The growth of brain abscesses

A retrospective study of brain abscess cases in Norway

Eirin Christina Roland Udnæs

Project thesis,

Department of Neurosurgery and Department of Neurohabilitation, Oslo University Hospital

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Project thesis by Eirin Christina Roland Udnæs,

University of Oslo, Faculty of Medicine

Candidate number: 2044

Subject: MED 5090

Supervisors:

Bjørnar Hassel, Department of Neurohabilitation

Daniel Dahlberg, Department of Neurosurgery

Geir Ringstad, Department of Neuroradiology

Oslo University Hospital

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Abstract

OBJECTIVE: Brain abscesses are rare microbial infections of the CNS. Recommended treatment is antibiotics and surgery, but guidelines are unclear regarding method, timing, and patient selection for surgery. This is partly because we lack an understanding of brain abscesses' potential to grow. This study aimed to find out if brain abscesses grew after hospitalisation. As brain abscess patients do not always present with signs of infection, the patients' clinical and biochemical responses were recorded. Investigations for factors influencing the haste to surgery, and for possible relationships between symptom duration, abscess volume, and systemic infection response were made. **METHODS**: I measured the growth of 14 brain abscesses, where two head scans were available from the first week of hospitalisation. Symptoms, signs and the infection parameters CRP and leucocytes in blood from 42 patients were recorded. Symptom duration, abscess volume, and infection parameters were analysed for possible relations, and for influence on the timing of surgery. **RESULTS**: Encapsulated brain abscesses grew significantly after patients were diagnosed, from 21% to 1060% during one to seven days. Growth occurred despite antibiotics. Only two of 42 patients showed the symptom triad of headache, focal neurological symptoms, and fever. Fever affected 22% at admission. Elevation of infection parameters was mostly mild to moderate. A longer symptom duration correlated with increased CRP levels and abscess volumes at admission. CRP levels and abscess volumes were positively correlated. **CONCLUSION**: The growth of encapsulated brain abscesses adds to the understanding of brain abscess development, and has clinical implications, suggesting that surgery should be performed sooner. The symptom triad is seldom present, and is therefore less useful as a clinical tool. Lack of fever and elevation of infection parameters obscure the infectious aetiology at an early stage. With a longer symptom duration, infection parameters may increase, and the brain abscess grows.

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Introduction

Brain abscesses are bacterial infections of the central nervous system. The disease is rare but may be fatal, and entails a risk for serious complications and long-term neurological difficulties. Despite their potentially hazardous consequences, not all brain abscesses are surgically removed, and when they are, surgery is not necessarily carried out immediately. Guidelines for treatment are lacking or unclear, as the behaviour of brain abscesses is far from fully understood. There are many things we do not know about the development and sequela of brain abscesses. Among these are the potential for brain abscesses to grow, why brain abscess patients often present without systemic signs of infection, or what factors might influence the systemic infection response. This paper has studied a subset of brain abscess cases in Norway. The main aim was to see if any brain abscesses grew. It also wanted to see how many patients received surgical treatment, and how soon surgery was performed, as well as looking for factors that influenced the haste to surgery. In addition, it investigated correlations between symptom duration, systemic response and abscess volume.

Epidemiology

The incidence of brain abscesses has been estimated to 0.3 to 1.3 per 100 000 people per year, but can be considerably higher in certain risk groups, for instance patients with HIV/AIDS (1). Often there is a predisposing condition involving some degree of immunosuppression. However, brain abscesses can occur in patients with previously good medical conditions (2). The disease may affect individuals of any age, with a median age around 34 years, and with a male predominance of 70% (1).

