Master of Science
A retrospective analysis of pineal cyst patients

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Abstract

Introduction: A pineal cyst is a cystic transformation of the pineal gland which is commonly considered benign. Despite that, larger pineal cysts can lead to hydrocephalus, regarding their location and patients can present headaches, vertigo, syncope, nausea and diplopia. The natural history of pineal cysts is not fully known. It is unclear what kind of headaches patients with pineal cysts have and whether there is a causal link between the headaches and the cyst and how patients with putative pineal cyst related headaches could be differentiated from other pain-patients. The natural history and suggested futility to follow patients with asymptomatic cysts needs to be corroborated. Finally, the spectacular results from case series of operated pineal cysts need to be corroborated and it is necessary to evaluate long-term headache outcomes in operated patients.

Aim: The aim of this study is a retrospective approach to pineal cysts patients. A structure evaluation of these patients will be conducted: 1. to determine the natural history of pineal cysts, 2. to describe the types of headaches in patients with pineal cysts and to study whether an association between cysts and symptoms can be demonstrated; Moreover, we aim to analyze critically and describe long-term surgical outcomes in a highly selected cohort of patients with headaches and pineal cysts.

Patients and Methods: A prospective cohort study was conducted of consecutive patients referred to the department of neurosurgery at Karolinska Hospital™ for evaluation of a pineal cyst > 6 mm from 17.06.1996 to 01.04.2017. After a pineal cyst radiological identification, subjects were referred to the neurosurgical department of Karolinska Universitetssjukhuset, between the 25-year period 05.11.1992 to 07.12.2017 and had undergone brain MR imaging between 05.11.1992 to 02.10.2017. A case-control comparison will be made between patients with a cyst and headaches, and patients with cysts without a complaint of headaches.

Conclusion: Our findings support previous claims of a causal relationship between headaches and pineal cysts. The natural history of most cysts is benign and radiological long-term follow-up is not warranted. Interestingly, two small selected subgroups of pineal cyst patients appeared to benefit from melatonin therapy and microsurgery, respectively. Prospective mechanistic trials are planned to better understand patient selection and pathophysiology of headaches.

Introduction

Background

A pineal cyst is a cystic transformation of the pineal gland which is commonly considered benign. Despite that, larger pineal cysts can lead to hydrocephalus, regarding their location and patients can present headaches, vertigo, syncope, nausea and diplopia (1). However there are few studies that describe symptoms and recommend surgical therapy for patients with pineal cysts without any signs of hydrocephalus (2–4).

Pineal cysts were reported to have a prevalence ranging from 1 to 41 % in the general population (5). This wide range could be explained by different diagnostic methods and different definitions of “pineal cyst”; the reported incidence varies with the minimum size of the cyst. Pineal cysts are best confirmed by MRI scanning, while a CT imaging can lead to confusion with the quadrigeminal cistern (6). The size, of an usually asymptomatic cyst, can range between 2 mm and 15 mm at time of initial
Michielsen et al reported an incidence of 4.3% of cysts larger than 5 mm (2). Y. Pu et al. made a study where a 23% incidence of pineal cysts was discovered used high resolution (1.9-T) MR imaging (7). Pineal cysts present a peak of prevalence (about 2.8 %) in late childhood (8). In contrast, autopsy studies have led to higher estimates, probably reflecting that small cysts have been included. Depending on the methods and size limits, incidences ranging between 21% and 41% were reported in autopsy studies (9).

Increased neuroimaging in the clinical routine, has led to an increased detection rate of incidental pineal cysts (5)(10). Typical indications for neuroimaging are neurological or mental symptoms, headaches and suspicion of seizures (8). As a result, a dilemma on the management of these patients can be created when cysts are detected. On one hand, cysts are common and frequently incidental on the other hand, something abnormal is detectable in a symptomatic patient. El Holou et. al illustrate a prevalence of 1.0% where headache (21%) between other neurological deficits were the indication for imaging (8).

The natural history of pineal cysts is not fully known (5). Al-Holou et.al, with a follow-up interval ranging from 6 months to 13 years, observed that a 2.6 % of cysts increased, a 15 % decreased, while a 84% of cysts remained at the same size (8). This study agrees with several similar studies, where a 15.5% of patients present worsening, an 11.8% improvement and 73.8% stable symptoms in a 71.2 months follow-up study of Majovsky et. al. (1,5,7,10) and even more Y. Pu et. al found cystic changes in a 13% of subjects (with a significant tendency to cystic change in women (7).

Usually, pineal cysts are asymptomatic. In rare cases, cysts have caused unequivocal symptoms. Obstruction of the cerebral aqueducts can lead to hydrocephalus (1,11). Recently, Parinaud syndrome caused by pineal cysts were reported (1). Rarely, cases of sudden death due to pineal apoplexy were described (2,8). The dilemma arises when causality is less obvious. Several reports describe a relationship between pineal cysts and headaches. It is, however, not established to what extend headaches and which type of headache can be attributed to the pineal cyst (1,3,4,12,13). Consequently, there are surgeons who consider headaches as an indication for surgical treatment of pineal cysts (1,8,14,15). A recent worldwide survey reported that neurosurgeons proceed to pineal cyst resection when hydrocephalus, Parinaud’s syndrome and growth of cyst are present (14). Even more challenging is presented improvement or even relief of neurological symptoms in patients who do not suffer hydrocephalus (15) or Parinaud syndrome (10) (15) after surgical treatment.

Many patients with pineal cysts and headaches appear to have headaches that can be diagnosed as typical vascular or tension headaches. Recently a relationship between pineal cysts and migraine has been observed (12). Recent studies with resting state fMRI have described specific patterns in patients with migraine and cluster headaches, indicating that typical headache syndromes can be diagnosed with imaging modes (16,17). Majovsky et al. discovered tension type headaches in patients with pineal cyst (1). Furthermore, intermittent type, paroxysmal and acute persisting type of headaches have been reported (2). Thus, there is evidence of an association between headaches and pineal cysts, but the evidence is weak, and the findings are controversial. However, Seifert et. al. indicates how low melatonin levels can be related to headaches and generally to neurological deficits, as a 51% of patients in the pineal cyst-group was suffering from headaches, especially migraines (12).

