ± 2,83	12,66 ± 2,12	25,11 ± 2,12	36,2 ± 19,1	28,42 ± 7,78	1,84 ± 0,78	1,16 ± 0,67	59,71 ± 7,07
GBM R	3	3	60,5 ± 4,09	76 ± 16,97	9,34 ± 9,19	14,7 ± 7,8	39,67± 4,95	34,65 ± 8,48	1,13 ± 0,14	0,8 ± 0,1	53,34 ± 28,29
MT	4	3	65,28 ± 9,19	53,57 ± 39,6	16,28 ± 1,41	18,85 ± 15,76	40,71 ± 3,53	22,71 ± 0,71	1,67± 0,7	1,64 ± 0,6	42,86 ± 28,29
MA I	9	11	51,5 ± 14,84	66 ± 7,8	8 ± 6,95	20,56 ± 2,83	38,34 ± 24,04	27,94 ± 16,97	1,57 ± 1,49	1,13 ± 0,7	7,6 ± 8,49
MA II, III	0	3	62,66 ± 0,7	71,7 ± 41	11 ± 6,35	17,34 ± 14,85	44,67± 11,31	29 ± 3,54	1,66 ± 1,34	1,05 ± 0,77	16± 14,14
LGG	2	1	30 ± 6,36	67,7 ± 21,9	20,7 ± 17,68	11,67 ± 4,25	33 ± 18,39	34 ± 8,48	0,67 ± 0,14	1,2 ± 0,4	28 ± 12,02

Table 1*. Percentage of immune effector cells in 75 patients included in the study. Mean value plus range of mean is presented (Mean ± Standard Deviation).* ***Abbreviations****: CD: Cluster of Differentiation, F: Female, M: Male, NKC: Natural Killer Cells, GBM: Glioblastoma Multiforme, GBM R: Glioblastoma Multiforme Recurrence, MA I: Meningioma Grade I, MA II, III: Meningioma Grade II, III, LGG: Low Grade Glioma, MT: Metastasis, Tregs: T-regulatory Cells.*

DISCUSSION

Central nervous system has long been regarded as a privileged immune region, evidenced by the presence of blood-brain barrier, lack of lymphatic vessels, and the absence of cells expressing major histocompatibility antigens (MHCs), or antigen presenting cells (APCs) [3,11,17].

NK cells constitute the 2.11% of the cells of the immune system in glioma with the majority being of CD56dimCD16+phenotype, which is also found in other neoplasms [17,18]. NK cells have in the intratumoral environment cytotoxic activity; this may constitute a novel therapeutic option for glioblastoma. Glioma cells carry high levels of MHC class I molecules and HLA-A,-B,-C antigens that interact with and inhibit NK cells receptors on their surface[7,17,18]. One of the features of glioblastoma is the accumulation of CD4+CD25+Foxp3+ (Tregs). In particular, Tregs appear to be among the major factors contributing to immunotherapeutic failure, leading to rapid tumor progression [19,20]. Experimentally therefore, Tregs have been detected intravenously in the peripheral blood of patients with glioblastoma [19-21]. Based on their involvement in other cancers, Tregs are targeted for a therapeutic approach in order to prolong survival, especially for aggressive forms such as glioblastoma [21,22]. In experimental studies with animal models, targeting of Tregs and limiting their activity led to enhanced activity of cytotoxic T-lymphocytes and a combination with vaccines led to improved survival [21,22].

In the present study we found that the ratio of CD4/CD8 was significant higher in high-grade tumors with higher Ki-67 expression. Ki-67 protein or Ki-67 antigen is an efficient indicator for cell proliferation. During interphase, Ki-67 antigen can be detected exclusively in the nucleus, whereas in mitosis most of the protein is transferred to the chromosome surface. Ki-67 protein is present in all active phases of the cell cycle (G1, S, G2 and mitosis) but is absent in the resting phase (G0). The intracellular content of Ki-67 protein is significantly increased during cell transition through the S phase of the cell cycle. The role of Ki-67 as a prognostic marker for gliomas remains unclear. A 2015 meta-analysis and a 2016 study found that increased expression of Ki-67 may be a factor for poor prognosis of glioma patients. A recent study in patients with highly malignant gliomas found a marginally significant correlation between Ki-67 expression and the location of lesion. Lesions located in the left frontal lobe had higher Ki-67 expression [23-25].

The invasive nature of glioblastoma requires alternative clinical markers for defining tumor margins and improving therapeutic response, so the potential of analyzing a factor on peripheral blood with the potential to be associated with the presence of glioma could have a significant impact on clinical decision-making. Flow cytometry is a key methodology in the study of peripheral blood cell populations found in different types of disease such as in cases of a glioblastoma [15,16].

The biomarkers that have been studied in cases of malignant brain tumor have higher intracellular concentrations, lower in the extracellular space and even less in peripheral blood, due to the aforementioned barriers between the brain and the circulatory system. In brain tumors, studies on peripheral bloodmarkers have included circulating tumor cells, circulating nucleic acids, circulating proteins, hematopoietic stem cells, and endothelial cells [27-30]. A study of peripheral blood circulating immunosuppressive cells in patients with glioblastoma and other types of tumors by Alban et al concluded that decreased MDSCs and increased DCs are associated with better prognosis, while NK cells were increased in lower-grade malignancies in comparison with high-grade malignancies, indicating a stronger antitumor response [31]. In our study the immunosuppression in cases of brain tumor was studied based on detection of NK cells, Tregs and other immune cells of peripheral blood.The initial results confirm that preoperatively we have a high suspicion of malignancy using a cost effective method both for gliomas as well as for meningiomas in combination with MRI scan findings and clinical signs. The limitation of this study is the small number of patients and the disproportion of brain tumor histological types (mainly gliomas and meningiomas).

CONCLUSIONS

Several molecules have been identified as candidate biomarkers for glioblastoma, where the immunosuppression is a well-known intratumoral condition. Based on this concept we studied the immunologic profile of peripheral blood in brain tumor patients who were operated. The suitable approach for efficacious therapy in case of malignant tumors should be based on a personalized profile according to tumor (imagine, histology) and peripheral blood (biomarkers, immune system cells) characteristics. Further studies are therefore needed in order to verify our preliminary results.

REFERENCES

1. Alexiou G.A., Kyritsis A.P. Immunotherapeutic strategies for glioma treatment. J Neuroimmunol Neuroinflammation 2016; 3:51-56
2. Yang I, Han S.J., Kaur G et al: The Role of Microglia in Central Nervous System Immunity and Glioma Immunology. J Clin Neurosci. 2010 Jan; 17(1): 6–10
3. Ransohoff, R.M., Engelhardt B: The anatomical and cellular basis of immune surveillance in the central nervous system. Nat RevImmunol. 2012 Sep;12(9):623-635
4. Domingues P.H., Teodósio C, Ortiz J et al: Immunophenotypic identification and characterization of tumor cells and infiltrating cell populations in meningiomas. Am J Pathol. 2012 Nov;181(5):1749-61
5. Trifilo, M.J., C. Montalto-Morrison, L.N., Stiles K.R. et al: CXC chemokine ligand 10 controls viral infection in the central nervoussystem: evidence for a role in innate immune response through recruitment and activation of natural killer cells. J. Virol. 2004; 78:585–594
6. Alsharifi M, Lobigs M, Simon M et al: NK cell-mediated immunopathology during an acute viral infection of the CNS. Eur. J. Immunol. 2006; 36: 887–896.
7. Lowenstein P.R., Castro M.G. The Long and Winding Road: from the high affinity choline uptake site to clinical trials for malignantbrain tumors.Advances in Pharmacology 2016; 76:147-173.
8. Biassoni R: Natural killer cell receptors. Adv Exp Med Biol. 2008; 640:35-52.
9. Caligiuri M.A. Human natural killer cells. Blood 2008 Aug 1; 112(3):461-9.
10. Ljunggren H.G., Kärre K: In search of the 'missing self': MHC molecules and NK cell recognition. Immunol Today 1990; 11:237–41.
11. Kärre K: NK cells, MHC class I molecules and the missing self. Scand J Immunol. 2002 Mar; 55(3):221-8
12. Lünemann A, Lünemann J.D., Münz C: Regulatory NK-cell functions in inflammation and autoimmunity. Mol. Med. 2009; 15: 352–358.
13. Vivier E, Tomasello E, Baratin M et al: Functions of natural killer cells. Nat Immunol. 2008 May; 9(5):503-10.
14. Vivier E, Nunès JA, Vély F: Natural killer cell signaling pathways. Science. 2004 Nov 26; 306(5701):1517-9.
15. Craig J.W., Dorfman D.M. Flow Cytometry of T cells and T-cell Neoplasms. Clin Lab Med. 2017 Dec; 37(4):725-751.
16. Adan A, Alizada G, Kiraz Y et al: Flow cytometry: basic principles and applications. Crit Rev Biotechnol. 2017 Mar; 37(2):163-176.
17. Poli A, Kmiecik J, Domingues O et al: NK cells in central nervous system disorders. J Immunol. 2013 Jun 1; 190(11):5355-62.
18. Levy E.M., Roberti M.P., Mordoh J: Natural killer cells in human cancer: from biological functions to clinical applications. J BiomedBiotechnol. 2011; 2011:676198.
19. Bluestone J.A., Abbas A.K. Natural versus adaptive regulatory T cells. Nat Rev Immunol 2003; 3:253-257.
20. El Andaloussi A, Lesniak M.S. An increase in CD4+CD25+FoxP3+ regulatory T cells in tumor-infiltrating lymphocytes of humanglioblastoma multiforme. NeuroOncol. 2006 Jul; 8(3):234-43.
21. Heimberger A.B., Abou-Ghazal M, Reina-Ortiz C et al: Incidence and prognostic impact of FoxP3+ regulatory T cells in human gliomas. Clin Cancer Res. 2008 Aug 15; 14(16):5166-72.
22. Humphries W, Wei J, Sampson J.H. et al: The role of Tregs in glioma-mediated immunosuppression: potential target for intervention. Neurosurg Clin N Am. 2010 Jan; 21(1):125-37.
23. Chen W.J., He D.S., Tang R.X. et al: Ki-67 is a valuable prognostic factor in gliomas: evidence from a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2015; 16(2):411-20.
24. Ahmed S, Rashed H, Hegazy A et al: Prognostic Value of ALDH1, EZH2 and Ki-67 in Astrocytic Gliomas. Turk PatolojiDerg. 2016;32(2):70-81
25. Altieri R, Zenga F, Ducati A et al: Tumor location and patient age predict biological signatures of high-grade gliomas. Neurosurg Rev.2018 Apr; 41(2):599-604.
26. Schmidt S, Tramsen L, Rais B et al: Natural killer cells as a therapeutic tool for infectious diseases – current status and future perspectives. Oncotarget. 2018 Apr 17; 9(29): 20891–20907.
27. Kmiecik J, Zimmer J, Chekenya M: Natural killer cells in intracranial neoplasms: presence and therapeutic efficacy against brain tumors. J Neurooncol. 2014; 116:1–9.
28. Paolillo M, Boselli C, Schinelli S: Glioblastoma under Siege: An Overview of Current Therapeutic Strategies. Brain Sci. 2018 Jan 16;8(1):15.
29. Holdhoff M, Yovino S.G., Boadu O et al: Blood-based biomarkers for malignant gliomas. J Neurooncol. 2013 Jul; 113(3):345-352.
30. Tanase C, Albulescu R, Codrici E et al: Circulating biomarker panels for targeted therapy in brain tumors. Future Oncol. 2015;11(3):511–524.
31. Alban T.J. Global immune fingerprinting in glioblastoma patient peripheral blood reveals immune suppression signatures associated with prognosis. JCIInsight. 2018; 3(21):e122264.