Pathology

Brain abscesses may be caused by a variety of pathogens. Bacterial brain abscesses are the most common, and the subjects of this study. When bacteria invade the brain tissue, an infected area that gets encapsulated may appear – a brain abscess (3). The majority of brain abscesses are metastatic of origin, meaning that the bacteria spread hematogenously from other parts of the body to the brain (3). The bacteria may also spread otogenic or rhinogenic, reaching the brain by infecting nearby bones, before travelling along intracranial veins into the brain (3). Though not yet scientifically explored, one could ask if the brain's lymphatic pathways is another possible way in for bacteria. The lymphatic system of the brain, referred

to as *the glymphatic system,* is thought to be an astrocyte mediated pathway for fluid and mediator transport from the brain parenchyma to the cerebrovascular fluid, driven by arterial pulsation (4). In approximately 20 percent of brain abscesses, we do not know where the bacteria came from (3).

As the bacteria reach the brain, the brain's immune system responds and creates a local inflammation at the site, recruiting leucocytes through leaking vessels. As leucocytes, bacteria, and brain cells die, necrotic tissue appears, surrounded by interstitial oedema. This vaguely demarcated area of inflammation is called an *early cerebritis,* and appears within 1-3 days (3). As the infection progresses, fibroblasts arrive to form a granulation tissue around the inflammation. This tissue is vascularized, and can sometimes be envisioned on radiological pictures as a ring shaped contrast enhancement already by day 3 (5). After 10-13 days, an *early capsule* with a higher integrity is established. By two weeks, the granulation tissue is replaced by a stronger *late capsule,* made up by well vascularized collagenous connective tissue, typically clearly visualized as the characteristic ring shaped contrast enhancement of a brain abscess (3, 5).

The current knowledge of brain abscess pathology lacks an understanding of their development in *size.* We do not know if the abscess starts from a cerebritis of a certain size, becomes encapsulated and remains within the same range, or if the abscess appears in a smaller area of cerebritis and then expands in its encapsulated form.

Another aspect of brain abscess pathology is their limited ability to create a systemic infection response. Slight fever is believed to be characteristic of the early invasive phase of cerebral abscesses, but the temperature seems to return to normal as the abscess becomes encapsulated (3). The same is assumed for leukocytosis (3). This weak systemic infection response may be seen as evidence to an impermeable quality of the capsule, but it could also be due to immunological functions of the central nervous system that limits systemic response. Animal studies have shown that antigens and immune cells from the brain may access cervical lymph nodes through the glymphatic system, and create an immune response peripherally (6). Recent research suggest that what is traditionally referred to as the brain's *immune privilege,* restricting response to infection, may be caused by a combination of tightly regulated antigen flow and response by endothelial cells in the glymphatic system, as well as possible unique abilities of cervical lymph nodes to restrain the immune response to mediators drained from the brain's lymphatics (6). Whatever the cause of the weak, or absent, systemic response, brain abscess patients may be admitted without clinical or laboratory findings of infectious disease.

Bacterial aetiology

Identifying the causative microbe by culturing samples from abscess pus is important to guide antimicrobial treatment. Identification may also give valuable clues to predisposing conditions and probable causes of the brain abscess in a patient, as some agents more often give rise to infection in immunocompromised patients, and different microbes are known to stem from different locations and ways of spreading (7).

Previous brain abscess research is consistent regarding bacterial aetiology, showing that many bacterial agents may cause brain abscesses, but that some bacterial strains are far more common than others. *Streptococci* and *Staphylococci* species are often the causative agents. In a large systematic review by Brouwer et al., *Streptococci* was cultured from 34% of brain abscesses (1). Among these, the *Streptococcus Anginosus* group is found to be the most common bacteria in several studies (8-10). Names of Streptococci from the *Anginosus group* are commonly interchanged with *Streptococcus Milleri* in brain abscess literature. The Anginosus bacteria *Streptococcus intermedius* has been reported as the most frequent brain abscess bacteria (2). Quite often we do not succeed in identifying a causative agent. Brouwer et al. found that only 68% of cultures were positive. Of these 77% were monomicrobial, and 23% were polymicrobial (1).