An association between the size of the cyst and headaches has been suggested (8). Several authors found that larger pineal cysts can lead to headaches (1,3). Subsequently, hydrocephalus form intermittent obstruction of the cerebral aqueduct is a possible mechanism which was in referred to recent studies (10) On the other hand, headaches were found in patients with smaller cysts and
several theories attempt to explain how these can provoke symptoms. Melatonin secretion found decreased in patients with pineal cyst. Subsequently, it is hypothesized that low melatonin levels could cause headaches in pineal cyst patients until (4,12). Eide et al. recently suggested a possible correlation to internal cerebral vein compression (11). Interestingly, there are reports that demonstrate a close relationship between low melatonin levels and both episodic and chronic migraine (18)(19), as well as, cluster headaches (20), reviewed in 2005 (21) (18–21). Finally, the pineal gland may harbor trigeminal fibers (22,23).

Taken together, there are several gaps of knowledge regarding pineal cysts and possible symptoms. It is unclear what kind of headaches patients with pineal cysts have and whether there is a causal link between the headaches and the cyst and how patients with putative pineal cyst related headaches could be differentiated from other pain-patients. The natural history and suggested futility to follow patients with asymptomatic cysts needs to be corroborated. Finally, the spectacular results from case series of operated pineal cysts need to be corroborated and it is necessary to evaluate long-term headache outcomes in operated patients.

The aim of this study is a retrospective approach to pineal cysts patients. A structure evaluation of these patients will be conducted: 1. to determine the natural history of pineal cysts, 2. to describe the types of headaches in patients with pineal cysts and to study whether an association between cysts and symptoms can be demonstrated; Moreover, we aim to analyze critically and describe long-term surgical outcomes in a highly selected cohort of patients with headaches and pineal cysts.

Classification of headaches

According to the International Classification of Headache Disorders (ICHD 3-beta), third edition-beta, there are specific criteria that lead to the diagnosis and classification of headaches. In this study patients are diagnosed with primary headaches according to their headache phenotype. Primary headache disorders are by definition not the result of any other underlying disease or process. In more details primary headache characteristics will be described in order to clarify the diagnosis of study subjects.

*Migraine (with or without aura)*: It is also known as hemicrania complex, which includes specific characteristics such as unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity while during the headache the patient complains for nausea and/or photophobia and phonophobia. This condition can last 4 to 72 hours.

*Tension – type headache*: Common type known also as ordinary or stress headache, with a lifetime prevalence in the general population ranging between 30% and 78% in different studies, and it has a very high socio-economic impact. Is typically characterized by recurrent, bilateral tightening headaches of mild to modest intensity that do not worsen with routine physical intensity lasting minutes to days. Sometimes phonophobia or photophobia can also occur in this type but not at the same time. From the other hand, symptoms such as nausea or vomiting are not common here.

*Trigeminal autonomic cephalalgias (TACs)*: In this classification cluster headaches or previously known as Harris-Horton’s disease is also included. Cluster headache is maximal orbitally, supraorbitally, temporally or in any combination of these sites, but may spread to other regions. It is
a severe situation accompanied to prominent ipsilateral to the pain region autonomic features such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation.

Patients and Methods

Study design

A prospective cohort study was conducted of consecutive patients referred to the department of neurosurgery at Karolinska Hospital for evaluation of a pineal cyst ≥ 5 mm from 17.06.1996 to 01.04.2017. After a pineal cyst radiological identification, subjects were referred to the neurosurgical department of Karolinska Universitetssjukhuset, between the 25-year period 05.11.1992 to 07.12.2017 and had undergone brain MR imaging between 05.11.1992 to 02.10.2017. A case-control comparison will be made between patients with a cyst and headaches, and patients with cysts without a complaint of headaches. A diverse group of consecutive patients undergoing surgery for pineal cyst at the neurosurgical department of Karolinska Universitetssjukhuset was evaluated separately. The medical and radiological records were collected and evaluated manually and patients that met the inclusion criteria (are described below) were included. They were anonymized, and data was registered to an electronic database (in Excel 2016).

Study hypothesis

We hypothesize that there is a relationship between patients with identified pineal cyst in a brain imaging (MRI) and headaches in general and/or specific headache classification (primary headaches). Moreover, this study aims to investigate whether a relationship between size of the cyst, compression of the quadrigeminal plate and headaches can be demonstrated. Lastly, study aims to determine whether sleep compliance is related to pineal cysts. The study hypothesis can be constructed to a PICO question as below:

**Patients:** Patients with radiologically identified pineal cysts and headache.

**Intervention:** (diagnostic procedure): cerebral MRI scanning and clinical neurological evaluation.

**Comparison:** Patients with radiological identification of pineal cysts and without headache.

**Outcome:** Primary, an association between pineal cysts and headache. Secondary, 1. An association between types of headache and pineal cysts size, 2. An association between headache and local mass effect of the quadrigeminal plate, 3. Relationship between sleep compliant and pineal cysts.

Moreover, a second study-hypothesis resulting from the highly selected patients that underwent surgical intervention of the cyst. The PICO question again accrues as below:

**Patients:** Patients with radiologically identified pineal cysts and headache.

**Intervention:** surgical treatment of cyst with two different techniques, total cyst removal or cyst stereotactic puncture.

**Comparison:** There is no comparison group, as there is a difference between patients who underwent conservative treatment and patients underwent surgical treatment.
Outcome: description of long-term surgical outcomes in a highly selected cohort of patients with headaches and pineal cysts

Patients

Patients with pineal cysts ≥ 5mm were prospectively collected and data was retrospectively reviewed through the electronic medical records. We collected demographic information such as age and gender, clinical information and clinical follow-up data. All patients were referred after detection of a pineal cyst either from their primary-care physicians or neurologists. All patients with persisting headaches or other neurological complaints were evaluated at the neurological department. We did not restrict our subjects to age or gender variation.

Clinical data

Clinical information was retrospectively collected through the medical records. The presence of headache was recorded, and the specific types of headache were classified according to the International Classification of Headache Disorders (ICHD). Patients were grouped as having headache or not. In addition, the indication of imaging was recorded. Patients were divided into two groups, depending of if the cysts were found in patients with headaches (group 1) or incidental in relation to headaches (group 2). Hence, group 1 comprised all patients where the indication for imaging was headaches and group 2 the patients who underwent imaging for other neurological symptoms (2a) or routine work-up for head-trauma or imaging for research purposes as healthy controls (2b). Group 2a included patients who were scanned either due to different neurological complains such as numbness, hearing loss, diplopia, visual disturbances, , epilepsy, MS (multiple sclerosis), Borreliosis and Parkinson’s disease. Pharmacological treatment for headache was recorded. Treatment with melatonin was recorded separately. The clinical records were scanned to detect any sleep complaints.