TITLE

The Role of Lumbar Epidural Clonidine Infusion for Post-Operative Analgesia in Spine Surgery

Dionysoula Skiada, Evaggelos Michos, Dimitrios Pachatouridis, George A. Alexiou, Spyridon Voulgaris

Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece

KEYWORDS

Clonidine, Radiculopathy, Lumbar Disc Herniation, Lumbar Stenosis, Microdiscectomy, Sciatic

FUNDING

No funding was received for this study

CORRESPONDENCE

Skiada D. Department of Neurosurgery, University Hospital of Ioannina, Stavrou Niarchou Avenue 45500, Tel.+30 2651099701, E-mail: skiada.silia@gmail.com

ABSTRACT

Objective: In this study, we report our clinical experience in intraoperative "open" epidural application of clonidine in order to enhance post-operative analgesia.

Material and Methods: We performed a prospective, randomized, double-blinded study at the Neurosurgical Department of the University Hospital of Ioannina, Greece. Forty patients (22 female, 18 male, mean age 46.4±14.4 years, range 27 to 78 years) met the inclusion criteria and were included in the study. Twenty patients suffered from lumbar disc herniation and twenty suffered from lumbar stenosis. The intensity of preoperative and postoperative pain was assessed by using the Visual Analogue Scale of pain (VAS) and the Oswestry Low Back Disability Questionnaire.

Results: There was no statistically significant difference as far as the post-operative pain was concerned between the patients which received the epidural infusion of clonidine and the ones who didn't.

Conclusions: The use of epidural clonidine infusion as an adjuvant to post-operative analgesia in lumbar spine surgeries cannot be considered as an analgesic factor on it' s own.

ΠΕΡΙΛΗΨΗ

Σκοπός: Η εμπειρία της κλινικής μας στη διεγχειρητική επισκληρίδια έγχυση κλονιδίνης με σκοπό την ενίσχυση της μετεγχειρητικής αναλγησίας.

Υλικό και Μέθοδος: Πρόκειται για μια προοπτική τυχαιοποιημένη διπλά τυφλή μελέτη. Συνολικά συμμετείχαν 40 ασθενείς μέσης ηλικίας 46.4±14.4 έτη και εύρος 27 με 78 έτη. Είκοσι ασθενείς έπασχαν από οσφυική στένωση και 20 από οσφυική δισκοκήλη. Η ένταση του πόνου πριν και μετά το χειρουργείο αξιολογήθηκε με την Visual Analogue Scale of pain (VAS) και την Oswestry Low Back Disability Questionnaire.

Αποτελέσματα: Δεν βρέθηκε στατιστικά σημαντική διαφορά στην ένταση του πόνου μεταξύ των ασθενών που έλαβαν διεγχειρητική επισκληρίδια έγχυση κλονιδίνης και αυτών που δεν έλαβαν.

Συμπεράσματα: Η διεγχειρητική επισκληρίδια έγχυση κλονιδίνης σε επεμβάσεις οσφυικής στένωσης και οσφυικής δισκοκήλης δεν είχε κάποια επίδραση στον έλεγχο του πόνου μετεγχειρητικά.

INTRODUCTION

Intervertebral disc herniation with radiculopathy and lumbar stenosis with consequent neurogenic claudication, are both common clinical problems in western world. The mechanical compression of nerve roots leads to local inflammation and release of local pain mediators that constitute the main cause of pain [1].

In addition to opiate mechanisms, there are other spinal mechanisms that produce endogenous analgesic factors, as well as other receptor-specific agents that may produce analgesia when injected in the epidural space [2]. Clonidine, an α2-adrenergic agonist [3], has been traditionally administrated in oral form as an antihypertensive agent. The large expression of α2-adrenergic receptors in the central nervous system (locus coeruleus and dorsal horn of the spinal cord) led to the conclusion that may produce analgesia when applied near the spinal cord [4]. Clonidine can actually block the transmission of pain information by activating pre-synaptic and post-synaptic α2-adrenoreceptors in the spinal cord, which block substance P release and dorsal horn neuron firing, respectively. As for its toxicity, clinical trials suggested that clonidine is safe, but it may produce side effects, depending on the route of administration, such as hypotension, bradycardia, sedation, decreased serum cortisol, hyperglycemia, and hypoxemia. Recently, more emphasis has being given on the use of low doses of clonidine due to a remarkable decrease of these side effects [5].

In this study, we report our clinical experience in intraoperative "open" epidural application of clonidine in order to enhance post-operative analgesia and, of course, to avoid all the complications mentioned above related to the classic epidural injection technique.

MATERIALS AND METHODS

After obtaining approval from the institutional ethics committee [2/31-01-2023 (θ.21)], we performed a prospective, randomized, double-blinded study at the Neurosurgical Department of the University Hospital of Ioannina, Greece. The inclusion criteria involved patients ASA physical status classification system graded I or II, operated on for lumbar disc herniation and lumbar stenosis with symptoms lasting more than 6 weeks. On lumbar MRI we evaluated the grade of intravertebral disc degeneration, the grade of disc prolapse, the type of end- plates changes and the modic changes of the vertebra. We also recorded patients' demographic data, BMI, allergies, smoking or alcohol drinking, marriage status, educational level, the length of symptomatology, profession and previous trauma. We excluded patients with recurrent lumbar disc herniation, recent spinal trauma, cauda-equina syndrome, allergy to clonidine, hypotension, congestive heart failure, angina, diabetes mellitus, and respiratory diseases requiring treatment.

The intensity of preoperative and postoperative pain was assessed by using the Visual Analogue Scale of pain (VAS) and the Oswestry Low Back Disability Questionnaire. Preoperative all patients underwent a lumbar MRI and x-ray of the lumbosacral spine in order to exclude spina bifida, chest x-ray and ECG. A series of blood analysis, such as complete blood test, coagulation profile, glucose levels, renal and liver function were performed preoperatively. All patients provided written informed consent before study inclusion.

RANDOMIZATION – CLONIDINE ADMINISTRATION

The patients were randomly allocated in two categories, those that would receive the intraoperative epidural infusion of clonidine and those that would receive a mock infusion using a randomization program (http://www.randomization.com/). All patients received the standard perioperative prophylactic administration of broad spectrum antibiotics and prophylactic low-molecular weight heparin (according to BMI). Concerning pain management medications, paracetamol or tramadol were used as needed. As per protocol during the first postoperative day all patients received paracetamol at a dose of 1000mg X 3 and tramadol 100mg in addition if needed. The second postoperative day we used exclusively NSAIDs (Diclofenac 75mg X 2 or Nimesulide 100mg X 2).

In the operation theater standard intravenous access was secured and non-invasive monitoring of the patient was performed (pulse oxymeter, non-invasive blood pressure – NIBP-, electrocardiograph adhesive leads). All operations were performed under general anesthesia in prone position. The surgical procedure consisted of microdiscectomy, hemilaminectomy or laminectomy for lumbar disc herniations and laminectomy for lumbar stenosis. After performing the laminectomy, a reinforcement of the dura with an eterologous dural patch was performed. In all cases epidural application of clonidine or mock infusion before closure was performed (Figure 1).

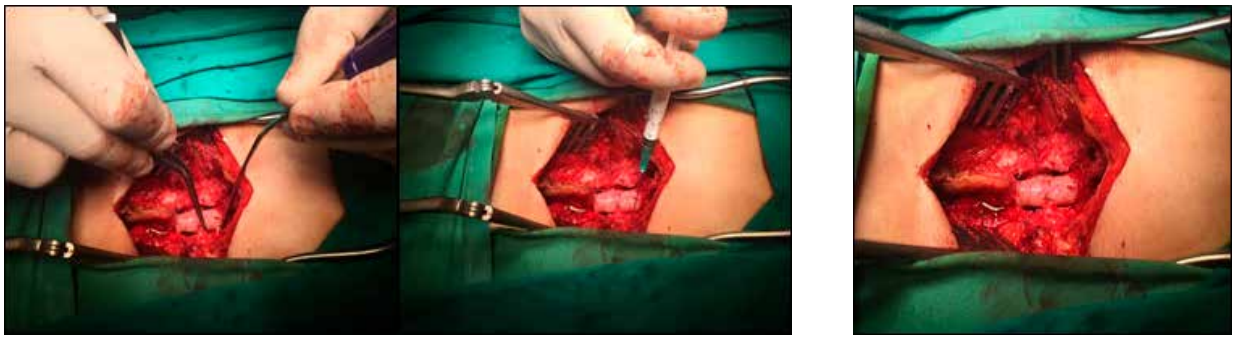

Figure 1.
A two-level laminectomy, discectomy and bilateral foraminotomy of the corresponding nerve roots, ending with meticulous hemostasis of the surgical field. Following, the "open" epidural clonidine infusion (1amp. of 1ml of clonidine-150ug of active ingredient). Finally, overview of the surgical field and closure of the surgical trauma.

RESULTS

During the study period 40 patients (22 female, 18 male, mean age 46.4±14.4 years, range 27 to 78 years) met the inclusion criteria and were included in the study. Twenty patients suffered from lumbar disc herniation and twenty suffered from lumbar stenosis (Table 1).

Table 1. Patients' demographic data.

SEX	NUMBER OF PATIENTS	AGE RANGE	LUMBAR STENOSIS	DISK HERNIATION
MALE	18	27-68	8	10
FEMALE	22	34-78	12	10

During epidural infusion of clonidine no hypotension or bradycardia was recorded. The infusion was performed by using 1ml of clonidine, which means 150ug of the active ingredient. As far as the patients affected from lumbar stenosis were concerned, single-level laminectomy was performed at 10 patients, two-level laminectomy at 9 patients and three-level laminectomy at 1 patient. There was no statistically significant difference as far as the post-operative pain between patients which received the epidural infusion of clonidine and those who didn't (preoperative median VAS SCORE 7.1 vs 6.15, postoperative median 1.6 vs 1.2, $p>0.05$). All the patients presenting lumbar herniation underwent microdiscectomy. There was no statistically significant difference as far as the post-operative pain is concerned between the patients that received clonidine and the others that didn't (pre-operatively 6.9 vs 8.1, post-operatively 1 vs 1.3, $p>0.05$). The mean hospitalization time of all patients was 4 days. No case of wound infection was recorded.

DISCUSSION

Nowadays, both lumbar radiculopathy and lumbar stenosis have become two of the most costly and ubiquitous medical problems. In the present study, diagnosis of sciatica was primarily made on the basis of history taking and physical examination. The level of the stenosis or of the disc herniation was identified and confirmed by MRI [6]. MRI, introduced in the early 70s, constitute the most efficient and optimal tool for the screening of the patients with sciatica and radicular pain, as it can provide more information about the aspect and the localization of the lesion in respect of the dural sac, the nerve roots and the ligaments involved.