Symptoms and presentation

The clinical presentation of brain abscess patients is heterogeneous. It's natural to assume that an expansive intracranial process would render the patient with headache and focal neurological symptoms, as well as signs of infection due to the microbial aetiology. This is probably why brain abscesses have been given a "symptom triad" of fever, headache and focal neurological symptoms (1). Brouwer et al.'s systematic review of 123 studies on brain abscesses, from 1970 to 2013, showed that this classic symptom triad was present in only 20% of the patients (1). Headache was reported in 69% of cases, fever in 53%, and focal neurological deficits in 48% (1) – but these symptoms were not necessarily present together. Other studies report incidence rates for symptoms and signs that vary from this systematic review. A study of 49 patients had just one patient with the classic symptom triad (10). Another found only 8.5% of patients with signs of systemic infection (2). This underlines that patients may not exhibit signs of infection at admission. Other common manifestations are changes in level of consciousness, seizures, nausea and/or vomiting (11).

A brain abscess may be difficult to diagnose at an early stage, due to its varied symptomatology, the absence of fever in a substantial proportion of the patients, and the rareness of the disease. In Brouwer et al.'s systematic review, the mean duration of symptoms before admittance was 8.3 days (1). Furthermore, the symptom development is highly unpredictable, particularly in children. When a patient's condition seems to have stabilized, it may suddenly deteriorate to an irreversible state of coma, often caused by a rupture of the abscess into the subarachnoid or ventricular space (3).

Diagnostics

As it may be hard to distinguish between brain abscesses and other intracranial lesions based on the clinical picture, accurate diagnostic procedures are needed. Standard indicators of infection are prolonged erythrocyte sedimentation rate, leucocytosis, and elevation of CRP in blood. With brain abscesses, blood parameters of infection are within the normal range in 30-40% of patients (7). Normal leucocyte count is also found in cerebrospinal fluid in 30% of cases (7). Consequently, we need radiological imaging for diagnostics. Both CT and MRI of the brain may show the classic ring enhancement of a brain abscess. Cranial CT has a false negativity rate of 6% (1), and a lower sensitivity than MRI for distinguishing brain abscesses from other intracranial processes, such as primary brain tumours and metastases (7). MRI is better at distinguishing these entities, and is often needed for diagnostics. A final microbiological diagnosis require surgical aspiration of the lesion's contents (7).

Treatment

The recommended treatment for brain abscesses is prolonged antibiotics and surgical treatment (12, 13). However, one is left with a feeling of uncertainty regarding surgery method, timing of surgery, and what patients to perform surgery on, after reading somewhat ambiguous medical databases. Studies displaying different traditions in different institutions do not make it any clearer. Both *Up To Date* and *BMJ Best Practice* underscore the value of surgical intervention to obtain a sample for culturing that may direct or redirect antibiotic treatment. Other aspects regarding surgery remain unclear. *Up To Date* recommends needle aspiration over surgical excision, because the neurological sequela have been shown to be reduced. Confusingly, the database contradicts its own advice, by referring to a study showing that abscess resection had lower reoperation rate and higher rate of improvement in neurological status within one month, compared to aspiration (12). Further on, *Up To Date*

states that surgery may be delayed or not required in specific instances, namely "early cerebritis without evidence of cerebral necrosis", and "abscesses located in vital regions of the brain or those inaccessible to aspiration" (12). If a decision to not drain immediately is made, no advice for timing of follow-up imaging is given. *BMJ Best Practice* recommends surgical evacuation for all patients with suspected or confirmed bacterial aetiology in acute settings. If the setting is not acute, they recommend surgery for *some* patients, without further specifying who these patients may be (13).