Depending on concomitant disease, symptoms and symptom severity, patients were followed by their primary care physicians, neurologists or neurosurgeon. The radiological follow-up of cysts was between 25 years and 6 months; originally, annual follow-up was used, while length of follow-up was reduced to 1 year towards the end of the inclusion period. Clinical follow-up was conducted until symptom resolution or as necessitated by other morbidity; all patients were screened for residual or new clinically significant headache that required medical attention or prescription medication during Patients were included in the natural history analysis only if at least 6 months of clinical and imaging follow-up was achieved. Improvement of symptoms were considered when the intensity (according to the VAS- Visual Analogue Scale), the frequency and the duration of headaches were disappeared or reduced. Worsening of symptoms, were characterized by increase of the above parameters or a probable appearance of a new secondary type of headache. On-study date was considered as the time of the pineal cyst identification and event date the time of the event diagnosis. Then, by the two dates were subtracted to assess the time variable for the assess. Patients are recommended a control follow-up and MRI brain imaging every one or two years.

Concerning the patients that underwent invasive treatment, electronic medical records were retrospectively reviewed and information such as long-term surgical outcomes were registered.
**MRI findings**

Original MRI scans were analyzed and cyst maximal diameter, mass effect, hydrocephalus and frontal horn index were recorded. For 16 patients, original scans could not be retrieved, and data were obtained from original MRI-reports. The on-study time was set as the time of cyst radiological identification. The cyst size was determined from the maximum anterior-posterior (AP) diameter using the midsagittal MRI. Cysts size $\geq$ 5mm were considered valid for the study qualification. We considered as cyst size the maximum dimension of the cyst size measurement. Patients with cystic tumor identification were not included to our study. Then, the registered size was that at the time of cyst identification. Detailed description of cysts such as compression of quadraminal plate or hydrocephalous condition were recorded. Subsequent brain images (MR-C) were examined for the follow-up purpose, to determine the natural history of cyst size at the study’s follow-up time. A difference of $\geq$ 2mm in the cyst size was recorded.

**Exclusion – Inclusion criteria, summary**

In this study were recorded patients that represented in the neurological department, complaining with headaches or other neurological deficits and identified with pineal cysts after brain imaging. Patients with pineal cysts $\geq$ 5mm size were included. Additional inclusion criteria recommend sleep compliance, compression of quadraminal plate, presence of hydrocephalous, melatonin treatment.

Exclusion criteria to this study include cystic tumors and pineal cysts size $< 5$mm.

During the 25-year study period (from 1992 to 2017), 157 patients were identified (50 males and 107 females, average age: 37 years) with a pineal cyst (confirmed with an MRI). Three patients were excluded; one patient was confirmed with arachnoid cyst of third ventricle and not a pineal cyst, after stereotactic puncture and biopsy, one patient was diagnosed with a cystic glioma and one patient was excluded due to cyst size (4mm).

**Statistical analysis**

The statistical analyses were performed using the Rstudio software Version 1.1.383 – © 2009-2017 RStudio, Inc.

**Prevalence**

The analysis was first conducted by summary measurements of qualitative and quantitative data. In details, we summarized our subjects’ gender distribution and the mean of sample’s age. Frequency distribution of qualitative data was assessed, such as presence of headache, compression of aqueduct, sleep compliant, medication and effect after melatonin treatment. Thereafter, we assumed the frequency distribution for any independent type of headache. Additionally, the prevalence of pineal cysts size was calculated for all patients as well as for gender and age groups. For the prevalence analysis patients were grouped according to age by decade. Then univariate One-way analysis of variance ANOVA test was performed for this study and two-sample t-test for the analysis between gender and pineal cyst size. Different age profiles were analyses in every group.

**Clinical analysis**
Consecutive series of two-sample t-tests were performed to determine the relationship between pineal cyst size and a. headaches, b. sleep compliance, c. effect of melatonin treatment respectively. Additionally, for assess the relationship between compression of quadrigeminal plate and a. headache, b. sleep complaints, chi-square tests of independence and Fisher’s exact test were respectively performed.

In the surgical group, subjects were evaluated for the long-term postoperative condition regarding headaches and general outcome.

A multivariate logistic regression of age, gender, cyst size and compression of quadrigeminal plate was performed to determine the relationship of these explanatory variables to the binary outcome (presence of headache or not). For the purpose of this study, age was divided to three groups by twenty years, in order to ensure a safer multivariate model (according to the rule of thumb maximum 5 variables can be considered since the minority outcome of the binary variable includes 49 outcomes, (24)). We recorded results for the age, the rest variables in the model (local mass effect of quadrigeminal plate, gender, size) where excluded by the multivariate model.

Natural History Data Analysis

Univariate analysis (long-rank test) was performed to evaluate the time to event analysis. More specific, study aimed to assess the natural history of the cyst size (decrease or increase), as well as the condition of symptoms (improvement or worsening), over the time of study’s interval.

Individually, a survival analysis was performed to identify any relationship between the prognosis and the compression of quadrigeminal plate. The results were clarified with a long-rank test.

The results were viewed to Kaplan-Meier curves.

Thereby, a statistical threshold of $P < .05$ was considered to be significant

Results

Clinical evaluation

In this study, 103 pineal cysts (67.1%) were detected during work-up for headaches and considered non-incidental (group 1) and 51 (32.9%) were incidental pineal cysts (group 2) that were detected during work-up for other neurological symptoms or during CT-scanning after trauma. Of the incidental cysts, two patients complained of headaches after diagnosis while 49 patients (31.6%) never complained about headache within the study interval.

Among the patients with headache, 44.3% (46 patients) were considered non-specific. Eighteen of them had a limited duration of headache complaints (< 3 months). Fifty-seven patients were classified according to the International Classification of Headache Disorders (ICHD). Among patients with primary headaches, tension-type was the most prevalent diagnosis 24.5% (26 patients), followed by migraine (15.1%, 16 patients), a combination of primary headaches ($n=12$ patients) and lastly secondary headaches (borreliosis related, facial pain) in 3 patients respectively for both groups. Details of headache types are presented on Figure 1.

Headaches disappeared or were attenuated to become insignificant life events in 26 patients (4 migraine, 4 tension-type, 5 that suffered from a combination of migraine and tension-type, 1 cluster, 2 secondary and 10 non-specific. Three patients were operated for headaches (non-specific) after less than 3 months and not included to the analysis because of limited follow-up interval for (less
than 3 months). One patient died from parietal malignant glioma (August 2015) and 150 patients were evaluated within the study’s period for worsening or improvement of symptoms. The criteria for characterizing the “worsening” or “improvement” are already described.