The aim of post-operative pain relief is to provide subjective comfort, in addition to inhibiting nociceptive impulses caused by trauma as well as somatic reflexes to pain [7,8]. In our study, VAS score was used to evaluate the efficacy of the epidural administration of clonidine infusion.

The present study has several limitations. First, we recorded the pain post-operatively. Thus, the residual effects of general anaesthesia drugs make the perception of mild pain (VAS <4) to differ among patients as most patients tolerate minimal pain in the post-operative period due to residual analgesia. Furthermore, the immediate post-operative analgesic protocol applied in our department on these patients might influence study's results. Post-operative analgesics could be better given when needed by the patient itself, but that would be against the medical ethics towards an operated patient. Finally, both microdiscectomy and laminectomy can provide immediate relief of pain, as they are considered decompressive surgical procedures, so the patient cannot estimate the extra benefit of any other intervention.

Several methods have been used in order to treat pain, which is commonly the symptom that forces the patient to visit the physician [9], including per os administered medications, physical therapy, epidural steroid and opioid injection and, of course, surgery [10]. According to clinical observations and findings from several studies, epidural injection and surgery appear to be more effective than any other conservative method [6,11]. However, corticosteroid administration is limited by systemic toxicity [12] and opioid administration may produce side effects (urinary retention, pruritus, nausea and life-threatening respiratory depression). In addition, serious complications regarding the injection technique have been reported, such as epidural haematomas, traumatic radiculopathy, creation of commissures or leptomeningeal inflammation, subcutaneous CNS fistula and intracranial hypotension, or even paraplegia [13,14].

CONCLUSIONS

We conclude that the use of epidural clonidine infusion as an adjuvant to post-operative analgesia in lumbar spine surgeries provides no extra benefit. Further studies with larger number of patients are needed.

REFERENCES

1. Deyo RA, Weinstein JN. Low back pain. New England Journal of Medicine. 2001;344(5):363-70.

2. Cheng K, Martin LF, Slepian MJ, Patwardhan AM, Ibrahim MM. Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review. J Pain. 2021 Jul;22(7):763-777. doi: 10.1016/j.jpain.2021.02.005.

3. Madabhushi L, Reuben SS, Steinberg RB, Adesioye J. The efficacy of postoperative perineural infusion of bupivacaine and clonidine after lower extremity amputation in preventing phantom limb and stump pain. J Clin Anesth. 2007 May;19(3):226-9.

4. Bylund DB: Subtypes of alpha 2-adrenoceptors: pharmacological and molecular biological evidence converge. Trends Pharmacol.Sci. 1988; 9: 356-6127. Taenzer AH, Clark C. Effi- cacy of postoperative epidural analgesia in adolescent scoliosis surgery: A meta-analysis. Paediatr Anaesth 2010;20:135-43.

5. Rechtine GR, Love LC. The postoperative laminectomy pain control using bupivacaine and epidural morphine. Br J Anaesth 2005;95:59-68.

6. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA. 2006;296(20):2451-9.

7. Kalajdzija M, Cero I, Prnjavorac B, Ljuca S. Influence of clonidine on the hemodynamic stability and stress response in the course of surgery on general anesthesia. Med Ath 2011;65;210-2Kumar RJ, Menon KV, Ranjith TC. Use of epidural analge- sia for pain management after major spinal surgery. J Orthop Surg (Hong Kong) 2003;11:67-72.

8. Bouknaitir JB, Carreon LY, Brorson S, Pedersen CF, Andersen MØ. Wide Laminectomy, Segmental Bilateral Laminotomies, or Unilateral Hemi-Laminectomy for Lumbar Spinal Stenosis: Five-year Patient-reported Outcomes in Propensity-matched Cohorts. Spine (Phila Pa 1976). 2021 Nov 1;46(21):1509-1515.

9. Rhee JM, Schaufele M, Abdu WA. Radiculopathy and the herniated lumbar disc. Controversies regarding pathophysiology and management. J Bone Joint Surg Am. 2006;88(9):2070-80

10. Tosteson AN, Skinner JS, Tosteson TD, et al. The cost effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: evidence from the Spine Patient Outcomes Research Trial (SPORT) Spine. 2008;33(19):2108-15

11. Armon C., Argoff CE, Samuels J, et al. Therapeutics and Technology Assesment Subcommittee of the American Academy of N Assessment: use of epidural steroid injection to treat radicular lumbosacral pain: report of the Therapeutics and Tech- nology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2007;68(10):723-9.

12. Ito Y, Bhagwat A. Intrathecal haematoma after an epidural blood patch. BMJ Case Rep. 2022 Sep 29;15(9):e246725.

13. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. Regional Anes- thesia & Pain Medicine. 2004;29(5):494-5.

TITLE

Demographics of Spinal Cord Tumours as Predictors of their Diagnosis

Sotirios Apostolakis, Konstantinos Vlachos

Department of Neurosurgery, KAT General Hospital of Attica, Athens 145 61, Greece

KEYWORDS
Epidemiology, Neurosurgery, Meningioma, Oncology, Schwannoma

CONFLICTS OF INTEREST
The authors declare that there is no conflicts of interest

FUNDING
No funding was received for this research

ETHICAL APPROVAL
This study was approved by the Institutional Review Board (IRB) of KAT General Hospital of Attica

CORRESPONDENCE
Sotirios Apostolakis, 2 Nikis street, Kifisia 145 61, Greece, tel: +30 2132086401, e-mail: sotapostolakis@gmail.com

ABSTRACT

Objective: Spinal cord tumours are a rare entity, consisting less than 16% of all central nervous system masses. Previous reports on their demographics are inconsistent among different geographic regions. The aim of this study is to investigate the demographic profiles of patients with spinal cord tumours and assess potential correlations with histologic diagnoses.

Material and Methods: A retrospective study of the medical records from 2010 to 2019 was conducted, in order to identify the cases of spinal cord tumours managed in our department. Parameters of interest were age at the time of operation, sex, location of the lesion and histological diagnosis.

Results: A total of 105 patients with spinal cord tumours were identified. For those managed surgically, the mean age was 56 years. Primary tumours were located in the thoracic, lumbar and cervical spine, in decreasing order of frequency. Schwannomas were more frequently diagnosed in males and meningiomas in females. Schwannomas were more commonly found in the lumbar spine, whereas meningiomas were predominantly located in the thoracic segment of the spinal cord. Histological diagnosis correlated with gender, but not with age or tumour location.

Conclusions: Of all parameters examined, only gender was correlated with the final diagnosis. Previous reports on the relative rations of nerve sheath cell tumours and meningiomas are inconsistent. In addition, in contrast to a reported slight male predominance, no gender difference was found in our series. The wide discrepancy among the studies could be attributed to potential environmental or genetic factors or even to sampling and detection bias.

ΠΕΡΙΛΗΨΗ

Σκοπός: Οι όγκοι της σπονδυλικής στήλης είναι μια σπάνια οντότητα, αποτελώντας λιγότερο από το 16% όλων των νεοπλασιών του κεντρικού νευρικού συστήματος. Προηγούμενες μελέτες για τα δημογραφικά τους στοιχεία παρουσιάζουν έντονη ασυμφωνία μεταξύ των διαφορετικών γεωγραφικών περιοχών στις οποίες διενεργήθησαν. Σκοπός αυτής της μελέτης είναι η διερεύνηση των δημογραφικών χαρακτηριστικών των ασθενών με όγκους της σπονδυλικής στήλης και η αξιολόγηση πιθανής συσχέτισής τους με την ιστολογική διάγνωση.

Υλικό και Μέθοδος: Πραγματοποιήθηκε αναδρομική μελέτη των ιατρικών αρχείων από την 2010 έως τις 2019, προκειμένου να εντοπιστούν οι περιπτώσεις όγκων της σπονδυλικής στήλης που αντιμετωπίσθηκαν στην κλινική μας. Παράμετροι ενδιαφέροντος ήταν η ηλικία κατά τη στιγμή της επέμβασης, το φύλο, η εντόπιση της βλάβης και η τελική ιστολογική διάγνωση.

Αποτελέσματα: Συνολικά εντοπίστηκαν 105 ασθενείς. Για αυτούς που αντιμετωπίσθηκαν χειρουργικά, η μέση ηλικία ήταν τα 56 έτη. Οι πρωτοπαθείς όγκοι εντοπίζονταν στη θωρακική, οσφυϊκή και αυχενική μοίρα της σπονδυλικής στήλης, κατά φθίνουσα σειρά συχνότητας. Τα σβαννώματα διεγνώσθησαν συχνότερα σε άνδρες και τα μηνιγγιώματα σε γυναίκες. Τα πρώτα εντοπίζονταν συχνότερα στην οσφυϊκή μοίρα ενώ τα δεύτερα κυρίως στη θωρακική μοίρα της σπονδυλικής στήλης. Η ιστολογική διάγνωση βρέθηκε να συσχετίζεται με το φύλο, αλλά όχι με την ηλικία ή την εντόπιση του όγκου.

Συμπεράσματα: Από όλες τις παραμέτρους που εξετάσθηκαν, μόνο το φύλο βρέθηκε να συσχετίζεται με την τελική διάγνωση. Προηγούμενες μελέτες αναφορικά με το σχετικό λόγο μεταξύ των όγκων του νευρικού ελύτρου και των μηνιγγιωμάτων είναι ασυνεπείς. Επιπλέον, στη δική μας σειρά δεν βρέθηκε κάποια διαφορά στις συχνότητες μεταξύ των φύλων, ωστόσο σε προηγούμενες μελέτες έχει περιγραφεί μια μικρή υπεροχή στους άνδρες. Η μεγάλη απόκλιση μεταξύ των μελετών θα μπορούσε να αποδοθεί σε πιθανούς περιβαλλοντικούς ή γενετικούς παράγοντες ή ακόμη και σε συστηματικό σφάλμα σχετιζόμενο με τη μεθοδολογία δειγματοληψίας και ανίχνευσης.

INTRODUCTION

Spinal cord tumours are a relatively rare entity, consisting 3-16% of all central nervous system masses [1, 2]. Subdivided into three major categories, extradural, intradural – extramedullary and intradural – intramedullary, spinal cord tumours may present with a variety of clinical symptomatology ranging from the most subtle to utterly devastating.

Wide discrepancy among the various studies exists in terms of the demographics of these patients and the relative frequency of each histological subtype. The most striking feature is the high variability of ratios of meningiomas and nerve sheath cell tumours (NSCT), in spite of the popular belief for a predominance of the former [3]. Interestingly, in their study, Hirano et al [4] observed a different geographic distribution of the two histologic subtypes in Asian and non-Asian countries. In particular, a predominance of NSCT has been reported in Asia and Oceania, whereas the opposite trend can be observed in Europe and the Americas.

In addition, the importance of the preoperative mental preparation of the surgeon as well as the adequate informed consent of the patient, cannot be stressed sufficiently. This is further underlined by the similar radiologic features of the two most common tumours of the spinal cord [5]. For this reason, the need for indices of the potential diagnosis of a spinal cord mass prior to the operation is considered crucial.

As only a few studies have been conducted addressing the relative frequencies of spinal cord tumours, providing conflicting results, the present article aims to investigate the demographics of patients with spinal cord tumours managed in a single centre in south-east Europe and assess the potential correlation of demographic parameters with the histologic diagnoses. Such information could serve as a preoperative tool for more accurate planning of surgery but also for patient counselling in advance while awaiting official histologic diagnosis.