It seems that the choice whether to operate, how to do it, and what is the optimal timing is not interpreted similarly in all institutions. Lange et al. confirms that when deciding on surgery, there's a lack of evidence-based recommendations for the timing of surgery and surgical technique (2). In Lange's study, they performed surgery on all patients with a mortality rate of 0%, and a surgery performance of 1.5 surgeries per patient (2). A 2010 review from India experienced that all pyogenic abscesses required surgical intervention, and that adequate drainage produced an immediate clinical improvement (11). Brouwer et al., on the other hand, found that 16% were treated with only antibiotics and no neurosurgical procedures. In addition, a frequent need for reoperation, at 31%, was reported (1). In another systematic review, Brouwer et al. write that for neurosurgical treatment other than for acquisition of pathogens, one should consider the patient's clinical condition, the location and size of the abscess, and the chance of achieving successful decompression (7). It should be noted that few data are available to provide a cut-off in abscess *size* when deciding if surgery should be performed (7).

Prognosis and long-term effects

We know that brain abscesses, despite improved survival, may disturb and impair neurological functions after treatment. This field of knowledge is unfortunately small, and we do not know much about the long term effects of brain abscesses, and how different treatments may affect neurological outcomes. Brain abscesses used to be fatal, but mortality rates have fallen from around 50% in 1950, to less than 10% after 2000, due to improved radiological methods facilitating more precise diagnostic and surgical methods (1). After treatment, surviving patients may be left with neurologic residua, which of focal epilepsy is frequently reported (3, 14). Few studies have been conducted on long term effects of brain abscesses. To my knowledge, Visani et al. have performed the only study to assess neuropsychological sequela over several years, from 6 months to 42 years. They found that

despite the focal character of the lesion, long-term sequelae follow a more diffuse subcortical pattern. 65% of their patients exhibited neuropsychological deficits in some cognitive tasks, and more than half experienced increased irritability, depression, and aggression (15). Other studies have found neurological complications in a shorter time perspective. One study performed follow-ups 12 months after surgery, finding a poor neurological outcome (defined as Modified Ranking Scale score > 2) in 23.5% of patients (16). Another study found that neurological outcome (measured by Glasgow Outcome Score) after surgical treatment tends to worsen by two factors: the patients' age ($p=0.132$), and delay from imaging to surgery ($p<0.05$) (9).

Beside these evidences of adverse effects on neurological functions, recent studies by Dahlberg et al. show that brain abscess pus contains high amounts of potentially neurotoxic substances. They found that the pus can reach high concentrations of the excitatory amino acids glutamate and aspartate (17), potassium and several trace metals (18), as well as toxic levels of ammonia (19). Glutamate and aspartate may interfere with excitatory neurotransmission in the surrounding brain tissue, and contribute to seizure generation (17). High potassium concentration may give both neuronal inactivation and activation, and thereby add to the cause of seizures, as well as focal neurological deficits. Of the trace metals that were found to be increased, iron and copper may facilitate formation of reactive oxygen species (18). Regarding ammonia, Dahlberg et al. conclude that brain abscesses should probably be included among diseases that can cause toxic levels of ammonia in the brain (19).

Aims of this study

This paper has looked into 42 brain abscess cases treated at Oslo University Hospital. Its main aim was to measure if the encapsulated brain abscess may grow after hospitalisation, and at what rate. The study asked if a potential growth is connected to a stronger systemic response, or to certain bacteria, and if growth may happen in the setting of antibiotic treatment.

As the guidelines are somewhat unclear as to who should receive surgery and at what time, I wanted to see how many patients underwent surgery among this study's subjects, and how soon surgery was performed. The number of preoperative hospital days were registered. The days were counted from the patients' entry at their local hospital, to transfer to the neurosurgical department, and from transfer to surgery, on order to see where a potential

delay before surgery lays. If there was a delay, I wanted to find out if abscess volume at admission or infection parameters in blood could influence the haste to perform surgery.

The study also mapped the epidemiology, symptomatology and aetiology of brain abscesses in its patient selection, in order to compare findings with previous studies. It also looked into the patients' biochemical response to the abscesses. The infection parameters CRP and leucocytes in blood reflect the systemic response to an infection. I registered the patients' CRP and leucocyte values, to see how many patients exhibited laboratory findings of infections, and to look for a potential development in these parameters. Lastly, I wanted to see if there are any correlations between symptom duration, systemic response, and abscess volume. Will a longer symptomatic phase increase the systemic infection response, or opposite? Will larger abscesses give a notably rise in systemic infection parameters? Or will a longer symptom duration give larger abscesses, as an indicator of growth over time?