Between the 150 patients, 26 patients (17.3%) presented reduce of symptoms, improvement of headache and 27 (18%) of the patients presented worse headache condition within the follow-up time (one of them was later operated and one patient suffers borreliosis related headache after the infection) Figure 2, Figure 3.

Compression of the quadrigeminal plate appeared to be more common in patients with refractory headaches than in those improving during follow-up. (Figure 4) However, the difference is not statistically significant (p=0.48).

We identified 51 incidental pineal cysts for patients that underwent MR imaging either for neurological complains such as numbness, hearing loss, diplopia or visual disturbances, or for different neurological diseases such as epilepsy, MS (multiple sclerosis), Borreliosis and Parkinson’s disease or as routine imaging after a head trauma.

Twenty-eight patients (18.4%) reported sleep disturbances. Additionally, two patients were treated with sedative-hypnotics (zopiclone), and consequently included in this group, making the group 30 (19.5%) Fifty-three of the 105 patients with headaches had records of pharmacological treatment. The majority (51%, 27 patients) was treated with a combination of ordinal analgesics (paracetamol, NSAIDs), opioids and/or migraine medication (Figure 5).

Thirteen patients in the study’s subjects were treated with melatonin, especially patients with the triad: headache, identified pineal cyst and sleep disorders, were indicated for melatonin treatment. Seven patients (54%) reported a positive effect of melatonin regarding both headaches and sleep, either by reduction of headache’s intensity (according to the VAS) and frequency or by total headache remission. The remaining 46% (6 out of 13 subjects) did not notice any difference in headache severity.

Age profiles

Table 1 shows the different age profiles according to headaches. We found a significant difference (6.03 years p=0.02, 95%CI: 0.95 to 11.12) in the mean age of group 1 and 2. Incidental pineal cysts were identified in older ages (mean: 41.71 years, SD: 15.46) compared to the non-incidental pineal cysts where patients underwent MR imaging for headache disorders (36.15, SD: 13.01). The mean age of patients with sleep problems did not differ from the others (42.07 vs 37.4, p=0.83 95%CI: -1.87 to 1.5).

After adjusting the model for demographic variables (age, gender) and MRI findings (cyst size, compression of quadrigeminal plate), we identified that the subjects that belong to the third group of age (age over and with 55 years and identified pineal cysts) are less likely (OR:0.22, p=0.004) to suffer from headache than the subjects from the first age group (reference group, age under 35 years), adjusted for all the other variables in the model (cyst size, local mass effect of quadrigeminal plate, gender). Additionally, patients that belong to the second age group (between 35-55 years) are less likely (OR: 0.69) to suffer from headaches than the first age group (reference group, age under 35 years), adjusted for all the other variables in the model (cyst size, local mass effect of quadrigeminal plate, gender).

Pineal Cyst size
Pineal cysts which identified with MR imaging, presented a mean size of 13.58 mm (standard deviation 4.32 mm), while males identified with larger cyst, mean cyst diameter 14.43 mm (standard deviation [SD] 4.9) than females which presented a mean cyst diameter of 13.21 mm (standard deviation [SD] 4.02 mm). However, there was no statistically significant difference on the cyst size between males and females; t (150) =1.62, p=0.11, 95%CI: -0.27 to 2.73. For the purpose of describing the prevalence of cyst size according to the age, sample’s individuals were divided to 6 groups by decade. Especially in the sixth group patients over 65 years were including, which means that there was one patient 78 years that included in the same group. All groups reported similar mean cyst size, with a tendency to higher mean cyst size of 15.71 mm (standard deviation [SD] 5.07 mm) in the sixth group of patients (decade >= 65 years) and lower mean cyst size of 11.35 mm (standard deviation [SD] 4.24 mm). Despite that, there were no significant differences in the mean cyst size between the 6 groups (with an estimated F-value corresponds to p=0.07), Table 1.

Pineal cysts and headache: The mean size cyst diameter was 13.3 mm (SD: 4.2 mm) in patients without headaches and 13.7 mm (SD: 4.4 mm) in the group with headache. The groups were not statistically different: t (100) =0.49, p=0.61, 95%CI: -1.83 to 1.09. Likewise, there was no statistical difference between cyst size in patients with sleep disturbances (13.53 mm, SD: 4.44 mm) compared to the group with no sleep complainst (13.71 mm, SD: 3.89 mm; p=0.83, 95%CI: -1.87 to 1.49) quality In the incidental group we pineal cyst size was measured to 13.16 mm (SD: 4.15 mm). The difference of means between the incidental and no-incidental group is not significant (p=0.39, 95%CI: -0.81 to 2.08). Moreover, patients that demonstrated beneficial effect of melatonin treatment do not present significant difference (1.97 mm) in mean cyst size (14.86 mm, SD: 4.63mm) compared to the mean size of patients that did not notice any effect of melatonin treatment (Mean: 16.83 mm, SD:2.79 mm), with a p value estimated to 0.37 (95%CI: -2.68 to 6.63).

Natural history of pineal cyst size

All patients were recommended for MRI follow-up after 1 year. In the early part of the study, additional follow-up was undertaken in 130 patients. Sixty-three patients had a follow-up scanning between 2 months and 1 year after diagnoses, two patients a follow-up after one month and 17 patients never underwent a follow-up scanning. Among the 130 patients, 5 cysts (4%) decreased in size (estimated cumulative survivor function (sf.) 93%, with 95% CI: 0.86 to 0.99), 118 (90.7%) remained stable and 7 (5.3%) pineal cysts increased in size (sf.: 72.7%, 95%CI: 0.51 to 1). Figure 6.

Among 12 patients with longer radiological follow-up than 55 months, we found 11 pineal cysts that remained at the same size and one pineal cyst that increased.

Local mass effect of the quadrigeminal plate

Among the 155 subjects, 27 patients (11.9%) showed compression of the quadrigeminal plate, which was considered local mass effect. Two patients showed ventricular widening, considered two be hydrocephalus from partial quadraminal plate obstruction in one.

No association between local mass effect to the quadrigeminal plate and headache was detectable (df=1, p=0.45). In parallel, no association was found between local mass effect to the quadrigeminal plate and sleep complaints (p=0.58, 95%CI: 0.42 to 4.23) (Figure 6 and 7).

Natural history of headaches (patients with headaches who were not operated)
In this analysis, 142 Patients were analyzed for worsening or improvement of symptoms. Headaches either decreased to become clinically insignificant in 25 patients. Patients with tension headaches and migraine headaches underwent treatment (a combination of therapeutic medication and physiotherapy) which ameliorated the headaches to intensity and frequency, so no increasing or new symptoms led to neurological or neurosurgical new treatment or need to follow-up at study termination on August 2017. Figure 2 shows the patients that presented increased symptoms during the follow-up interval.