MATERIALS AND METHODS

A retrospective review of the clinical records of all the patients admitted in the Department of Neurosurgery with the diagnosis of spinal cord tumour (ICD-10 codes C72.0, C72.1, D33.4, D43.4) from 1/1/2010 through 31/12/2019 was conducted. In addition, all histological examination reports of the aforementioned period along with the department's surgical reports database were reviewed in order to identify any potential additional cases.

Parameters of interest were age at the time of operation, sex, location of the lesion, histological diagnosis and origin of the tumour (primary or metastatic). Only cases of primary tumours were included and metastatic tumours were excluded from further analysis. Patients were also excluded if any of the aforementioned data was missing.

For non-parametric variables, Mann-Whitney's test and Kruskal–Wallis H test were used to test for differences between two and multiple groups respectively and the general linear model and Spearman's test were applied to examine for potential correlations between the parameters. In all cases, the level of statistical significance was $p < .05$.

Statistical analysis was conducted using STATISTICA 10.0 (StatSoft 1984–2010) and MATLAB 2016 (The MathWorks, Inc., 2016). Figures were created using MATLAB 2016 (The MathWorks Inc., 2016) and Adobe Illustrator CS3 (Adobe Systems, 2007).

RESULTS

A total of 85 patients with primary spinal cord tumours, managed through posterior or posterolateral approach, were identified through the search. Forty-three of them were men, yielding a male to female ratio of 1:1. No statistically significant difference was found in the age profiles of male and female patients (U= 836, p=.56).

The tumour was most frequently located in the thoracic spine, followed by the lumbar and cervical segments (Table 1).

N	86
Male	43
Male:Female	1:1
Age (Mean ± SD)	56.03 (16.25)
Median (Range)	57 (19-87)
Location	
Cervical	8
Cervico-Thoracic	4
Thoracic	42
Thoraco-Lumbar	1
Lumbar	30

Table 1.
Demographics of the patients with primary tumours of the spinal cord.

This distribution was found to be significantly different from a theoretical homogeneous distribution along the spine ($X^2(4,85)=76.47$, $p<.001$). However, no statistically significant difference was found between the two sexes, in terms of the location of the tumour (U=902, p=.99).

The vast majority were extramedullary tumours, with only 9 cases (10% of all primary spinal cord tumours) being intramedullary (Table 2). About half of them were found to be ependymomas, three were identified as astrocytomas and 2 cases of tumours with highly undifferentiated neuroepithelial cells and occasional evidence of neuroectodermal differentiation, diagnosed as primary PNET, without evidence of concurrent lesions elsewhere in the CNS were encountered.

DIAGNOSIS	N	LOCATION
Schwannoma	30	Extramedullary
Meningioma	29	Extramedullary
Meningothelial	17	
Psammomatous	7	
Fibrous	1	
Clear cell	3	
Mixed	1	
Ependymoma	4	Intramedullary
Astrocytoma	3	Intramedullary
PNET	2	Intramedullary
Paraganglioma	3	Extramedullary
Neurofibroma	2	Extramedullary
Cavernoma	5	Extramedullary
Giant cell tumour	1	Extramedullary
Osteoma	1	Extramedullary
Lipoma	3	Extramedullary
Angiolipoma	2	Extramedullary

Table 2.
Histological diagnoses of the primary tumours.

The most frequent histologic diagnoses were schwannomas and meningiomas particularly of the meningothelial subtype (Table 2). A statistically significant difference was found in the distribution of the two most frequent diagnoses between the two sexes (U=234.5, p<.001), with the schwannomas being more frequent in males (19/30) and meningiomas in females (24/29), yet no statistically significant difference was found in their age profiles (U=409.5, p=.7).

Interestingly, the two tumour types showed different distributions in the spinal cord (U=249, p<.01), with schwannomas being more common in the lumbar spine (18/30), whereas meningiomas were predominantly located in the thoracic segment (25/29). Again, the observed versus expected distribution of these two tumours were significantly different for each individual sex (X2(3,42)=13.95, p<.001 for males and (X^2(3,42)=31.18, p<.001 for females). Schwannomas and meningiomas in male patients were equally found in the thoracic and lumbar spine, while in female patients they were predominantly located in the thoracic segment (Figure 1).

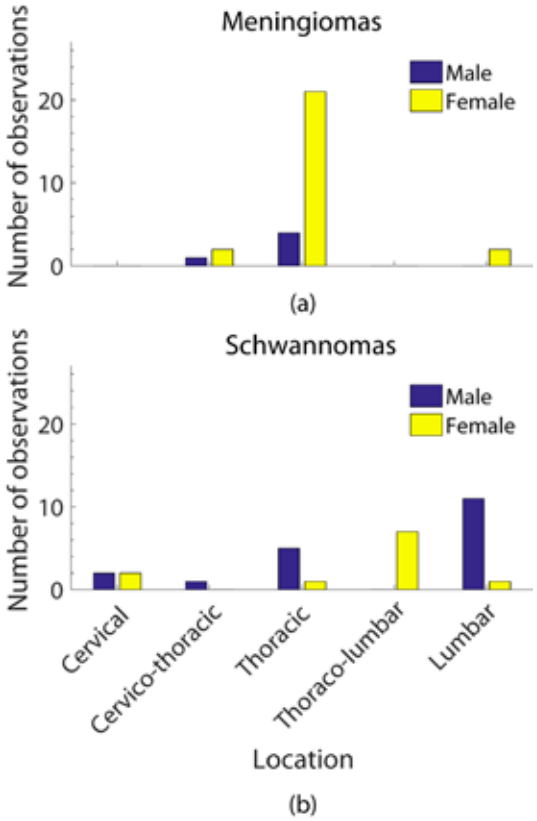

Figure 1. Spatial distribution of meningiomas (a) and schwannomas (b) grouped by gender.

Of the 19 cases of schwannomas found in male patients, 11 were located in the lumbar spine. Further analysis revealed a statistically different distribution from the homogeneous one (X2(3,19)=11.25, p=.01). The same applies for the 24 cases of meningiomas found in female patients, 21 of which were located in the thoracic spine (X2(2,24)=31.75, p<.001).

Histologic diagnosis was found to be correlated with gender (r=.47, p<.01) and location of the mass (r=.41, p<.01) (Figure 2). Examining further the parameters associated with these two histologic diagnoses, a main effect of gender (F=16.25, p<.001) was found using the general linear model. However, this was not the case for age (F=0.13, p=.72) and location of the tumour (F=2.98, p=.09).

Five cases of vascular tumours were treated in patients with a mean age of 54.2 years (SD 24.59). Three of them were men and all but one of the cases were located in the thoracic spine.

The interested reader could also refer to previous publications from our group reporting a case of a cavernoma of the cauda equina [6] and two cases of spinal angiolipomas [7].

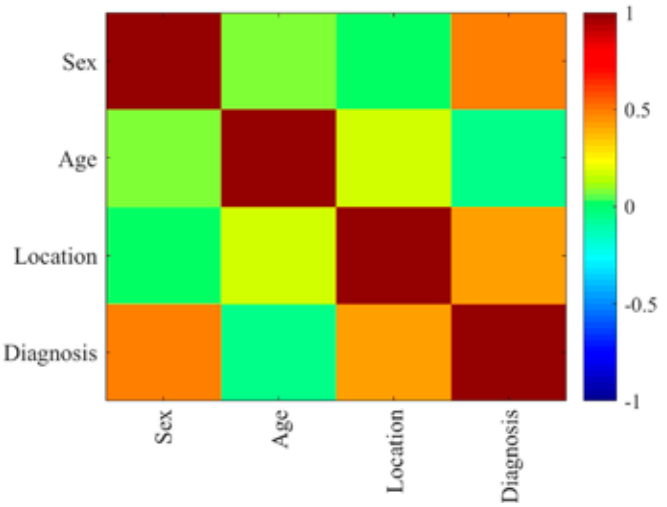

Figure 2. Correlation matrix of the parameters under investigation. Values correspond to Spearman's rank correlation coefficient r.

DISCUSSION

In the present work the demographic data from all spinal cord tumours managed in a single centre over the last decade are reviewed and analysed.

The two most common primary extramedullary tumours are those arising from the nerve sheath cells (represented primarily by schwannomas and neurofibromas) and the meningiomas. Other, less common diagnoses were paragangliomas, neurofibromas and vascular tumours, in this case, cavernomas.

As far as the schwannomas are concerned, most studies report equal frequencies in the two genders [8] or a slight male predominance [4, 9], whereas others challenge this claim suggesting a higher male to female ratio [10] or even a slight female predominance [11].

In turn, an annual incidence of 0.33 per 100,000 has been found in the United States of America for spinal menigniomas [12]. A higher incidence of meningiomas has been reported for the white, non-Hispanic population, compared to non-Hispanic blacks and Hispanics [12, 13]. Similarly, a higher incidence in female patients is reflected by the data [13-16].

In the present series of spinal tumours, female patients diagnosed with meningiomas were significantly more than male patients. This has been well-documented in previous studies [12, 17] and is further supported by a number of clinical and preclinical studies, in which alterations in the size of these masses has been observed throughout the

menstrual cycle [18], as well as an increased risk for presentation in multiparous women [19] and in females with a history of hormone replacement therapy for a prolonged period of time [20] has been established. These observations could be explained at a molecular level by the abundance of oestrogen receptors that have been identified in these tumours [21].

In contrast, the figures were the exact opposite for the case of schwannomas. This difference between genders and the predilection of the two tumour types for each gender, is supported by previous studies [13]. Nevertheless, the difference was not as pronounced. For example, Schellinger et al. found a male to female ratio of 0.29 for meningiomas and 1.25 for nerve sheath tumours, while in our work the respective figures are 0.21 and 1.67.

A key finding derived from our data, is that when investigating the two most frequent diagnoses, the sole predictor of histologic diagnosis is the gender of the patient. Even though schwannomas tend to appear slightly earlier in life and are more frequently encountered in the lower spine [2], our results suggest that when all parameters are being accounted for, the effect of age and location are insignificant.

A wide discrepancy among the results of various studies can be noted, with some of them reporting a higher incidence of menigniomas (e.g. [13, 22]), and others suggesting that nerve sheath tumours are more frequent (e.g. [4, 23]). In fact, their relative ratios have been found to vary depending on the geographic origin of the study.

This discrepancy could be attributed to four individual factors. First and foremost, are the genetic and the environmental factors, which will be examined as a group, since for some cases our level of knowledge does not allow us to differentiate between the two underlying factors.

To begin with, mutations to a number of genes have been identified to be linked to meningiomas [24] and schwannomas [25]. However, to the best of the authors' knowledge no comparative population based epidemiologic study exists. This gap in the available literature is of paramount importance, as it may hinder critical information regarding the aforementioned discrepancy among the various studies.

Next, the sampling bias is an equally important parameter to be considered. Sampling bias is an inherent flaw of all studies, affecting primarily those that address a rare entity, as in the present case. In the review that Hirano et al conducted [4], 14 studies reporting the histological diagnosis of spinal cord tumours were identified, with the number of patients ranging from 92 to 3,226. Importantly, some of these studies were single-centre and interestingly some works report findings of before MRI was readily available or even been invented. It is possible therefore, that some cases were not diagnosed as their symptoms were subtle. It can be expected that as national databases and registries are becoming more readily available, multi-centre studies with larger number of participants will provide a more accurate insight in the topic.

