

Natural history of non-traumatic intracranial arachnoid cysts: a literature review

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The natural history of arachnoid cysts is still a topic of debate in the medical literature and important to the neurosurgeon who intends to manage these cases. This article consists of a review of the literature available in the main digital libraries with wide access. This search resulted in six studies in which the developmental aspects of patients with this condition were specifically investigated. The analysis of those articles allowed us to conclude that the main and possibly only proven risk factor for cyst enlargement is age below five years, while among patients above this age group we can expect a benign evolution.

Keywords: arachnoid cyst, neurosurgery, natural history, intracranial cyst

INTRODUCTION

According to the CDC Organization, the natural history of a disease is defined as its process progression in an individual over time in the absence of treatment[1]. In other words, "What happens to a patient if I do nothing?" The lack of knowledge on natural history might lead to wrong medical decisions, such as unnecessary intervention or negligence.

Regarding the arachnoid cysts, the search for what behavior to expect over time is still happening, and their natural history remains a debate among doctors and scientists to date. This study consists of a literature review of papers available at digital libraries that investigated the natural history of arachnoid cysts, aiming to compile what is known until now about its behavior.

METHODS

In order to examine the available online articles the following digital platforms were used: (1) PubMed - National Center for Biotechnology Information, National Institutes of Health; (2) CAPES journal portal - Coordination for the Improvement of Higher Education Personnel of the Brazilian Ministry of Education (free translation); (3) Google Scholar;

(4) BIREME - Network of Virtual Health Libraries, Regional Library of Medicine, Pan American Health Organization (free translation); (5) LILACS - Latin-American and Caribbean Literature in Health Science (free translation); (6) CiteSeerX library - Pennsylvania State University's College of Information Sciences and Technology; (7) SciELO - Scientific Electronic Library Online, Research Support Foundation of the State of São Paulo (free translation); and (8) Cochrane library.

The online survey was conducted from May to June 2022, in English language. It was done through an "advanced search", using the keywords: "Arachnoid cyst" and "Natural history", looking for both terms throughout all documents ("all fields"). The only platform on which it was necessary to filter the presence of terms based on the title was Google Scholar to refine the search, having seen an extensive list of results that were inappropriate for the purpose of this paper. The list obtained from this initial survey was evaluated, article by article, and those whose title or topic covered were outside the scope of this study were excluded.

All studies found on the different platforms were then compared, excluding those repeated and published in



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oriental languages. No initial or final date limit was established, and no other filters were added.

Finally, in these selected articles, a detailed search was done in the bibliographic references of each one, looking for studies whose title had references to the keyword "Natural history". Those who met this specification, and who were not already included in the list of references under analysis, were then included in the work.

After the initial selection, each study was read individually and those whose body of text contained specific data regarding the natural history of arachnoid cysts were selected. Articles that did not detail this topic in their composition were excluded, as well as those whose data presented on this topic were taken entirely from another article already contained in the list of references under analysis. The natural history data was then organized separately in charts in order to ease the understanding of it.

RESULTS

Studies selection

The search for the keywords: "Arachnoid cyst" and "Natural history", searching for both terms throughout the document ("all fields"), separated by platforms, resulted in the following findings: PubMed: 41 articles ; CAPES: 12 articles; Google Scholar: 53 articles; BIREME: 43 articles; LILACS: 43 articles; CiteSeerX library, SciELO and Cochrane library: no article. After evaluating each article and selecting those whose theme was in the scope of the present study, according to the title and abstract, it was obtained: 19 articles from PubMed, 11 from CAPES, 24 from Google Scholar and 18 from BVS/LILACS-BIREME. Of these, repeated articles found on different platforms were excluded resulting in 24 articles whose topic of debate, based on either the title and/or abstract, focused on the natural history of the arachnoid cyst. In our first analysis, 4 of these were excluded: 2 because they were written in Japanese, one because it was an editorial and the last one because it was an unavailable indexing of congress. The final 20 articles were then entirely read to search for data for this study. Furthermore, they had their bibliographies searched for the term "Natural history", although no new article was obtained through this methodology.