**Operated patients**

All patients (13 subjects, 8 females and 5 males) were suffering from headaches: 11 nonspecific (76.9%) type, one migraine (8%) and two patients represented a combination of tension-type and migraine (15.3%). Pineal cyst size had a mean value of 16.3 mm (SD: 4.2 mm). Three of the thirteen patients underwent a stereotactic puncture, which ameliorated headaches immediately. However, all three patients reported recurrent headaches and MRI revealed cyst recurrences. One of these patients underwent open surgery, while two found headaches tolerable, and did not ask for additional invasive treatment. Eleven patients in total underwent microsurgical pineal cyst excision. All reported immediate relief of previous headaches while recurrences were reported during long-term follow-up. Four patients (30.7%, 13 patients in total) reported postoperative recurrence of headaches although of lower intensity (according to VAS) and frequency compared to preoperative condition. The estimated cumulative survivor function at the end of the interval for the operated patients was estimated to 63% (with 95%CI 0.41 to 0.99); 63% of the operated patients did not present headache after the operation (Figure 8).

**Discussion**

During follow-up of 153 patients with pineal we detected five cysts (4%) that decreased in size, 118 (90.7%) that remained stable and 7 (5.3%) that increased. The increasing cysts were either operated (n=12) or further followed, at which time they stabilized. The majority of cysts were detected during work-up for headaches while a minority were incidentally found during work-up for trauma or other neurological symptoms. Thirteen patients underwent surgery for their cysts, which lead to immediate resolution of headaches in all, but recurrence at lower intensity during long term follow-up in 3/3 patients who underwent stereotactic cyst puncture and 4/11 who underwent microsurgical cyst extirpation (subjects seem to be 14 in number here due to one patient that underwent open microsurgery after 2 stereotactic punctures).

The natural history of clinical symptoms is not clearly correlated to the cystic size changes in our subjects. Depending on concomitant disease, symptoms and symptom severity, patients were followed by their primary care physicians, neurologists or neurosurgeon. Clinical follow-up (between 05.11.1992 to 07.12.2017) was conducted until symptom resolution or as necessitated by other morbidity; all patients were screened for residual or new clinically significant headache that required medical attention or prescription medication during 01.01.2017-07.12.2017. Four patients were not included to this analysis. Between the 150 patients, 26 patients (17.3%) presented reduce of symptoms, improvement of headache and 27 (18%) of the patients presented worse headache condition within the follow-up time (one of them was later operated and one patient suffers borreliosis related headache after the infection) Figure 5. Improvement of symptoms were considered when the intensity (according to the VAS- Visual Analogue Scale), the frequency and the duration of headaches were disappeared or reduced. Worsening of symptoms, were characterized by increase of the above parameters or a probable appearance of a new secondary type of headache.
There have been frequent reports of headaches in patients with pineal cysts, but the evidence is weak and the causality controversial. Three case-series found headache resolution after surgery (15,10,25) and Seifert et al (12) found a statistically significant association between pineal cysts and headaches. Our findings do support an association between cysts and headaches. It is remarkable that all operated patients improved immediately from surgery, that less than 40% had recurrences and that all patients considered themselves better after surgery than before during long-term follow-up. In addition, of all cysts found during scanning, the majority (67%) were actually found during work-up for headaches; these figures agree with Seifert’s prospective findings, since less than 20% of neurological patients seek medical attention for a complaint of headaches (26,27). Seifert et al. found that 51% of patients with pineal cysts suffered from headaches, especially migraines (12). We identified a total of 105 patients (68.4%) suffering from headache and 49 patients (31.6%) without any headache complaints. Among the primary headaches, tension-type was the most prevalent diagnosis 24.8% (26 patients, 105 in total). That could agree with the study of Majovsky et al. who found tension type headaches in patients with pineal cyst (1). Afterwards a percentage of 15.2% (16 patients) of subject was diagnosed with migraine. Ten patients were diagnosed by both migraine and tension-type and two patients presented a combination of migraine and cluster headache. Recently a relationship between pineal cysts and migraine has been observed (12).

The possible causal mechanism of headaches in pineal cyst patients is unknown. Several authors suggested that larger pineal cysts lead to headaches (1,3). However, neither we nor Seifert et.al found any relationship between cysts size and headaches and hydrocephalus is not associated (11). It is reported that hydrocephalus from intermittent obstruction of the cerebral quadrigeminal plate is a possible mechanism (10,12). Eide et al. suggested central venous hypertension as a causal (11). We found no association between mass effect to the quadrigeminal plate and headache in this study. Taken together, the hypothesis that headache is related to mass effect is doubtful. There is evidence that the pineal gland may harbor trigeminal fibers (23,24) which can cause pain if stimulated or stretched. Furthermore, intermittent type, paroxysmal and acute persisting type of headaches have been reported (2). These types of headaches were described in three patients who were operated.

Recently, Peres et. al suggested low melatonin levels in patients with pineal cysts could be related to headaches. Melatonin is hypothesized to increase pain thresholds (28), while it is suggested to be beneficial for the treatment of primary headaches (29,30) especially for migraine (31) but also in other headache type disorders (32). We did not measure melatonin, but there is literature data claiming low levels of melatonin in patients with pineal cysts (21). The positive response to melatonin treatment in a large proportion of patients would agree with the hypothesis of low melatonin levels in patients with headaches and pineal cysts. We identified 19.1% of patients with sleep complaints, which could be speculated to reflect lack of melatonin signaling. Thirteen patients were treated with melatonin, seven patients (a percentage of 54% in 13 total subjects) had a positive effect of melatonin.

Our data also confirmed previous claims of a benign natural history of pineal cysts. Only one patient had mild findings of obstructive hydrocephalus, and long-term follow-up did not lead to any case of symptomatic deterioration and symptomatic growth of pineal cysts. During inclusion of patients, favorable findings in our patients and literature reports (33,34) led to shortening of radiological
follow-up, which was functional since no cases of clinical deterioration were detected among the 153 patients during clinical follow-up.