Last but not least, one cannot oversee the potential for a detection bias. This arises from the fact that in some regions physicians are less reluctant to order imaging of the spinal cord over minimal symptomatology. As a result, the tendency to over-diagnose some benign conditions arises. Without doubt the exact opposite also applies, due to restrictions imposed by financial burdens. This is reflected in the higher abidance with the indications for spinal cord MRI in the private sector compared to the public one [26], but also at an international level, with 44.3% [27], 65% and 88% [28] of MRI scans of the spinal cord being considered appropriate in Canada, the USA and Spain respectively. Finally, a recent study demonstrated that physicians were less reluctant to prescribe an MRI of the lumbar spine before conservative therapy if the patient was male, older, black, Hispanic and of low economic status [29].

Finally, with regards to the intramedullary tumours, which account for less than 10% of all spinal cord tumours, the most common histological subtype are ependymomas followed by astrocytomas and hemangioblastomas [30]. All of them are more frequently found in the cervical spine and in male patients [30-32]. In agreement with the available literature, gliomas predominate among the intramedullary spinal cord tumours of the patients managed surgically in the present series, with 78% of them being of glial origin and the remaining two cases being of neuroectodermal origin. The majority of the patients are men with an overall mean age at the time of intervention at 44.2 years (SD 12.77)

CONCLUSIONS

Previous reports on the incidence of nerve sheath cell tumours and meningiomas are inconsistent, which could be attributed to potential environmental or genetic factors or even to sampling and detection bias. As a result, more multi-centre studies are needed to establish a definitive answer to the incidence of spinal tumours. Through the analysis of the collected data, gender was the only parameter to be distinctive of the two most prominent diagnoses. Hence, when encountering an extramedullary tumour, in a female patient, the most probable diagnosis is a meningioma, regardless of her age and location of the mass.

REFERENCES

1. Ostrom, Q.T., et al., CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. Neuro Oncol, 2016. 18(suppl_5): p. v1-v75.
2. Çağlar, Y.Ş. and İ. Doğan, Epidemiology of Spinal Cord Tumors, in Spinal Cord Tumors, K.I. Arnautović and Z.L. Gokaslan, Editors. 2019, Springer International Publishing: Cham. p. 31-42.
3. Ostrom, Q.T., et al., CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol, 2014. 16 Suppl 4(Suppl 4): p. iv1-63.
4. Hirano, K., et al., Primary spinal cord tumors: review of 678 surgically treated patients in Japan. A multicenter study. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 2012. 21(10): p. 2019-2026.
5. Liu, W.C., et al., Radiological findings of spinal schwannomas and meningiomas: focus on discrimination of two disease entities. Eur Radiol, 2009. 19(11): p. 2707-15.

6. Apostolakis, S., et al., Cavernoma of the cauda equina. Surg Neurol Int, 2018. 9: p. 174.

7. Apostolakis, S., et al., Spinal angiolipoma: Presentation of two cases and review of the literature for the years 2012-2017. Neurocirugia (Astur : Engl Ed), 2020. 31(2): p. 76-86.

8. Lenzi, J., et al., Spinal Nerves Schwannomas: Experience on 367 Cases-Historic Overview on How Clinical, Radiological, and Surgical Practices Have Changed over a Course of 60 Years. Neurology research international, 2017. 2017: p. 3568359-3568359.

9. McCormick, P.C., K.D. Post, and B.M. Stein, Intradural extramedullary tumors in adults. Neurosurg Clin N Am, 1990. 1(3): p. 591-608.

10. Jeon, J.H., et al., Spinal schwannoma; analysis of 40 cases. J Korean Neurosurg Soc, 2008. 43(3): p. 135-8.

11. Emel, E., et al., Long-term Surgical Outcomes of Spinal Schwannomas: Retrospective Analysis of 49 Consecutive Cases. Turk Neurosurg, 2017. 27(2): p. 217-225.

12. Kshettry, V.R., et al., Descriptive Epidemiology of Spinal Meningiomas in the United States. Spine (Phila Pa 1976), 2015. 40(15): p. E886-9.

13. Schellinger, K.A., et al., Descriptive epidemiology of primary spinal cord tumors. J Neurooncol, 2008. 87(2): p. 173-9.

14. Preston-Martin, S., Descriptive epidemiology of primary tumors of the spinal cord and spinal meninges in Los Angeles County, 1972-1985. Neuroepidemiology, 1990. 9(2): p. 106-11.

15. Helseth, A. and S.J. Mørk, Primary intraspinal neoplasms in Norway, 1955 to 1986. A population-based survey of 467 patients. J Neurosurg, 1989. 71(6): p. 842-5.

16. Westwick, H.J. and M.F. Shamji, Effects of sex on the incidence and prognosis of spinal meningiomas: a Surveillance, Epidemiology, and End Results study. J Neurosurg Spine, 2015. 23(3): p. 368-73.

17. Duong, L.M., et al., Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004-2007. Cancer, 2012. 118(17): p. 4220-4227.

18. Bickerstaff, E.R., J.M. Small, and I.A. Guest, The relapsing course of certain meningiomas in relation to pregnancy and menstruation. J Neurol Neurosurg Psychiatry, 1958. 21(2): p. 89-91.

19. Wigertz, A., et al., Reproductive factors and risk of meningioma and glioma. Cancer Epidemiol Biomarkers Prev, 2008. 17(10): p. 2663-70.

20. Blitshteyn, S., J.E. Crook, and K.A. Jaeckle, Is there an association between meningioma and hormone replacement therapy? J Clin Oncol, 2008. 26(2): p. 279-82.

21. Cahill, D.W., et al., Estrogen and progesterone receptors in meningiomas. J Neurosurg, 1984. 60(5): p. 985-93.

22. Helseth, A., et al., Neoplasms of the central nervous system in Norway. IV. A population-based epidemiological study of meningiomas. Apmis, 1989. 97(7): p. 646-54.

23. Cheng, M.K., Spinal cord tumors in the People's Republic of China: a statistical review. Neurosurgery, 1982. 10(1): p. 22-4.

24. Yuzawa, S., H. Nishihara, and S. Tanaka, Genetic landscape of meningioma. Brain Tumor Pathol, 2016. 33(4): p. 237-247.

25. Agnihotri, S., et al., The genomic landscape of schwannoma. 2016. 48(11): p. 1339-1348.

26. Mohammadi, N., et al., Appropriateness of physicians' lumbosacral MRI requests in private and public centers in Tehran, Iran. Medical journal of the Islamic Republic of Iran, 2016. 30: p. 415-415.

27. Emery, D.J., et al., Overuse of Magnetic Resonance Imaging. JAMA Internal Medicine, 2013. 173(9): p. 823-825.

28. Kovacs, F.M., et al., Appropriateness of lumbar spine magnetic resonance imaging in Spain. Eur J Radiol, 2013. 82(6): p. 1008-14.

29. Lind, K.E. and J.A. Flug, Sociodemographic Variation in the Use of Conservative Therapy Before MRI of the Lumbar Spine for Low Back Pain in the Era of Public Reporting. J Am Coll Radiol, 2019. 16(4 Pt B): p. 560-569.

30. Chamberlain, M.C. and T.L. Tredway, Adult primary intradural spinal cord tumors: a review. Curr Neurol Neurosci Rep, 2011. 11(3): p. 320-8.

31. Tobin, M.K., et al., Intramedullary spinal cord tumors: a review of current and future treatment strategies. Neurosurg Focus, 2015. 39(2): p. E14.

32. Ogunlade, J., et al., Primary Spinal Astrocytomas: A Literature Review. Cureus, 2019. 11(7): p. e5247-e5247.

TITLE

Infected subdural hematoma in the elderly: a case report

Andreas Zigouris, Anastasios Nasios, George A. Alexiou, Spyridon Voulgaris

Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece

KEYWORDS
Chronic subdural hematoma, Escherichia Coli, Subdural empyema

CONFLICTS OF INTEREST
Nil

CORRESPONDENCE
Andreas Zigouris, Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece 455 00, E-mail andzy76@hotmail.com

FUNDING
None

ABSTRACT
A rare cause of an infected chronic subdural hematoma is the hematogenous spread of an infectious site, such as the urinary tract towards the intracranial space, especially in elderly patients. We report a case of a 92-year old woman with a subdural hematoma of the right cerebral hemisphere, that was infected by Escherichia Coli from an urinary tract infection with review of the literature. The presence of an infected subdural hematoma should be considered, in cases of chronic subdural collections in elderly patients with suspected preexisting extra-cranial infectious processes.

ΠΕΡΙΛΗΨΗ
Μία σπάνια αιτία επιμολυσμένου χρονίου υποσκληριδίου αιματώματος αποτελεί η αιματογενής διασπορά από απομακρυσμένη λοιμώδη εστία, όπως το ουροποιητικό σύστημα, συνήθως σε ηλικιωμένους ασθενείς. Παρουσιάζουμε την περίπτωση μιας γυναίκας 92 ετών με εμπύρετο και χρόνιο υποσκληρίδιο αιμάτωμα, το οποίο απεδείχθη μετά αποστολή καλλιεργειών επιμολυσμένο με Escherichia Coli από αντίστοιχη λοίμωξη στο ουροποιητικό σύστημα. Η ανασκόπηση της βιβλιογραφίας ανέδειξε 16 άρθρα τα τελευταία 50 έτη με καταγραφή επιμολυσμένης υποσκληριδίου συλλογής αίματος σε ασθενείς 70 ετών και άνω. Το συνηθέστερο μικρόβιο ήταν όπως και στη δική μας περίπτωση η Escherichia Coli. Η επιμόλυνση ενός προϋπάρχοντος αιματώματος πρέπει να συμπεριλαμβάνεται στη διαφοροδιάγνωση εμπύρετων ασθενών σε προχωρημένη ηλικία, λόγω συνοδού συννοσηρότητας και μειωμένης ανταπόκρισης του ανοσοποιητικού συστήματος.

INTRODUCTION

The clinical and radiological entity of chronic subdural hematoma is well studied as a common neurosurgical entity, especially in elderly patients who receive anticoagulant medication. A rare cause of an infected chronic subdural hematoma is the hematogenous spread from an infectious site, such as the urinary tract [1, 2]. On the other hand, subdural empyema refers to a rare condition associated with parasinusitis, otitis media and open depressed fractures of frontal and / or temporal bones [1]. The spread of an infection to an altered subdural space where blood exists, protein and cerebrospinal fluid is a rare condition, but in the case of coexistence of an infection and a hematoma, the neurosurgeon should always be mindful and collect subdural fluid samples for analysis and culture [2]. We report a case of an infected subdural hematoma in an elderly patient and we perform a review of the literature.

CASE REPORT

A 92-year old woman was admitted to the emergency department with fever (38°C), shudders and disorientation. Laboratory examination revealed leukocytosis and a 40-fold increased c-reactive protein. The urine analysis of the patient revealed an increased number of pyospheres and high levels of protein. Past history included dementia, uterine cancer three years prior to admission with adjunct radiotherapy and bilateral hip arthroplasty due to osteoarthritis. She was admitted to the internal medicine department, in order to determine the cause of the fever. After 72 hours she became lethargic, developed left hemiparesis and focal seizures. Computed tomography scan revealed a right-sided subdural hematoma with a 13 mm midline shift and global hemispheric edema (Fig.1,2).