Hopefully, this study will provide greater understanding of the development and behaviour of brain abscesses.

Methods

This study is a retrospective, clinical study based on 42 brain abscess cases treated at the Neurosurgical Department of Oslo University Hospital between 2011 and 2018. The patients were recruited to a prospective study on brain abscess pus, conducted by Dahlberg, Hassel et al. Their study was approved by the Regional Ethics Committee for Medical Research in the South East region of Norway. Medical information recorded during the time the patients were diagnosed and treated have been approved for use in my study by the same Regional Ethics Committee. All patients have consented to their data being used for research. This study is thereby acting in accordance with the *Health Personnel Law §29* and the *Health Research Law Chapter 4* in Norway.

Patients – presentation, inclusion and exclusion

In the study on brain abscess pus, 43 patients were recruited consecutively as they were transferred to Oslo University Hospital. There were no particular inclusion or exclusion criteria – on the contrary the researchers wanted to examine pus from abscesses of a variety of patients. Therefore, the patients in this study vary in age and sex.

For this study, some data was missing or had to be excluded. For measurements of abscess volume change, there were two available head scans taken within a week after admission from 14 patients. 11 of these patients had two head scans taken preoperatively, two patients had no surgery, and one had an unsuccessful surgical intervention and a new head scan taken shortly after, still showing the abscess. When gathering symptom data, one patient had no recorded symptoms, as the abscess was an incidental finding during hospitalisation for another condition. Data on infection parameters in blood were excluded from 13 patients, who either received strong immunosuppressive treatment or chemotherapy, suffered from an infection elsewhere in the body, or had a more widespread brain infection (meningitis or ventriculitis). In these cases, CRP and leucocyte levels would be unreliable sources of the body's response to the brain abscess. CRP and leucocyte values were excluded from 11 patients due to other infections (meningitis with/without ventriculitis, urinary tract infection, pneumonia and otitis media), and from 2 patients who received strong immunosuppression and/or chemotherapy. Additionally, the study wanted to compare only abscesses of bacterial origin. One patient suffered from a fungus brain infection, and was excluded from the study altogether. This left 42 patients in my dataset, whereof abscess growth was evaluated in 14

patients, 29 cases are included in description and analysis of infection markers, and information about symptomatology was gathered from 41 patients. All 42 were analysed with regard to abscess aetiology, and abscess volume from the first head scan.

The diagnose brain abscess was considered in most patients after a head scan, subsequent to neurological symptoms. The suspected diagnosis after a head scan could also be a primary cerebral tumour or a metastasis. In these cases, a brain abscess diagnosis was often made after a new head scan, or re-evaluation of the first, but a few patients did not receive the diagnosis before pus was discovered during surgery. Pus was sampled for the final diagnosis in 40 of 42 patients. In the two remaining patients, the diagnosis brain abscess was not confirmed by microbiological analysis.

Measuring abscess volumes and volume changes

I used the radiology program Sectra IDS7 to study MRI and CT head scans. I calculated the volume of the abscesses, including the capsule surrounding it, by measuring the longest abscess diameter in three orthogonal planes, from the outer edge of the capsule to the opposite outer end. The formula I used was:

$$\text{Volume } (cm^3) = \frac{\text{anterioposterior dimension} \cdot \text{vertical dimension} \cdot \text{horizontal dimension}}{2}$$

This formula is regularly used to calculate volumes of intracranial lesions (20, 21). Brain abscesses often have a fairly elliptical form, which gives quite accurate volume measurements. Some lesions are more irregular. The measurements should therefore be considered estimates. A few abscesses are multilobar, or even consists of multiple separate abscesses. When I came across particularly challenging abscess shapes, I did the measurements in cooperation with an experienced neuroradiologist (Geir Ringstad, MD PhD, Oslo University Hospital). For multilobar or multiple abscesses, I measured the lobes or the abscesses separately and summarized the calculated volumes. A volume change was considered significant when it exceeded 20% of the original size. This threshold value is commonly used when measuring change in size of intracranial tumours, and takes into account limitations when estimating diameters from different scans taken with slightly different projections (20). I measured the growth in cm^3 and in percentage, as well as the average growth rate per day in percentage. I also recorded if patients were treated with antibiotics between the two head scans.