Limitations

The series is a retrospective analysis of prospectively collected patient data and not a prospective trial of predefined hypotheses. The study is suitable for forming hypotheses, and it suffers from the retrospective lack of prospective data; the surgical cases were offered surgery based on selection for persistent severe symptoms. Controls are lacking, and any beneficial outcomes cannot be logically separated from other beneficial effects such as placebo or regression to the mean (35). The retrospective nature of the study, limited information on precise usage of medication. Consequently, it was difficult to identify whether headache could be classified as medicine-overuse headache. From the other hand all patients have been screened for their dominant disease by their primary care physicians, neurologists or neurosurgeon. Any suspicion of medicine-overuse headache could be reported. Besides, all patients were screened for residual or new clinically significant headache that required medical attention or prescription medication during 01.01.2017-07.12.2017. The continuity and follow-up clearly show that the risk of deterioration is small in a large majority of patients and support the strategy of short poutine radiological follow-up

We plan prospective studies to measure melatonin, study sleep patterns and classify headache semiology prospectively.

Conclusion:

Our findings support previous claims of a causal relationship between headaches and pineal cysts. The natural history of most cysts is benign and radiological long-term follow-up is not warranted. Interestingly, two small selected subgroups of pineal cyst patients appeared to benefit from melatonin therapy and microsurgery, respectively. Prospective mechanistic trials are planned to better understand patient selection and pathophysiology of headaches.

Ethics

In this study, patients gave consent to the use of the data for scientific research, patients were anonymized after the review of electronical medical records

Tables and Figures

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<th>Groups</th>
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<th>Size mean (mm)</th>
<th>P-value &gt;0.05</th>
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<td>95%CI: -1.83 to 1.09</td>
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<tr>
<td></td>
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**Table 1.** Demographic data in diverse groups
Figure 1. Type of headaches and percentage according to gender.
Figure 2. Kaplan Meier curve according to event, reduce symptoms

Figure 3. Kaplan Meier curve according to event, worsening of symptoms
Figure 4. Kaplan-Meier curve of clinical symptoms worsening according to the local mass effect of the quadrigeminal plate.
Figure 5. Medication according to the medical records. Amitryptilin is reported as a principal therapeutic treatment for tension-type headaches, GABA-derivates/agonists are mostly used for the treatments of atypical facial pain or trigeminus neuralgia and for any kind of neuropathical pain. Note that Naproxen belongs to NSAIDs group, is considered separately due to its spread administration to study’s population.

Figure 6. Kaplan-Meier curve showing the decrease or increase of pineal cyst size at the follow-up time (in months).
Figure 7. Comparison of local mass effect and headaches, 0 = no headaches and 1 = headaches,

Note the difference of 4.94% in patients with headaches and positive local mass effect in contrast to the no-headache group, however the difference was not significant.
**Figure 8.** Comparison of local mass effect and sleep complaints, 0 = no sleep complaints and 1 = sleep complaints.

Note the difference of 5.3% in patients with sleep complaints and positive local mass effect in contrast to the no-sleep complaints group, however the difference was not significant.

**Figure 9.** Kaplan-Meier for the postoperative outcome of 12 patients in a long-term follow up. Note that the figure shows the median survival time for the operated patients leads to a point under the survival curve (Kaplan-Meier curve), consequently the latter line cannot intersect with the y-axis, which practically means that all patients are benefited from the operation in time. Beneficial results of operation.
References


25. Má M, Netuka D, Bene V. Conservative and Surgical Treatment of Patients with Pineal Cysts: Prospective Case Series of 110 Patients.;


Appendix

library(readxl)

DataBaseCysts <- read_excel("C:/mrm/DataBaseCysts.xlsx")

View(DataBaseCysts)

DataBaseCysts$gender <- factor(DataBaseCysts$gender, levels = c(0, 1), labels = c("Male", "Female"))

summary(DataBaseCysts$gender)

DataBaseCysts$headache <- factor(DataBaseCysts$headache, levels = c(0, 1), labels = c("No Headache", "Headache"))

summary(DataBaseCysts$headache)

DataBaseCysts$kompAdeq <- factor(DataBaseCysts$kompAdeq, levels = c(0, 1), labels = c("No local mass effect", "Local mass effect"))

summary(DataBaseCysts$kompAdeq, na.rm=T)

DataBaseCysts$SleepComp <- factor(DataBaseCysts$SleepComp, levels = c(0, 1), labels = c("No", "Yes"))

summary(DataBaseCysts$SleepComp, na.rm=T)

DataBaseCysts$Medication <- factor(DataBaseCysts$Medication, levels = c(0, 1, 2, 3, 4, 5, 6, 7), labels = c("Naproxen", "PCM", "NSAIDS", "opioids", "Triptans", "Amitriptilin", "GABA-agonists", "combination"))

summary(DataBaseCysts$Medication, na.rm=T)

DataBaseCysts$circadinEffect <- factor(DataBaseCysts$circadinEffect, levels = c(0, 1), labels = c("No", "Yes"))

summary(DataBaseCysts$circadinEffect)

DataBaseCysts$typeHead <- as.factor(DataBaseCysts$typeHead)

summary(DataBaseCysts$typeHead, na.rm=T)

DataBaseCysts$diagnosis <- factor(DataBaseCysts$diagnosis, levels = c(0, 1), labels = c("Non-incidental", "Incidental"))

summary(DataBaseCysts$diagnosis)

summary(DataBaseCysts$age)

summary(DataBaseCysts$size, na.rm=T)

psych::describeBy(DataBaseCysts$size, na.rm=T)
table(DataBaseCysts$diagnosis)
prop.table(DataBaseCysts$diagnosis, margin=1)

tb<-with(DataBaseCysts,table(gender,typeHead))
row.prop<-prop.table(tb,1)*100
row.prop<-round(row.prop, digits=2)

##size-gender
Mean_size.male<-with(DataBaseCysts,mean(size[gender=="male"], na.rm=T))
Median_size.male<-with(DataBaseCysts, median(size[gender=="male"], na.rm=T))
Dif.male<- Mean_size.male-Median_size.male
cbind(Mean_size.male,Median_size.male,Dif.male)
Mean_size.female<-with(DataBaseCysts,mean(size[gender=="female"], na.rm=T))
Median_size.female<-with(DataBaseCysts, median(size[gender=="female"], na.rm=T))
Dif.female<- Mean_size.female-Median_size.female
cbind(Mean_size.female,Median_size.female,Dif.female)

psych::describeBy(DataBaseCysts:size, group = DataBaseCysts$gender, range = T, IQR = T, na.rm=T)
Mean_age.male<-with(DataBaseCysts,mean(size[gender=="male"], na.rm=T))
Median_age.male<-with(DataBaseCysts, median(size[gender=="male"], na.rm=T))
Dif.male<- Mean_age.male-Median_age.male
cbind(Mean_age.male,Median_age.male, Dif.male)

library(nortest)
with(DataBaseCysts, lillie.test(size[gender=="female"]))
with(DataBaseCysts, shapiro.test(size[gender=="male"]))

library(car)
leveneTest(size~gender, data=DataBaseCysts, center="mean")
t.test(size~gender, data=DataBaseCysts, var.equal=T)