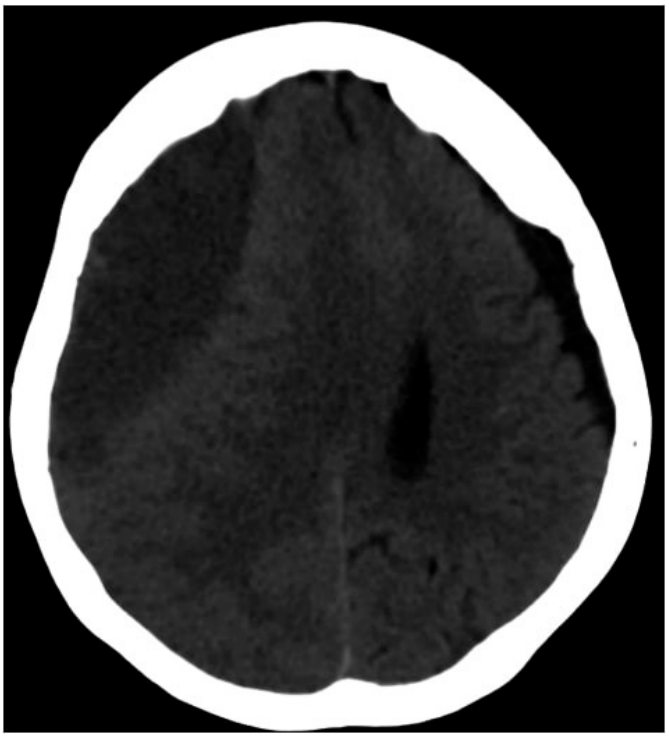

Figure 1.
A right-sided subdural hematoma with a 13 mm midline shift and global hemispheric edema (upper section cut).

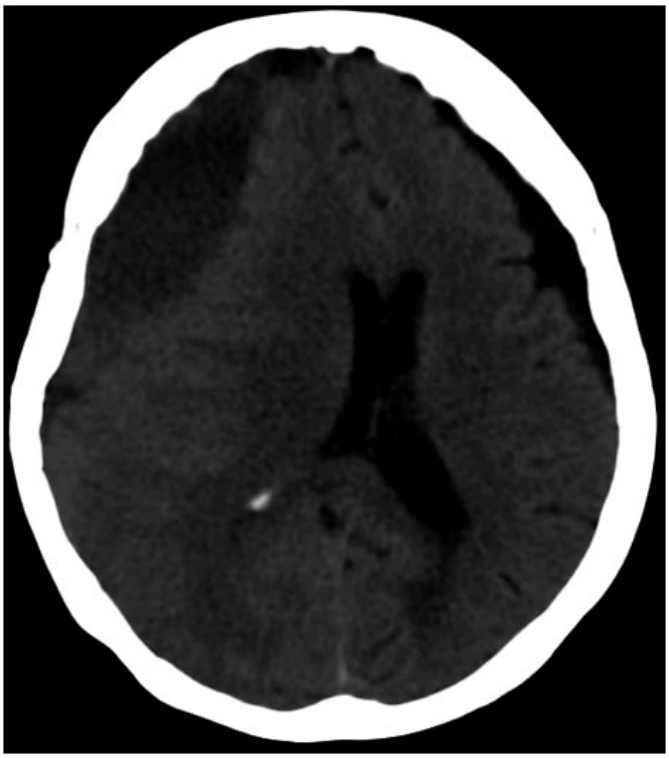

Figure 2.
A right-sided subdural hematoma with a 13 mm midline shift and global hemispheric edema (lower section cut).

She underwent urgent evacuation of the hematoma with two burr holes (frontal, parietal) and placement of a subdural drain for 48 hours. The color of the subdural fluid was blurred yellowish-brown and appeared not to be purulent. She was hospitalized in the intensive care unit for 48 hours and was admitted to the neurosurgical department afterwards with Glasgow Coma Scale of 13/15 and slight left hemiparesis. Based on the results of the bacterial cultures received from the urine and the subdural fluid, the common pathogen isolated was Escherichia Coli. The neurological deficits recovered significantly postoperatively. The patient received ceftriaxone, vancomycin and metronidazole intravenously for 6 weeks. The patient became afebrile in 2 days and demonstrated progressive improvement. Despite this clinical course, she passed away after 2 months because of acute respiratory failure.

DISCUSSION

Chronic subdural hematoma is a common neurosurgical entity that usually demands urgent evacuation. The surgical procedures include burr holes, craniotomy or craniectomy with or without placement of a subdural drain [3]. On the other hand, purulent fluid exists in empyema, a rare clinical entity correlated with otitis media, parasinusitis or anterior/middle cranial fossa skull base fractures [1]. Hematogenous seeding from a distant infection to the subdural space is uncommon. The aforementioned predisposing factors were not present in our case. An encapsulated hematoma is vulnerable to bacterial dissemination from a distant source due to neovascularization and bridging fragile veins with vascular hyperpermeability [4]. It is not a common complication of a preexisting hematoma, but could be fatal especially in elderly patients.

Previous reports strongly suggest that old and compromised patients with an underlying disease such as cancer are susceptible to emerge an infected subdural hematoma. Bacteria might have been transferred hematogenously on the capsule of the chronic subdural hematoma by bacteremia derived from immunological dysfunction. An additional factor is the contemporary presence of a well-described inflammatory state in cases of chronic subdural hematoma [5,6].

An interesting theme is to distinguish the results of bacterial dissemination in the subdural space according to terms such as subdural empyema, infected subdural hematoma and subdural abscess. A subdural empyema is a distinct pathology from an infected subdural hematoma because in the first case the subdural space is clearly filled with pus, when in the second case the fluid resembles a typical chronic hematoma where the lab cultures isolate a pathogen. Additionally, the subdural abscess is an encapsulated mass over the brain convexity where the purulent fluid inside could be contaminated from more than one bacteria and a distinct feature is the high thickness of the capsule [3,4] .

In the last 50 years there were cases reported in the literature of infected subdural hematomas in patients > 70 years old, as it is shown in table 1 [6-21]. Escherichia Coli was the most common bacteria which was isolated from the subdural fluid and the urinary tract the most common site of infection. Vetrovec et al. reported three cases of infected subdural hematomas during bacteremia, two with Salmonellae and one with Escherichia Coli [22]. Kaminogo et al in

AUTHORS	YEAR OF PUBLISH	SEX	AGE	BACTERIA
Braun CW et al. [7]	1980	F	77	β-hemolytic Streptococcus
Casson IR et al. [8]	1981	M	70	Escherichia Coli
Kaminogo M et al. [9]	1984	F	76	Escherichia Coli
Bakker S et al. [10]	1995	F	88	Escherichia Coli
Hirano A et al. [6]	1995	M	86	Escherichia Coli
Aoki N et al. [11]	1997	M	70	Campylobacter fetus
Sawauchi S et al. [12]	1998	F	77	Escherichia Coli
Honda M et al. [13]	2002	F	71	Klebsiella pneumoniae
Otsuka T et al. [14]	2007	M	87	Unknown
Narita E et al. [15]	2009	M	80	Escherichia Coli
Kobayashi N et al. [16]	2009	F	75	Escherichia Coli
Dost L et al. [17]	2012	M	86	Campylobacter fetus
Fujii N et al. [18]	2013	M	76	MRS (Methicillin-Resistant Staphylococcus Aureus)
Nagao T et al. [19]	2015	F	78	Proteus mirabilis
Anno T et al. [20]	2018	M	76	Edwardsiella tarda
Akiyama T et al. [21]	2021	M	72	Helicobacter cinaedi

Table 1.
Previously reported cases with an infected subdural hematoma.

a 76-year-old man observed that both culture of subdural fluid and urine yielded Escherichia coli [9]. Sawauchi et al. reported that in the majority of cases the causative organisms were Escherichia coli, Salmonella, and the systemic sources of infection were the urinary tract, gastrointestinal tract, or unknown [12]. Dabdoub et al proposed craniotomy as the method of surgical drainage in adults, because it ensures maximal drainage of the loculated contaminated fluid and allows the total removal of the capsule [1]. In our case two burr holes allowed excellent visuallization of the cavity and the inner membrane, which was opened as in all cases of chronic subdural hematomas [23].

CONCLUSIONS

The presence of an infected subdural hematoma should be considered when computed tomography findings indicative of a chronic subdural hematoma exist in an elderly patient with a suspected preexisting infectious process. Surgical evacuation and a 6-8-week antibiotic therapy are considered mandatory, although the co-morbidities of the elderly patients may affect the clinical outcome negatively.

REFERENCES

1. Dabdoub CB, Adorno JO, Urbano J, Silveira EN, Orlandi BM. Review of the Management of Infected Subdural Hematoma. World Neurosurg. 2016 Mar; 87:663.e1-8.
2. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. J Neuroinflammation. 2017 May 30; 14(1):108.
3. Greenlee JE: Subdural empyema. Curr Treat Options Neurol. 2003 Jan; 5(1):13-22.
4. Kaminogo M, Kurihara M, Kawano T, Mori K, Yasuda M: A case of infected subdural hematoma (subdural empyema) secondary to septicemia caused by agranulocytosiS. No Shinkei Geka. 1984 Mar; 12(3 Suppl):353-7.
5. M Kan , T Kim, T Miyaichi, H Rinka, Y Matsuo, T Shigemoto, T Yoshimura, A Kaji, K Tsukioka, T Ukai, M Nishikawa, K Yamanaka: A case of Salmonella subdural empyema developed in chronic subdural hematoma. No Shinkei Geka. 1998 Oct;26(10):903-7.
6. Hirano A, Takamura T, Murayama N, Ohyama K, Matsumura S, Niwa J. Subdural abscess following chronic subdural hematoma (in Japanese) No Shinkei Geka. 1995;23:643–646.
7. Braun CW, Axelrod J: Hematogenous infection of subdural hematoma. Arch Neurol 1980;37:467–468.
8. Casson IR, Patel P, Blair D, Bergtraum M: Subdural empyema. Caused by infection of preexisting subdural hematoma. NY State Med J 1981;81:389–391.
9. Kaminogo M, Kurihara M, Kawano T, Mori K, Yasuda M: A case of infected subdural hematoma (subdural empyema) secondary to septicemia caused by agranulocytosis (in Japanese). No Shinkei Geka 1984;12:353–357.
10. Bakker S, Kluytmans J, den Hollander JC, Lie ST: Subdural empyema caused by Escherichia coli: hematogeneous dissemination to a preexisting chronic subdural hematoma. Clin Infect Dis 1995;21:458–459.
11. Aoki N, Sakai T, Oikawa A, Takizawa T, Shishido T: Infected subdural effusion associated with resolving subdural hematoma – case report. Neurol Med Chir (Tokyo) 1997;37:637–639.
12. Sawauchi S, Saguchi T, Miyazaki Y, Ikeuchi S, Ogawa T, Yuhki K, Abe T: Infected subdural hematoma. J Clin Neurosci 1998;5:233–237.
13. Honda M, Tanaka K, Tanaka S, Nakayama T, Kaneko M, Ozawa A: A case of infected subdural hematoma following chronic subdural hematoma irrigation (in Japanese). No To Shinkei 2002;54:703–706.
14. Otsuka T, Kato N, Kajiwara I, Tanaka T, Sawauchi S, Numoto RT, Murakami S, Abe T: A case of infected subdural hematoma (in Japanese). No Shinkei Geka 2007;35:59–63.
15. Narita E, Maruya J, Nishimaki K, Heianna J, Miyauchi T, Nakahata J, Kitahara H, Minakawa T: Case of infected subdural hematoma diagnosed by diffusion-weighted imaging. Brain Nerve 2009;61:319–323.
16. Kobayashi N, Ishikawa T, Muto T, Kawai H, Hikichi K, Moroi J, Suzuki A, Yasui N: Infected organized subdural hematoma after burr hole operation: a case report. Jpn J Neurosurg 2009;18:464–469.