After full reading of the 20 articles, fourteen were excluded. Five did not bring information about the natural history of the disease[2-6], they only mentioned this term in their text, hence being found during the initial search. Six only presented data already shown in other articles included in the protocol of this study[7-12]. Two had their analyzes based on outcomes of surgical interventions[13,14]. Finally, there was a book chapter[15], without any new information.

At last, the analysis resulted in 6 articles in which the evolutionary aspects of non-traumatic intracranial arachnoid cysts were researched.

Studies analysis

Al-Holou WN et al. published in 2010 and 2013[16,17] two studies with a significant population sample within the pediatric and adult age groups, respectively.

In the 2010 study[17], conducted with patients aged less than or equal to 18 years, 309 arachnoid cysts were selected. Of these, twenty-two underwent a neurosurgical approach, and 16 were treated immediately for present symptoms already attributed to the cyst, of which one failed to follow-up. Two were operated on for symptoms starting less than 3 months after initiation of follow-up and four after 5 months of follow-up. Within this subpopulation of operated patients, there was a statistically significant correlation with the presence or development of symptoms and surgical treatment: cysts with greater initial size, and location in the topography of the quadrigeminal cistern and anterior fossa. Posterior fossa cysts were not significantly related.

A separated analysis was performed with 111 patients who, in addition to imaging diagnosis, had previously asymptomatic cysts, which had not been considered for surgical treatment, and who had clinical and radiological follow-up for a period longer than 5 months, to allow evaluation of natural history. The mean follow-up period was 3.5 years +/- 2.7 years (range 5 months to 16.5 years). Of these, 87 remained stable, 13 reduced and 11 increased in size, of which 3 presented new symptoms, attributable to the cyst, thus underwent surgical treatment. The statistical analysis of these patients whose cysts grew over the follow-up period concluded that the only factor with statistical significance in predicting the risk of disease progression ($p = 0.001$), and need for surgery ($p = 0.05$) was the younger age. No patient older than 4 years old at the time of diagnosis had an enlarged cyst, new symptoms, or a need for neurosurgical intervention.

In 2013, the study was conducted at the same institution[16], using a similar methodology, with patients aged 19 years or older. Six hundred and ninety-six cysts were identified in 661 patients. Of these, 213 cysts had a minimum follow-up of 6 months to allow evolutionary analysis. The mean follow-up period was 3.8 years +/- 2.8 years. Of the 213 cysts, 2 reduced and 5 increased, and in only one of those that presented an increase, an association with the emergence of new neurological symptoms was detected. Statistical analysis concluded that there were no predictors of volumetric increase in cysts among the adult population.

In 2012, Lee JY et al.[18] published a study with a methodology similar to that of Al-Holou WN et al.[17] aiming

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to evaluate the natural history of arachnoid cysts within the pediatric population under 5 years of age. 86 patients were then selected, with a total of 90 cysts with at least 5 months of follow-up (mean follow-up period: 56.6 months). In this study the authors subdivided the pediatric population into four groups according to age groups at the time of diagnosis, as follows: Group I: 0-0.5 years (24 patients); Group II 0.5-1 year (7 patients); Group III: 1-3 years (28 patients); Group IV: 3-5 years (27 patients).

Of the 86 patients, twelve required a surgical approach, six related to cyst increase (five in Group I and one in Group III), and another six for reasons unrelated to the presence of the cyst (one in Group I and five in Groups III or IV). Seventeen patients had cyst growth during follow-up, of which 11 belonged to Group I, and 14 were younger than 1 year. Of these 17 cysts that grew, six were operated on during the follow-up period because of the growth and 11 were not operated on. Of these 11 treated conservatively, despite their increase, six stabilized after the initial growth, three reduced in volume and two presented additional increase during the remainder of the follow-up period, nevertheless, they remained asymptomatic and without the need for surgery.