##age-size
DataBaseCysts$age[DataBaseCysts$age < 25] <- "first"
DataBaseCysts$age[DataBaseCysts$age >= 25 & DataBaseCysts$age < 35] <- "second"
DataBaseCysts$age[DataBaseCysts$age >= 35 & DataBaseCysts$age < 45] <- "third"
DataBaseCysts$age[DataBaseCysts$age >= 45 & DataBaseCysts$age < 55] <- "fourth"
DataBaseCysts$age[DataBaseCysts$age >= 55 & DataBaseCysts$age < 65] <- "fifth"
DataBaseCysts$age[DataBaseCysts$age >=65 & DataBaseCysts$age < 85] <- "sixth"
DataBaseCysts$age <- as.factor(DataBaseCysts$age)
summary(DataBaseCysts$age)
with(DataBaseCysts,shapiro.test(size[age=="first"]))
with(DataBaseCysts,shapiro.test(size[age=="second"]))
with(DataBaseCysts,shapiro.test(size[age=="third"]))
with(DataBaseCysts,shapiro.test(size[age=="fourth"]))
with(DataBaseCysts,shapiro.test(size[age=="fifth"]))
with(DataBaseCysts,shapiro.test(size[age=="sixth"]))
leveneTest(size~age,center="mean", data=DataBaseCysts)
anova<-aov(size ~ age,data= DataBaseCysts)
summary(anova)
psych::describeBy(DataBaseCysts=size, group = DataBaseCysts$age, range = T, IQR = T, na.rm=T)
oneway.test(size ~ age, data= DataBaseCysts, var.equal=F)

#age-headaches
psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$headache, range = T, IQR = T)
t.test(age~headache, data=DataBaseCysts, var.equal=F)
#age-sleep comp
psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$SleepComp, range = T, IQR = T)
t.test(size~SleepComp, data=DataBaseCysts, var.equal=F)
#age comp ad
psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$kompAdeq, range = T, IQR = T)
t.test(size~kompAdeq, data=DataBaseCysts, var.equal=F)
#age gender
psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$gender, range = T, IQR = T)
t.test(size~gender, data=DataBaseCysts, var.equal=F)
# age - melatonin

psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$circadinEffect, range = T, IQR = T, na.rm=T)

t.test(size~circadinEffect, data=DataBaseCysts, var.equal=F)

## size compaqueduct

psych::describeBy(DataBaseCysts<size, group = DataBaseCysts$kompAdeq, range = T, IQR = T, na.rm=T)

t.test(size~circadinEffect, data=DataBaseCysts, var.equal=F)

# age in op. pgroup

psych::describeBy(DataBaseCystsSur$age)

## incidental group

psych::describeBy(DataBaseCysts<size, group = DataBaseCysts$diagnosis, range = T, IQR = T, na.rm=T)

t.test(size~diagnosis, data=DataBaseCysts, var.equal=F)

psych::describeBy(DataBaseCysts$age, group = DataBaseCysts$diagnosis, range = T, IQR = T, na.rm=T)

t.test(age~diagnosis, data=DataBaseCysts, var.equal=F)

## size - headaches

psych::describeBy(DataBaseCysts<size, group = DataBaseCysts$headache, range = T, IQR = T)

with(DataBaseCysts, lillie.test(size[headache=="yes"]))

leveneTest(size~headache, data=DataBaseCysts, center="mean")

t.test(size~headache, data=DataBaseCysts, var.equal=F)

## size - sleepcom

psych::describeBy(DataBaseCysts<size, group = DataBaseCysts$SleepComp, range = T, IQR = T)

with(DataBaseCysts, lillie.test(size[SleepComp=="no"]))

with(DataBaseCysts, shapiro.test(size[SleepComp=="yes"]))

leveneTest(size~SleepComp, data=DataBaseCysts, center="mean")

t.test(size~SleepComp, data=DataBaseCysts, var.equal=F)

## size melatonin

psych::describeBy(DataBaseCysts$size, group = DataBaseCysts$circadinEffect, range = T, IQR = T)
with(DataBaseCysts, lillie.test(size[circadinEffect=="no"], na.rm=T))

with(DataBaseCysts, shapiro.test(size[circadinEffect=="yes"], na.rm=T))

leveneTest(size~circadinEffect, data=DataBaseCysts, center="mean")

t.test(size~circadinEffect, data=DataBaseCysts, var.equal=F, na.rm=T)

## comp. adeq - headache

tb <- with(DataBaseCysts, table(headache, kompAdeq))

sb <- addmargins(tb)

sb

expected <- chisq.test(tb)$expected

round(expected, digits=2)

row.prop <- prop.table(sb,1)*100

row.prop <- round(row.prop, digits=2)

row.prop

chisq.test(tb, correct=F)

##sleep-compadeq

tb1 <- with(DataBaseCysts, table(SleepComp, kompAdeq))

sb1 <- addmargins(tb1)

sb1

expected <- chisq.test(tb1)$expected

round(expected, digits=2)

row.prop1 <- prop.table(sb1,1)*100

row.prop1 <- round(row.prop1, digits=2)

row.prop1

fisher.test(tb1, alternative = "two.sided")