17. Dost L, Denes E, Hideri N, Ploy MC, Barraud O, Moreau JJ, Carie F: Chronic subdural hematoma infected by Campylobacter fetus: case report (in French). Neurochirugie 2012;58:52–54.

18. Fujii N, Naito Y, Takanashi S, Ueno T, Nakagomi T: A case of infected subdural hematoma accompanied by cerebral infarction (in Japanese). No Shinkei Geka 2013;41:407–413

19. Nagao T, Miyazaki C, Ando S, Haga D, Kuroki T, Sugo N, Nagao T. [Infected subdural hematoma having a surgery of chronic subdural hematoma 1 year ago:a case report]. No Shinkei Geka. 2015 Feb; 43(2):153-7.

20. Anno T, Kobayashi N. Infected subdural hematoma caused by Edwardsiella tarda. J Rural Med. 2018 May; 13(1):86-88. doi: 10.2185/jrm.2957. Epub 2018 May 29.

21. Akiyama T, Imamura H, Fukui N, Sakai N. Helicobacter cinaedi-infected chronic subdural hematoma mimicking an expanding hematoma: A case report. Surg Neurol Int. 2021 Jun 14; 12:288.

22. Vetrovec GW, Warner JF: Infected subfural hematoma: three case reports involving gram-negative organisms. Am J Med Sci. 1975 Jan-Feb; 269(1):113-5.

23. Pahatouridis D, Alexiou GA, Fotakopoulos G, Mihos E, Zigouris A, Drosos D, Voulgaris S: Chronic subdural hematomas: a comparative study of an enlarged single burr hole versus double burr hole drainage. Neurosurg Rev. 2012 Aug 7Meningiomas in the United States. Spine (Phila Pa 1976), 2015. 40(15): p. E886-9.

TITLE

Infratentorial meningioma presenting vocal cord palsy: A rare clinical case

Dionysoula Skiada, Evaggelos Michos, Dimitrios Pachatouridis, George A. Alexiou, Spyridon Voulgaris

Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece

KEYWORDS
Meningioma, infratentorial, vocal cord palsy

FUNDING
No funding was received for this study

CORRESPONDENCE
Skiada D. Department of Neurosurgery, University Hospital of Ioannina, Stavrou Niarchou Avenue 45500, Tel.+30 2651099701, E-mail: skiada.silia@gmail.com

CONFLICT OF INTEREST
None

ABSTRACT
Meningiomas are the most common primary central nervous system tumors in adults. Headache is the most common presenting symptom in both supratentorial and infratetorial lesions, while seizures concern the supratentorial ones. They are typically not infiltrative or fast-growing tumors, so they have an insidious symptom onset. We report an unusual clinical manifestation of an infratentorial meningioma. The patient presented with swallowing difficulties and hoarse voice as an outcome of vocal cord paresis, probably caused from an affection of the superior laryngeal nerve.

ΠΕΡΙΛΗΨΗ
Τα μηνιγγιώματα είναι ο πιο συχνός πρωτοπαθής όγκος του κεντρικού νευρικού συστήματος. Το 13% αυτών εντοπίζεται στον οπίσθιο κρανιακό βόθρο. Παρουσιάζεται η περίπτωση μιας ασθενούς με πάρεση κρανιακού νεύρου από χωροκατακτητική εξεργασία οπισθίου κρανιακού βόθρου, η οποία δεν ήταν σε σαφή επαφή με τη βλάβη. Υπεβλήθη σε χειρουργική επέμβαση ολικής εξαίρεσης της βλάβης και μετά ένα έτος παρατηρήθηκε μερική βελτίωση της αρχικής συμπτωματολογίας.

INTRODUCTION

Intracranial meningiomas account for about 32% of primary central nervous system tumors in adults, with an incidence peak at 45 years old and a sex ratio prevalence for female to male of 2.27/1. [1] Posterior fossa meningiomas, comprise the 13% of all meningiomas. They are usually presented with signs and symptoms of increased intracranial pressure (mass effect) and hydrocephalus (obstruction of the IV ventricle), including headache, nausea-vomiting, papilledema, ataxia, vertigo, diplopia. Other frequent location-related symptoms are dysmetria and intensional tremor (concerning cerebellar hemisphere), gait disturbance on broad base, truncal ataxia (concerning cerebellar vermis), multiple cranial nerve palsy and rotatory or vertical nystagmus when brainstem is involved.[2].

We report a rare clinical case, of a patient that presented with swallowing difficulty and hoarse voice as an outcome of vocal cord paresis, probably caused from an affection of the superior laryngeal nerve.

CASE PRESENTATION

A 59 year-old female patient presented with progressive dysphagia, paroxysmal cough, and frequent changes of voice tonality for a three week period, with a constant deterioration. The difficulty was either for liquid or solid food. At first she visited an ENT specialist, who performed an indirect laryngoscopy and discovered a left vocal cord paresis. The subsequent diagnostic tests according to guidelines for unilateral vocal cord paresis revealed no usual pathology, including neck ultrasonography, and finally the patient underwent a brain magnetic resonance imaging (MRI). MRI demonstrated a large extra-axial lesion, measuring 36 x28 x37 mm in the right cerebellar hemisphere, hypointense on both T1-weighted and T2-weighted sequences. After gadolinium infusion, the mass showed homogeneous contrast enhancement with dural attachment on the right tentorium [Figure 1]. The mass was not in direct contact with the cerebellopontine angle, did not obstruct the IV ventricle and did not cause displacement of the midline structures. Past medical history was unremarkable.

The patient was advised to visit our neurosurgical department, and after perfoming a cautious physical examination we did not find any other cranial nerve palsy. We also discovered right dysdiadohokinesia, very excitable reflexes on the right side and Babinski sign, without Romberg or Barre sign. Surgical intervention was recommended. A chest x-ray and an electrocardiogram were performed, as well as complete blood test, coagulation profile, glucose levels, renal and liver function, and a complete hormonological profile (T3, T4, TSH, FT4, E2, FSH, LH, PRL, TES, SHBG, DHEA-S, βHCB, PRG, CORT, AFP, CEA, CA19.9, CA 15.3, CA125) with no pathological findings. Preoperatively, the patient received the standard preoperative prophylactic administration of broad spectrum antibiotics.

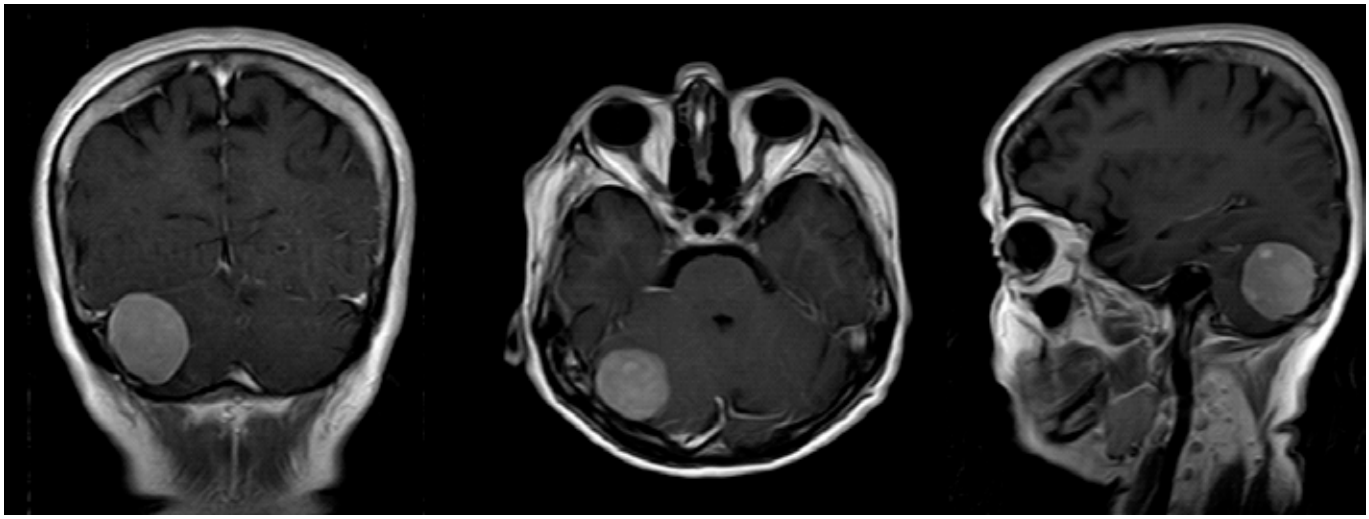

Figure 1. Gadolinium enhanced T1-weighted MRI demonstrating the posterior fossa meningioma.

OPERATIVE PROCEDURE

After an EVD placement the patient was positioned in prone – concorde – position. A right paramedian suboccipital craniectomy was performed [3,4] After the bone removal and the dural incision, the tumor appeared to have a broad base on the tentorium and a rich vascularization, and it was well-demarcated from the adjacent cerebellar tissue. Frozen section analysis confirmed the presence of a meningioma. The rest of the tumor was being debulked and totally resected with the use of Cavitron Ultrasonic Surgical Aspirator (CUSA) [Figure 2].