Only age was obtained as a factor with statistical significance ($p < 0.001$) for increased risk of cyst growth. Cysts diagnosed below 6 months of age grew during follow-up more often than what was seen in older groups. Follow-up data on untreated asymptomatic volumetric growth cysts revealed that most stabilized or even regressed spontaneously. This study therefore defined that the population with the greatest tendency to evolve with growth of arachnoid cysts is found among patients younger than 1 year old.

Huang JH et al.[19] published a study in 2015 with 488 pediatric patients aged between 0 and 14 years, with a mean age of 5.61 \pm 3.25 years. Of these, 412 patients were treated conservatively, with a mean follow-up period of 32.43 months \pm 8.92 months (ranging from 3 to 72 months). During observation, 407 cases remained stable, 3 increased resulting in worsening of symptoms, and 2 regressed. They concluded, consequently, that in the long term, 98.78% of the cysts remained stable within this population.

In 2019, Hall S et al.[20] developed a study with an adult and pediatric population, adding up to 485 patients, of which 116 were younger than 18 years, leaving 369 adults.

Among the 116 pediatric patients, 84 were asymptomatic, and the other 32 had symptoms directly related to the cyst and/or hydrocephalus derived from it. Of the 32 symptomatic patients, 30 underwent surgical approach at the initial presentation. Among the 84 patients in the asymptomatic group, 28 had radiological follow-up,

and the mean follow-up period was 14 months. In these, there was stability in the volume of the cyst in 24 patients, in 3 there was a reduction and only one experienced lesion growth. The latter was a patient diagnosed at age 8, without developing symptoms over this period. Clinical follow-up was performed on 56 patients in the pediatric group, with a mean follow-up period of 23.9 months. None of the previously asymptomatic patients developed symptoms during this period.

As for the 369 adult patients, 341 were asymptomatic. Of the 28 symptomatic patients, 25 underwent surgery. Serial radiological investigation was performed in 120 asymptomatic adult patients, with a mean follow-up of 30.8 months. In 114 patients there was no volume variation of the cysts, reduction was observed in 5 and complete resolution in one case. Clinical follow-up was performed in 147 of the 341 asymptomatic patients, with a mean duration of 23.3 months. No asymptomatic adult patient presented onset of symptoms during the analyzed period.

Finally, in 2021, Grossman TB et al.[21] performed a study with morphological obstetric ultrasound, aiming to evaluate the behavior of arachnoid cysts diagnosed in the prenatal period. For that purpose, 33,621 ultrasounds performed over 6 years were reviewed. They found 70 patients with findings compatible with arachnoid cysts. The mean gestational age at diagnosis was 21.46 weeks. Of the 70 patients with a cyst finding, 53 were followed up with other prenatal imaging and 7 with ultrasound or postnatal MRI imaging. Of the 53 with prenatal imaging follow-up, 5 evolved with progression of the cyst, and another 5 with regression. Forty-three cysts were no longer visualized on subsequent ultrasounds. Two patients required a surgical approach after birth. It was concluded that most of the cysts were no longer visualized in the last pregnancy screening exam, and this may be due to the spontaneous regression of the cysts; technical limitations of the examination in the third trimester of pregnancy, mainly because the vast majority were performed to evaluate fetal morphological parameters, and not aimed at evaluating the progression of cysts; or the cysts initially identified could represent normal developmental anatomical structures, such as septum pellucidum cavum or velum interpositum cavum. That said, the sample obtained was not sufficient to carry out significant statistical analyzes to correlate aspects of the cyst with its natural evolution.

The result data of the analysis by study are summarized in Table 1.

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TABLE 1 - Summary of the evolutionary behavior of arachnoid cysts according to the reviewed articles

Study	Age (years)	Average follow-up period (months)	Studied population		Cyst evolution (% ^b)			Predictors of cyst enlargement
			Total	Effective ^a	Increase	Stability	Decrease	
Al-Holou WN, 2010	≤18	42	309	111	11 (10%)	87 (78%)	13 (12%)	Age <5 years
Lee JY	≤5	56,6	86	80	17 (21%)	63 (79%)		Age <1 year
Al-Holou WN, 2013	>18	45,6	696	213	5 (2,35%)	206 (96,7%)	2 (0,95%)	No association
Huang JH	≤14	32,4	488	412	3 (0,7%)	407 (98,8%)	2 (0,5%)	- ^d
Hall S	<18	23,9	116	28	1 (3,6%)	24 (85,7%)	3 (10,7%)	- ^d
	≥18	23,3	369	120	0	114 (95%)	6 (5%)	
Grossman TB	0 ^c	-	70	10	5 (50%)	0	5 (50%)	- ^d