##multivariate

DataBaseCysts$age[DataBaseCysts$age < 35] <- "first"
DataBaseCysts$age[DataBaseCysts$age >= 35 & DataBaseCysts$age < 55] <- "second"
DataBaseCysts$age[DataBaseCysts$age >= 55 & DataBaseCysts$age < 85] <- "third"
model <- glm(headache ~ age, data = DataBaseCysts, family = binomial())
summary(model)
model1 <- glm(headache ~ size, data = DataBaseCysts, family = binomial())
summary(model1)
model2 <- glm(headache ~ kompAdeq, data = DataBaseCysts, family = binomial())
summary(model2)
model3 <- glm(headache ~ gender, data = DataBaseCysts, family = binomial())
summary(model3)
cbind(exp(coef(model)), exp(confint(model)))
cbind(exp(coef(model1)), exp(confint(model1)))
cbind(exp(coef(model2)), exp(confint(model2)))
cbind(exp(coef(model3)), exp(confint(model3)))
multilog <- glm(headache ~ age + size + kompAdeq + gender, data = DataBaseCysts,
               family = binomial())
summary(multilog)
cbind(exp(coef(multilog)), exp(confint(multilog)))
multilog.b <- step(multilog, direction = "backward", na.rm=T)
## to event decrease size
DataBaseCysts$DecreaseSize <- factor(DataBaseCysts$DecreaseSize, levels = c(0, 1), labels = c("No", "Yes"))
library(survival)
Surv(DataBaseCysts$EventSize, DataBaseCysts$DecreaseSize)
lf.t <- survfit(Surv(EventSize, DecreaseSize) ~ 1, data = DataBaseCysts, conf.type = "none")
summary(lf.t)
str(lf.t)
summary(survfit(Surv(EventSize, DecreaseSize) ~ 1, data = DataBaseCysts))
km <- survfit(Surv(EventSize, DecreaseSize) ~ 1, data = DataBaseCysts)
plot(km, xlab = "Time", ylab = "Cyst Size decreases")
## size
Surv(DataBaseCysts$EventSize, DataBaseCysts$IncreaseSize)
lf.tis <- survfit(Surv(EventSize, IncreaseSize) ~ 1, data = DataBaseCysts, conf.type = "none")
summary(lf.tis)
str(lf.tis)
summary(survfit(Surv(EventSize, IncreaseSize) ~ 1, data = DataBaseCysts))
kmis <- survfit(Surv(EventSize, IncreaseSize) ~ 1, data = DataBaseCysts)
plot(kmis, xlab = "Time", ylab = "Cyst size increases")

## Decrease sym
Surv(Pinealcystsno_op$EventSympt, Pinealcystsno_op$ReduceSympt)
lf.tdsm <- survfit(Surv(EventSympt, ReduceSympt) ~ 1, data = Pinealcystsno_op, conf.type = "none")
summary(lf.tdsm)
str(lf.tdsm)
summary(survfit(Surv(EventSympt, ReduceSympt) ~ 1, data = Pinealcystsno_op))
kmdsm <- survfit(Surv(EventSympt, ReduceSympt) ~ 1, data = Pinealcystsno_op)
plot(kmdsm, xlab = "Time", ylab = "Reduce Symptoms")

## Increase symptoms
Surv(Pinealcystsno_op$EventSympt, Pinealcystsno_op$IncreaseSympt)
lf.idsm <- survfit(Surv(EventSympt, IncreaseSympt) ~ 1, data = Pinealcystsno_op, conf.type = "none")
summary(lf.idsm)
str(lf.idsm)
summary(survfit(Surv(EventSympt, IncreaseSympt) ~ 1, data = Pinealcystsno_op))
kmism <- survfit(Surv(EventSympt, IncreaseSympt) ~ 1, data = Pinealcystsno_op)
plot(kmism, xlab = "Time", ylab = "Increase Symptoms")

survdiff(Surv(EventSympt, IncreaseSympt) ~ kompAdeq, data = Pinealcystsno_op, rho = 0)

## Surg patients
DataBaseCystsSur$gender <- factor(DataBaseCystsSur$gender, levels = c(0, 1), labels = c("Male", "Female"))
summary(DataBaseCystsSur$gender)

DataBaseCystsSur$headache <- factor(DataBaseCystsSur$headache, levels = c(0, 1), labels = c("No", "Yes"))

DataBaseCystsSur$kompAdeq <- factor(DataBaseCystsSur$kompAdeq, levels = c(0, 1), labels = c("No", "Yes"))

DataBaseCystsSur$SleepComp <- factor(DataBaseCystsSur$SleepComp, levels = c(0, 1), labels = c("No", "Yes"))

DataBaseCystsSur$typeHead <- as.factor(DataBaseCystsSur$typeHead)

summary(DataBaseCystsSur$typeHead, na.rm=T)

psych::describeBy(DataBaseCystsSur)

Surv(DataBaseCystsSur$optime, DataBaseCystsSur$PostopHead)

lf.top <- survfit(Surv(optime, PostopHead) ~ 1, data = DataBaseCystsSur, conf.type = "none")

summary(lf.top)

str(lf.top)

summary(survfit(Surv(optime, PostopHead) ~ 1, data = DataBaseCystsSur))

t(formula = Surv(optime, PostopHead) ~ 1)

kmop <- survfit(Surv(optime, PostopHead) ~ 1, data = DataBaseCystsSur)

plot(kmop, lty = 2:4, xlab = "Months", ylab = "Postoperative appearance of headache")

## Plots ##

### Figure 1 ###

barplot<-barplot(row.prop, main="Comparison of Row percentages between males and females \nfor different headache types", xlab="Headaches", ylab="Percentage (%)", ylim=c(0,100),
 col=c("blue4","azure3"), legend = rownames(row.prop), beside=TRUE)

text(barplot, row.prop, paste(label=row.prop,"%"), cex=1, pos=1)

library(help = "graphics")

x <- table(DataBaseCysts$gender, DataBaseCysts$typeHead)

barplot(x, main = "Type of headaches in women and men", beside = T, col = c("skyblue4", "violetred4"), ylim = c(0, 40))

barplot<-barplot(row.prop, main="Comparison of Row percentages between headache and no-headache \nfor no local mass effect and mass effect of quadrigeminal"
plate", xlab="Headache", ylab="Percentage (%)", ylim=c(0, 100), col=c("blue4", "azure3"), legend = rownames(row.prop), beside=TRUE)
text(barplot, row.prop, paste(label = row.prop, "\%"), cex = 0.8, pos = 1)

barplot1 <- barplot(row.prop1,
  main = "Comparison of Row percentages between 
Sleep Compliance according to local mass effect of quadrigeminal plate",
  xlab = "Sleep Compliance",
  ylab = "Percentage (%)",
  ylim = c(0, 100),
  col = c("blue4", "azure3"),
  legend = rownames(row.prop),
  beside = T)
text(barplot1, row.prop1, paste(label = row.prop1, "\%"), cex = 0.8, pos = 1)

a <- barplot(table(DataBaseCysts$Medication), width = 1, col = "skyblue4", main = "Medication categories", horiz = F, ylim = c(0, 30), xlim = c(0, 20))
tbsize <- with(DataBaseCysts, table(Mean(DataBaseCyst$size), age))

km.tr <- survfit(Surv(EventSympt, IncreaseSympt) ~ kompAdeq, data = DataBaseCysts)
plot(km.tr, lty = 2:3, xlab = "Months", ylab = "Worsening of Symptoms")
legend(x = "bottomleft", legend = c("No mass effect", "Mass effect"), lty = 2:3, cex = .75)