

# BMJ Open Current knowledge on spinal meningiomas: a systematic review protocol

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## ABSTRACT

**Introduction** Meningiomas are primary central nervous system tumours that arise from both cranial and spinal meninges. Spinal meningiomas occur less frequently than their cranial counterparts and are consequently given less attention in the literature. Therefore, systematic studies are needed to summarise the current knowledge on spinal meningiomas, providing a solid evidence base for treatment strategies. This systematic review of the literature will therefore assess studies describing spinal meningiomas, their epidemiology, diagnostics, treatment and outcomes.

**Methods and analysis** Electronic databases, including PubMed, Web of Science and Embase, will be searched using the keywords “spinal” and “meningioma”. The search will be set to provide only English studies published after 2000 to avoid any conflicts regarding terminology and classification, as well as to reflect the current status. Case reports, editorials, letters and reviews will also be excluded. Reference lists of relevant records will also be searched. Identified studies will be screened for inclusion, by one reviewer in a first step and then three in the next step to decrease the risk of bias. The results will be categorised to allow for a structured summary of the outcomes and their evidence grade conforming to the Grading of Recommendations, Assessment, Development and Evaluation approach. Categories may include: epidemiology, histopathology, radiological diagnostics, surgery, complications, non-surgical or adjuvant treatments, disease outcomes and predictors, and lastly recurrence. This review will summarise the current knowledge on spinal meningiomas to allow for a better understanding of the disease and contribute to improve its management. For clinicians, the systematic collection and grading of available evidence may aid in decision making and for those seeking to further the scientific field, this review may help to identify areas where knowledge is currently lacking.

**Ethics and dissemination** Ethics approval was not required for our systematic review as it is based on existing publications. The results will be disseminated via submission for publication in a peer-reviewed journal.

## INTRODUCTION

Meningiomas originate from the arachnoid cap cells in the leptomeninges surrounding the brain and spinal cord. Hence, they occur

## Strengths and limitations of this study

- ⇒ We developed a thorough strategy to assess both risk of bias in individual studies as well as the collective quality of evidence with respect to the Grading of Recommendations, Assessment, Development and Evaluation guidelines.
- ⇒ Our broad search strategy and limited set of exclusion criteria allows for more studies to be included, ensuring adequate coverage of the topic and identification of knowledge gaps.
- ⇒ By providing a comprehensive synthesis of the body of evidence, the possibility to focus future research efforts will be improved.
- ⇒ We suspect that the quality of data does not suffice to perform a meta-analysis, consequently limiting the level of evidence that can be achieved.

most frequently in an intradural extramedullary location. Meningiomas of the spinal cord are less common, making up only about 2%–12% of all meningiomas.<sup>1–3</sup> In fact, much of what we know today is derived from studies on intracranial meningiomas. Spinal meningiomas are the most common primary spinal tumour in adults, representing 25%–45% of all tumours and occur with an age-adjusted incidence of 0.33 per 100 000 population.<sup>1</sup> Most spinal meningiomas (90%) are benign, WHO I tumours,<sup>4–6</sup> mainly seen in the elderly with a peak incidence between the seventh and ninth decades of life.<sup>2,4</sup> Regardless of their location, meningiomas are more commonly found in females. For spinal meningiomas the female to male ratio is around 4:1.<sup>2,4,7,8</sup> Most meningiomas occur sporadically but a known genetic association to neurofibromatosis type 2 (NF2) is established, and it is estimated that up to 20% of patients with NF2 will develop spinal meningiomas, which might even appear earlier on in life.<sup>9,10</sup> Mutations of the NF2 tumour suppressor gene or loss of chromosome 22 harbouring this gene was found to be more frequent among spinal meningiomas of WHO grades II and III.<sup>11,12</sup>