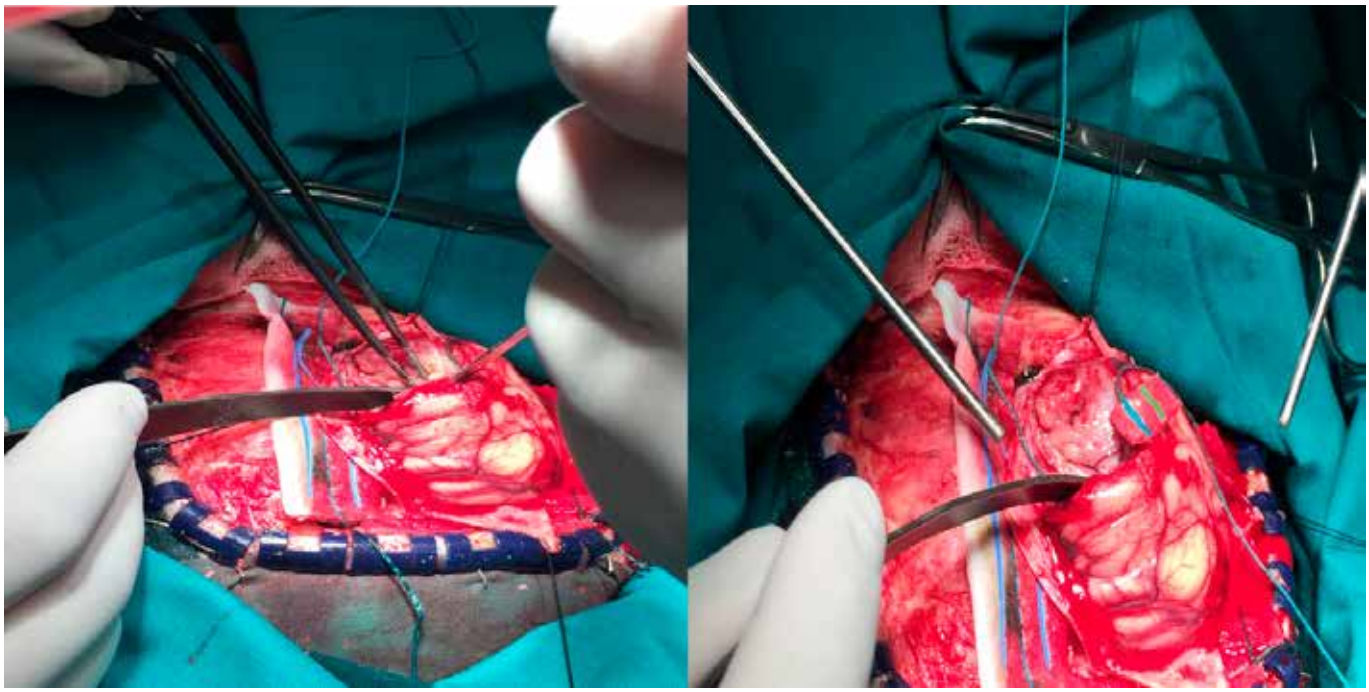

Figure2. Intraoperative photos.

A gross total resection was uneventful, and the patient admitted to the Intensive Care Unit for post-operative monitoring. A brain CT-scan was performed on postoperative Day 1, that demonstrated the complete resection of the tumor without any sign of ischemia or hemorrhage [Figure 3]. Pathology revealed the presence of a meningioma grade 1.

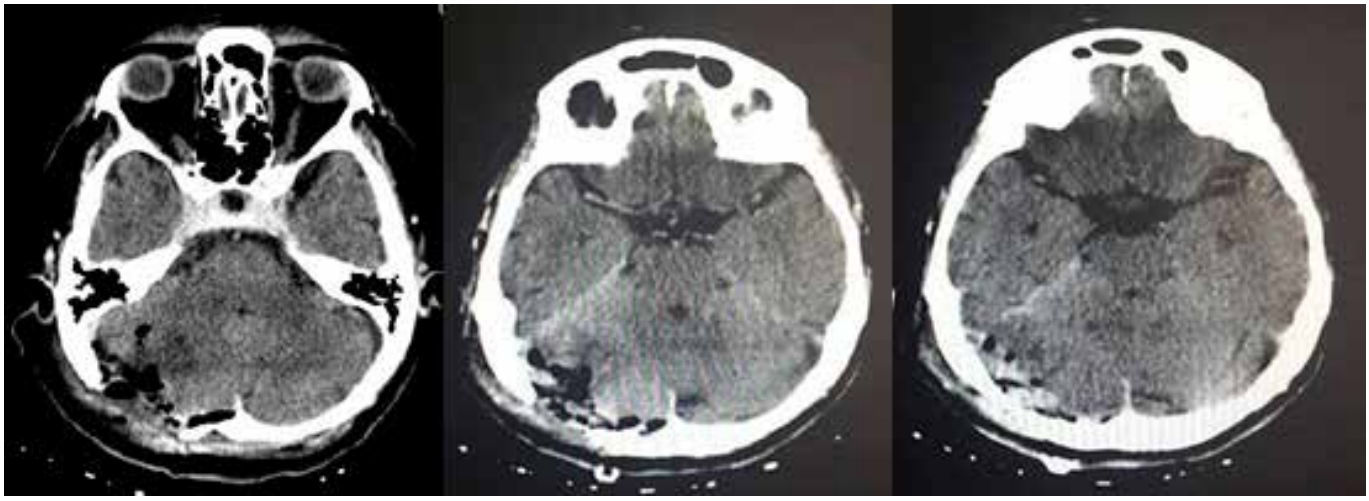

Figure 3. Postoperative CT revealing complete tumor removal.

During the post-operative period the patient did not present any focal neurological deficit, or other clinical symptoms such as fever, nausea and vomiting. All her initial symptoms disappeared apart from light dysphagia. Two-months later, a new indirect laryngoscopy was performed by the same ENT, that revealed the same hypokinesia of the left vocal cord. Four-months later, a brain MRI demonstrated the gross total resection of the meningioma without any damage to adjacent cerebellar [Figure 4]. The sensation of foreign body in the throat persisted but was slightly better.

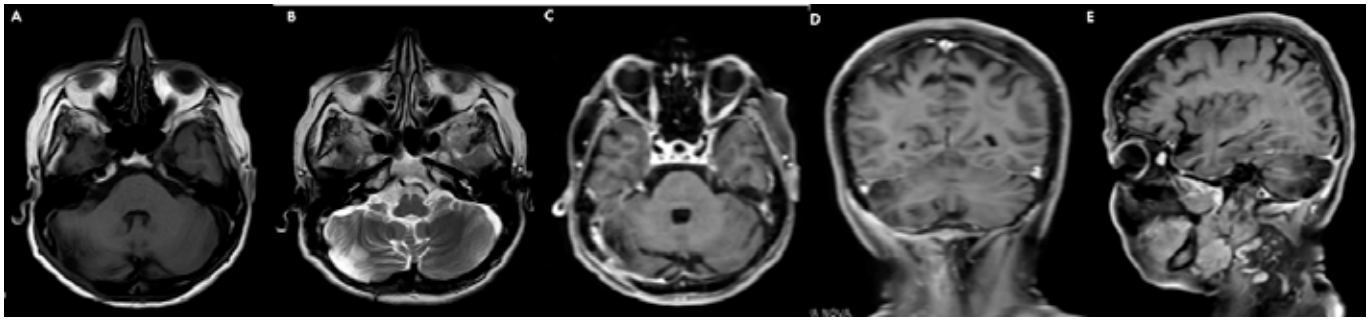

Figure 4. Postoperative MRI revealing complete tumor removal. A. T1 weighted MRI. B. T2-weighted MRI. Gadolinium enhanced T1 in 3 planes (C,D,E).

DISCUSSION

Laryngeal nerves are branches of vagus nerve (X) and are divided in the superior laryngeal nerve and the recurrent laryngeal nerve. The superior laryngeal nerve is sensorimotor and gives sensory innervation to all supraglottic areas (false vocal chords, epiglottis and aryepiglottic folds), via the internal branch, as well as motor innervation to cricothyroid muscles and lower pharyngeal muscles. Any loss of sensory innervation in the aforementioned areas has an important impact in protection of airway from saliva and food bolus. Patients with superior laryngeal nerve involvement will report symptoms due to motor function, such as changes in their voice pitch (cricothyroid muscle) or swallowing difficulties (pharyngeal constrictors) as well as symptoms due to sensorineural function loss [5]. These would be saliva aspirations and paroxysmal cough due to internal branch involvement. However, if only the superior laryngeal nerve is affected the voice symptom can be bitonal voice production due to unilateral loss of vocal cord tension (cricothyroid muscle). In unilateral paresis the symptoms can be mild but in bilateral lesions the complete loss of sensory innervations can lead to frequent aspirations and infections of the lower respiratory system.

When patients visit the ENT with hoarse voice and loss of sensation the physician must be aware of any kind of pathology within the entire length of the vagus nerve. The European guidelines for unilateral paralysis are the following [6,7] complete history, palpation, indirect laryngoscopy, thyroid examination and neck ultrasonography. If no clear pathology is found further diagnostic work-up must follow with brain MRI, CT of the thorax and skull base, stroboscopy and voice analysis, microlaryngoscopy. Barium swallowing test, functional respiratory test and laryngeal EMG. There is a long list of possible pathologies that can affect both superior and recurrent laryngeal nerves, especially unilaterally and the possible causes can be either neurogenic or mechanical. The main categories are neoplasmatic, traumatic (surgical and non-surgical), on basis of other systematic diseases and idiopathic.

The most commonly occurring meningiomas in the posterior cranial fossa are located in the cerebellopontine angle. Their usual clinical manifestation involves the lower cranial nerves compression. In this rare clinical case, there has been noticed a single cranial nerve affection from a lesion of the posterior fossa that was not anatomically related to the nerve, most probably from the surrounding edema, which, because of the

small space of the posterior fossa, was crucial in affecting the ipsilateral vagus nerve.

CONCLUSIONS

In the current case indirect laryngoscopy revealed a paresis of the left vocal cord with slight dysphonia (double pitch and hoarseness) while the patient didn't report any history of prior pathology/surgery in the neck or thoracic area. The neck U/S revealed no pathology and it was decided to perform a brain MRI scan which showed the presence of the enlarged meningioma. To the best of our knowledge no previous case has been reported to date. Thus, it is crucial to have in mind that the ENT specialists must examine the whole spectrum of the aforementioned pathologies

REFERENCES

1. Alexiou GA, Gogou P, Markoula S, Kyritsis AP. Management of meningiomas. Clin Neurol Neurosurg. 2010 Apr;112(3):177-82. doi: 10.1016/j.clineuro.2009.12.011.
2. Lemée JM, Corniola MV, Da Broi M, Joswig H, Scheie D, Schaller K, Helseth E, Meling TR. Extent of Resection in Meningioma: Predictive Factors and Clinical Implications. Sci Rep. 2019 Apr 11;9(1):5944. doi: 10.1038/s41598-019-42451-z.
3. Aguiar PH, Tahara A, de Almeida AN, Kurisu K. Microsurgical treatment of tentorial meningiomas: Report of 30 patients. Surg Neurol Int. 2010 Jul 29;1:36. doi: 10.4103/2152-7806.66851.
4. Choque-Velasquez J, Raj R, Hernesniemi J. One burr-hole craniotomy: Supracerebellar infratentorial paramedian approach in Helsinki Neurosurgery. Surg Neurol Int. 2018 Aug 14;9:162. doi: 10.4103/sni.sni_164_18.
5. Seyed Toutounchi SJ, Eydi M, Golzari SE, Ghaffari MR, Parvizian N. Vocal cord paralysis and its etiologies: a prospective study. J Cardiovasc Thorac Res. 2014;6(1):47-50. doi: 10.5681/jcvtr.2014.009.
6. Misono S, Merati AL. Evidence-based practice: evaluation and management of unilateral vocal fold paralysis. Otolaryngol Clin North Am. 2012 Oct;45(5):1083-108. doi: 10.1016/j.otc.2012.06.011
7. Korean Society of Laryngology; Phoniatrics and Logopedics Guideline Task Force; Ryu CH, Kwon TK, Kim H, Kim HS, Park IS, Woo JH, Lee SH, Lee SW, Lim JY, Kim ST, Jin SM, Choi SH. Guidelines for the Management of Unilateral Vocal Fold Paralysis From the Korean Society of Laryngology, Phoniatrics and Logopedics. Clin Exp Otorhinolaryngol. 2020 Nov;13(4):340-360. doi: 10.21053/ceo.2020.00409.

HELLENIC NEUROSURGERY
www.enxe.gr