^aPopulation that remains after the exclusion criterias and followed over time without surgical treatment; ^bBased on effective population; ^cStudy performed with intrauterine life population; ^dDid not perform risk/outcome

DISCUSSION

In 1975, Aicardi and Bauman[13] published a series of twelve cases of supratentorial extracerebral cysts in the pediatric age group evaluated by pneumoencephalography and angiography. Ten cases underwent surgical procedure, with macrocrania being the main cause for diagnosis and surgical indication. The authors brought up the question, is surgery really necessary in all cases? Or could natural history tend towards spontaneous stability or improvement? The study concluded that the lack of important information (about the nature and evolution of the lesions) did not make

it possible to categorically assert when and how to operate, and that, in the author's opinion, it would be better to observe the evolutionary behavior of asymptomatic cases. This paper reflects how the lack of knowledge of natural history shows how difficult is the decision making about the best course of action to be adopted.

Despite the clear relevance of this question, the first large study aimed at defining the evolutionary behavior of arachnoid cysts was only performed in 2010 by Al-Holou et al.[17] In this study, which, in addition to being unprecedented, included one of the largest pediatric series

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among the studies surveyed, concluded that the only factor with statistical significance common to those who progressed with imaging worsening was age below 5 years. Corroborating these findings, Lee et al[18] published, in 2012, a study replicating the Al-Holou protocol[17], with the aim of refining the age at greatest risk for disease progression and concluded that age less than 1 year was significant for risk of volumetric expansion. These analyzes allow us to suppose that, within the pediatric population, patients over 5 years of age who have not presented symptoms related to the presence or expansion of the arachnoid cyst are very likely to follow a benign course, and that their follow-up will likely reveal clinical stability and volumetric, without the need for surgical intervention. Contrastingly, patients under 5 years of age, especially under 1 year of age, should be closely monitored as they may present an unfavorable evolution and, therefore, require surgery.

Still within the studies that sought to find predictors of risk of cystic enlargement or surgical indication, Grossman et al.[21] performed a protocol with patients still in intrauterine life. Nonetheless, after reviewing an extensive series of morphological obstetric ultrasounds, they realized that a large majority of patients with an ultrasound diagnosis of arachnoid cyst in a first examination did not have this data described in the subsequent examination, making an adequate statistical analysis of risk factors impossible. Therefore, despite the great relevance of this thesis in seeking the natural history of arachnoid cysts in the prenatal period, its results were inconclusive, leaving doubt as to what to expect from the evolution of these lesions diagnosed in obstetric imaging tests.

Other selected studies by the present authors did not provide statistical data that predicted the relationship between risk factors and disease progression, but also assessed the rate of worsening of images and/or symptoms over time. The articles of Huang et al. and Hall et al.[20,19], performed with patients of different age groups, concluded that the greatest tendency of arachnoid cysts, among all populations, is to maintain clinical-radiological stability over time. Therefore, in line with what Al-Holou's team[16] in 2013, when replicating their research protocol already used in 2010, but this time among adults. In this study, among the 213 cysts followed up for more than six months, only five increased, again suggesting a trend towards stability and, this time, there was no statistically significant correlation between age and the risk of lesion expansion. Finally, one can see that the studies results with adult patients lead to the same conclusion as observed within the pediatric population over five years of age, there is a general trend towards long-term stability of arachnoid cysts. Therefore, except for those who become symptomatic as a result of the presence of the cyst, a benign and stable evolution should be

expected, without the need for early surgical intervention or even frequent serial imaging studies.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee

Conflict of interest

The authors declare no conflicts of interest with respect to the content, authorship, and/or publication of this article.

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