Exposure to high-dose ionising radiation is also associated with earlier onset of spinal meningioma.<sup>113</sup> Meningiomas often carry oestrogen or progesterone receptors,<sup>14</sup> suggesting pregnancy as a potential risk factor for tumour growth.<sup>1516</sup> This association was however refuted by a large population-based cohort study.<sup>17</sup> Spinal meningiomas may produce neurological deficits and pain related to local compression of the spinal cord, nerves and adjacent structures.<sup>418</sup> The diagnosis is best made using MRI where meningiomas show homogeneous enhancement on gadolinium enhanced T1 sequences. Meningiomas also typically display dural tails, enhancement and thickening of the dura extending from the tumour.<sup>19</sup> The treatment of choice is surgery, where tumour removal typically alleviates symptoms with little risk of complications or recurrence.<sup>47</sup> In surgery of meningiomas, Simpson grading is used to describe the radicality of tumour removal and to predict the risk for tumour recurrence. Whether Simpson grade I, which includes complete removal of dural attachments, should be the goal of spinal meningioma surgery, remains a topic of debate.<sup>420-23</sup> The Simpson scale also addresses the removal or coagulation of the affected dura. Aggressive removal of the dura may reduce the risk of recurrence but increases the risk of spinal cord injury and postoperative leakage of cerebrospinal fluid. Surgical techniques with removal of the inner dural layer, may constitute an intermediate solution.<sup>2425</sup> The most commonly reported postoperative complications are wound infections, cerebrospinal fluid leaks, kyphosis, venous thromboembolisms and transient or permanent neurologic deficits.<sup>4726-28</sup> However, these complications are rare and improvement of neurological function after tumour removal is expected in the majority of patients.<sup>429</sup> For patients having undergone Simpson grade 2 resection of a spinal meningioma, Kim *et al* have estimated a mean clinical recurrence-free survival period of 17 years.<sup>21</sup> Poor outcomes on the other hand are reportedly associated with factors like: WHO tumour grade >1, high Ki-67 index, long time to diagnosis, large tumour size and the degree of spinal cord compression<sup>4630</sup> while mortality mainly reflects high age or comorbidities.<sup>47</sup> Very little data on health-related quality of life after spinal meningioma surgery is available. Two studies with mixed groups of intradural extramedullary tumours found that the vast majority of patients who underwent surgery saw a significant improvement of activity, mood, walking ability, quality of relations, sleep and a decrease in pain.<sup>3132</sup>

These findings are consistent with the results of a quality-of-life questionnaire our group conducted on 84 spinal meningioma patients at an average of 8.7 years after surgery.<sup>33</sup> The need for alternative or adjuvant therapies is emphasised in the literature, especially for recurring tumours refractory to conventional therapies and higher-grade tumours (WHO II–III) or for patients who are poor surgical candidates.<sup>2834</sup> In these cases, other treatment modalities, including targeted, hormonal, micro-RNA or different forms of radiation therapy, may have to be explored. However, the role of non-surgical treatment options in the management of spinal meningiomas remains poorly defined.

The systematic review proposed with this protocol aims to create a comprehensive overview of the current understanding of spinal meningiomas, as well as to clarify the evidence base for the treatment strategies employed today. Topics which will be reviewed include epidemiology, tumour characteristics, diagnostics, treatment options with their potential risks and benefits, as well as outcomes including quality of life, mortality and recurrence. The created overview will serve as a foundation for treatment choices and possibly to identify areas of insufficient knowledge, warranting renewed scientific effort.

Instead of the more classic criteria (Population, Intervention, Comparison, Outcome), we decide to use the criteria<sup>35</sup> (Sample, Phenomenon of Interest, Design, Evaluation, Research type) which we believe are more suited to the purpose of this review (table 1).

## METHODS AND ANALYSIS

### Study registration

This protocol for an intended systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement of 2015.<sup>36</sup> The PRISMA-P checklist is provided as online supplemental file 1. The systematic review protocol will also be registered on PROSPERO, before submission of the final manuscript to a peer-reviewed journal.

### Eligibility criteria

#### Inclusion criteria

#### Type of studies

All peer reviewed and original studies, written in English and available in the PubMed, Embase or Web of Science

**Table 1** SPIDER criteria<sup>35</sup>

Sample	Any patient
Phenomenon of Interest	Spinal meningiomas
Design	Studies presenting original numeric data on the different topics of interest
Evaluation	Epidemiology, tumour characteristics, diagnostics, treatment, patient outcome and recurrence
Research type	Experimental and observational studies
SPIDER, Sample, Phenomenon of Interest, Design, Evaluation, Research.	

databases, will be eligible for inclusion. Only studies published after 2000 will be included to limit our review to the more current publications within the field.

#### Type of participant

All patients will be included, regardless of age, ethnicity and sex. Similarly, all spinal meningiomas irrespective of size, tumour grading or anatomical locations along the spine will be included. However, an adequate diagnosis of the tumour must be available and based on histological examination or MRI investigations.

#### Type of interventions

All modes of diagnosis and treatment of spinal meningiomas will be included.

#### Type of outcome measurements

Epidemiological data such as age, sex and socioeconomic factors, possible predictors of poor preoperative or postoperative decline such as comorbidity and spinal cord compression will also be addressed. Furthermore, outcome parameters including pain, neurological function, quality of life, tumour recurrence and mortality, tumour characteristics including expression of specific receptors, markers of proliferative activity, and WHO grade will also be included. Additional outcomes used in the selected studies may be considered. In those cases, the possibility of reporting biases will be recognised.

#### Exclusion criteria

Non-original publications such as reviews, editorials and letters to the editor will be disregarded together with case reports and conference abstracts. Studies found in languages other than English will be excluded for practical reasons. Publications prior to the year of 2000 will also be excluded to reduce the number of included studies and give priority to more current publications.

#### Databases and search strategy

An electronic database search will be performed on PubMed, Embase and Web of Science. The search will be broad, excluding case reports by adding a filter to the search. Appropriate filters will also be used to exclude non-English studies and those published prior to the year 2000. To illustrate the process, the preliminary search strategy for each of the databases is provided (see online supplemental file 2). A reference list search of the included studies will be performed, to screen for any eligible article that was missed.

#### Study selection

The records retrieved from the different databases will be exported into Zotero,<sup>37</sup> to eliminate duplicates. The records will then be screened based on title and abstract by one reviewer, to eliminate records that are plainly irrelevant. This is necessary as an unmanageable number of records is foreseen due to the broad search strategy that will be used. In the next step, three independent and blinded reviewers will be assigned the task of examining

the remaining records applying the eligibility criteria based on full-text reading. This will be performed using Rayyan Software.<sup>38</sup> Potential disagreements after pooling of the results will be resolved by discussion with a fourth reviewer. Finally, reference lists of the selected articles will be reviewed for any potentially eligible studies that were previously missed. The process will be illustrated in a PRISMA flow chart which will be provided.

#### Data extraction

Data from selected records will be extracted using a predefined extraction template, preliminarily including (1) general information—title, first author, journal, publication year, etc; (2) patient characteristics and epidemiology—age, sex, tumour location, and grade, etc; (3) intervention characteristics—imaging, Simpson grade, adjuvant therapy, etc; (4) study characteristics—study type, sample size, follow-up time, etc and (5) outcomes—neurological outcomes, quality of life, recurrence rate, mortality rate, follow-up time, adverse events and their management, main conclusions, etc. The collaboration of multiple reviewers will be sought to achieve thorough extraction of the data. The final work will even be assessed and cross-checked to prevent any error.

#### Assessment of risk of bias

The Oxford Center for Evidence-Based Medicine system,<sup>39</sup> modified by Wright *et al*, will be used to assess evidence levels<sup>40 41</sup> (table 2). The selected articles will first be allocated to one of only four levels based on methodological quality, since the fifth level (V) is solely associated to expert opinions which are systematically excluded from our study. Then, an individual score (IS) will be proposed, as we account for the risk of bias accordingly: studies with lower risk of bias will be upgraded while those with higher risk of bias will get downgraded. Risk of bias will be assessed using the appropriate tools specific to the type of study, as defined by Ma *et al*.<sup>42</sup> The final IS will also range from I to IV.

#### Quality of evidence across studies

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)<sup>43</sup> approach will be used to rate the body of evidence behind key study outcomes assessing their strength or certainty level. First, a baseline level will be set for each study outcome based on the IS of the majority of studies contributing to that specific outcome, such as: if the majority of studies have an IS of I or II the baseline grade of evidence supporting the study outcome will be classified as ‘high’, and if the majority have ISs of either III or IV, the baseline grade of evidence will be classified as ‘low’. After that, we will properly adjust the baseline score after different factors like, large effect magnitude, dose-response gradient, inconsistency, indirectness, imprecision, etc<sup>43</sup> to obtain a final quality of evidence grade of ‘high’, ‘moderate’, ‘low’ or ‘very low’<sup>41</sup> (table 3).

**Table 2** Level of evidence based on primary research question, by Wright *et al*<sup>40</sup>

	Therapeutic studies—investigating the results of treatment	Prognostic studies—investigating the outcome of disease	Diagnostic studies—investigating a diagnostic test
Level I	1. Good-quality randomised controlled trial, 2. Systematic review of Level-I studies	1. Prospective study 2. Systematic review of level-I studies	1. Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference 'gold' standard), 2. Systematic review of level-I studies
Level II	1. Prospective cohort study 2. Poor-quality randomised controlled trial 3. Systematic review 1. Level-II studies 2. Nonhomogeneous level-I studies	1. Retrospective study 2. Study of untreated controls from a previous randomised controlled trial, 3. Systematic review of level-II studies	1. Development of diagnostic criteria on basis of consecutive patients (with universally applied reference 'gold' standard) 2. Systematic review of level-II studies
Level III	1. Case–control study, 2. Retrospective cohort study 3. Systematic review of level-III studies		1. Study of nonconsecutive patients (no consistently applied reference 'gold' standard) 2. Systematic review of level-III studies
Level IV	Case series (with no, or historical, control group)	Case series	1. Case–control study 2. Poor reference standard
Level V	Expert opinion	Expert opinion	Expert opinion

We will refer to the GRADE handbook<sup>43</sup> for further assistance on this approach.

A summary of findings table will be generated using the Guideline development tool (GRADEpro GDT).<sup>44</sup> The table will convey the key study outcomes with their corresponding level of certainty (grade of evidence), in a structured and transparent manner.

### Data synthesis

After extraction, the data obtained from eligible studies will be systematically presented. Topics of interest to this review are chosen as follows:

1. Patient characteristics: epidemiology.
2. Tumour characteristics: histopathology, WHO grading.
3. Radiological diagnostics.
4. Surgical treatment: technique, Simpson grading, intra-operative monitoring.
5. Complications and their management.

6. Non-surgical or adjuvant treatment including radio-therapy.
7. Patient outcomes: neurological outcomes, quality of life, mortality.
8. Recurrence.

Relevant data will be compiled under corresponding headings. Areas with lack of data will still be mentioned. After going through the GRADE approach, all study outcomes will be condensed in a summary of findings table, each contrasted to their respective grade of evidence. Meta-analysis will not be performed due to the anticipated high heterogeneity across the selected studies, with regard to participant and tumour characteristics as well as outcomes. In these settings, a quantitative study would therefore likely be less valuable. If an adequate number of studies is identified, subgroup analyses regarding interethnic variations and socioeconomic

**Table 3** Quality of evidence grades, from the GRADE Handbook (chapter 5)<sup>43</sup>

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there it may be substantially different
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.



factors may be performed. Moreover, other subgroups reported in the eligible studies will be considered, as long as an adequate number of studies exists to support the analysis. When dealing with any such subgroups the possibility of selective reporting bias will be closely monitored.<sup>45</sup>

### Patient and public involvement

Patients were not involved in the design or conception of the study.

### Ethics and dissemination

Ethics approval is not required for this systematic review as it is based on existing publications. We also plan to submit our work to a peer-reviewed journal where the results will be openly available.

## DISCUSSION

The intended systematic review outlined in this protocol aims to summarise the current scientific literature on spinal meningiomas to provide guidance to clinicians and identify areas in need of further study. The available literature covers many aspects of spinal meningiomas, such as incidence,<sup>2 8 46</sup> age<sup>2 4</sup> and gender distribution,<sup>2 4 7 8</sup> treatments and their outcomes,<sup>4 47 48</sup> but many studies are limited by small sample<sup>3 48–56</sup> sizes and short follow-up times.<sup>3 50 52 57</sup> Regarding the effect of preoperative neurological impairment, tumour grade and size on postoperative outcomes<sup>3 30 50 52–59</sup> and adjuvant therapies,<sup>28 34</sup> the available data are conflicting. These issues will be addressed by the systematic review's design, as integrating data from diverse origins will allow for a more representative synthesis that reflects the population of patients with spinal meningiomas more accurately.<sup>60</sup> The absence of both randomised trials and high-quality evidence within the literature as well as the dominance of observational and cohort studies is already apparent, making up the largest limitation to our review. The high heterogeneity expected among studies, with regard to populations and outcome metrics, prevents the performance of a proper meta-analysis. This constitutes the main methodological limitation to this review. Other limitations eventually encountered during the writing of the manuscript will be discussed in the corresponding part of the review.

This study ought to be regarded as a reliable source for clinicians to access current evidence compiled in a systematic way and hence better understand the tumour, its epidemiology, management and prognosis. Greater knowledge of the subject will eventually contribute to improving the diagnosis and care delivery of affected patients. Moreover, the planned systematic review could also help disclose knowledge gaps in the field, identifying and highlighting future research priorities.<sup>61</sup> To the best of our knowledge, no systematic review outlining the current understanding of spinal meningiomas has been attempted to this date, making our study the first of its

kind. The protocol hereby presented is in accordance with the PRISMA-P guidelines (see online supplemental file 1). For further transparency, this protocol will also be registered on PROSPERO in due time. The record on PROSPERO will be updated should significant changes to the procedure take place. The final manuscript is intended for submission to peer-reviewing.

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# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Reference: Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

	Reporting Item	Section
<b>Title</b>		
Identification	<a href="#">#1a</a> Identify the report as a protocol of a systematic review	Title
Update	<a href="#">#1b</a> If the protocol is for an update of a previous systematic review, identify as such	n/a
<b>Registration</b>		
	<a href="#">#2</a> If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a (this protocol is planned for registration on PROSPERO)
<b>Authors</b>		
Contact	<a href="#">#3a</a> Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Author information
Contribution	<a href="#">#3b</a> Describe contributions of protocol authors and identify the guarantor of the review	Contributions
<b>Amendments</b>		
	<a href="#">#4</a> If the protocol represents an amendment of a previously completed or published protocol,	n/a

identify as such and list changes; otherwise, state plan for documenting important protocol amendments

## Support

Sources	<a href="#">#5a</a>	Indicate sources of financial or other support for the review	n/a
Sponsor	<a href="#">#5b</a>	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	<a href="#">#5c</a>	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a

## Introduction

Rationale	<a href="#">#6</a>	Describe the rationale for the review in the context of what is already known	Abstract and last part of Introduction
Objectives	<a href="#">#7</a>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Last part of introduction

## Methods

Eligibility criteria	<a href="#">#8</a>	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods and analysis: Eligibility criteria section
Information sources	<a href="#">#9</a>	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods and analysis: Databases and search strategy section
Search strategy	<a href="#">#10</a>	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Methods and analysis: Databases and search strategy section and



## supplementary file 2

Study records - data management	<a href="#">#11a</a>	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods and analysis: Study selection section
Study records - selection process	<a href="#">#11b</a>	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Methods and analysis: Study selection section
Study records - data collection process	<a href="#">#11c</a>	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods and analysis: Data extraction section
Data items	<a href="#">#12</a>	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods and analysis: Data extraction section
Outcomes and prioritization	<a href="#">#13</a>	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods and analysis: Data synthesis section
Risk of bias in individual studies	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods and analysis: Risk of bias assessment and Quality of evidence sections
Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively synthesised	n/a (only qualitative synthesis will be sought due to expected heterogeneity)
Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies,	n/a (qualitative synthesis only)

		including any planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type of summary planned	Methods and analysis: Data synthesis section
Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Methods and analysis: Risk of bias section
Confidence in cumulative evidence	<a href="#">#17</a>	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methods and analysis: Risk of bias and Quality of evidence sections

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Database	Queries
PubMed	((("spinal meningioma"*[Title] NOT "case report"[All Fields]) AND 2000/01/01:3000/12/31[Date - Publication] AND "english"[Language] AND ("loattrfull text"[Filter] AND "humans"[MeSH Terms] AND "english"[Language])) OR (((("spin"*[All Fields] AND ("meningioma"[MeSH Terms] OR "meningioma"[All Fields] OR "meningiomas"[All Fields])) NOT ("case reports"[Publication Type] OR "case report"[All Fields])) AND 2000/01/01:3000/12/31[Date - Publication] AND ("loattrfull text"[Filter] AND "humans"[MeSH Terms] AND "english"[Language]))) AND ((fft[Filter] AND (humans[Filter] AND (english[Filter])))
Web of Science	((ALL=("spinal meningioma") AND PY=(2000-2500) AND LA=(English) NOT TS=("CASE REPORT")) NOT (TASCA=("VETERINARY SCIENCES") OR DT=("EDITORIAL MATERIAL" OR "LETTER" OR "MEETING ABSTRACT"))) OR ((TI=(spinal AND meningioma*) AND PY=(2000-2500) AND LA=(English) NOT TI=(case report)) NOT (TASCA=("VETERINARY SCIENCES") OR DT=("EDITORIAL MATERIAL" OR "LETTER" OR "MEETING ABSTRACT")))
Embase	spinal meningioma*':ab,ti NOT 'case report' AND [2000-2021]/py NOT ('spinal meningioma*':ab,ti NOT 'case report' AND [2000-2021]/py) AND ('animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'nonhuman'/de)