Recording of symptoms

The patients' presenting symptoms and signs were registered by going through journal records. The symptoms and signs were grouped into nine categories to distinguish between different kinds of recurrent symptoms, sorting them by affection of likely associated brain structures or functions. Most patients experienced a number of different symptoms at the time before and during admission. All symptoms were registered, so that the total number of recorded symptoms exceeded the number of patients. The categories were as follows:

Focal neurological symptoms	Reflecting influence of primary sensory or motor cerebral cortex. Examples: loss of sensation/paraesthesia, motor dysfunction, dysarthria and loss of vision
Aphasia and dysphasia	Reflecting influence of speech areas of the brain
Nausea, with or without vomiting	Probably caused by an increase in intracranial pressure
Headache	May be caused by an increase in intracranial pressure
Dizziness, reduced balance and ataxia	Reflecting affection of the vestibular apparatus, cerebellum or connected pathways
Reduces consciousness	Probably caused by a significant rise in intracranial pressure
Reduced general condition	Might be due to the infection, or an intracranial expanding process
Fever	Sign of infection, inflammation, or cerebral affection
Seizures	Often produced by disturbance of normal neurotransmission in the cerebral cortex

I also noted the dates for symptom debut, admission, first contact between the local hospital and the neurosurgical department at Oslo University Hospital, transfer from local hospital to neurosurgical department, radiological investigations, and (if any) operation. I then measured the time interval in between these events.

Infection parameters

CRP and leucocyte values in blood were gathered from the patients' lab records. I used values from the day of admission and values during early hospital stay. Whenever available, I recorded values from the date of radiological examination. If there were no blood samples

taken at the day of the head scan, I used values from the day of transfer to Oslo University Hospital, which fell close to the head scan suspecting an abscess. The reason for obtaining lab values at this time, was to have infection parameter values that would closely reflect the situation at the time of radiological investigation, as they were to be used in correlation analysis with abscess size. Also, I wanted to have values from two time points for each patient, in order to demonstrate a potential change in infection parameters. To see the scope of the change, I needed to use the highest measurable second value in my analysis. For that, I computed variables of in-hospital values representing the maximum value for each patient, and measured the change between these values and the values at admission.

Categorical variables were made from the CRP and leucocyte variables, in order to visualise the variation in infection parameters between patients. The cut off for normal CRP is 0-4 mg/L (22). CRP was further categorised into mildly elevated (>4-10 mg/L), moderately elevated (>10-40 mg/L), significantly elevated (>40-80 mg/L), and highly elevated (>80 mg/L). Leucocyte counts was grouped into normal (3,5-11 $x10^9$/L)(23), mildly elevated (>11-15 $x10^9$/L), elevated (>15-20 $x10^9$/L), and highly elevated (>20 $x10^9$/L).

Analysing the data

I used the software program for statistical analytics *IBM SPSS Statistics, Version 26,* to store and analyse data. I used Multiple Answers Analysis to describe the aetiology and symptom distribution as abscesses could be polymicrobial, and patients presented with several symptoms and signs each.

Before going through with analysis, I assessed the normality of the variables by looking at skewness and kurtosis values, and normal probability plots in SPSS (24). Skewness and kurtosis values should be between ±1.0 to assume normal distribution (25). Deviating normality plots and high skewness and kurtosis values indicate that data is not normally distributed, in which case one should use non-parametric descriptive statistics and analysis, which do not assume normal distribution (24). When data is not normally distributed, median values are more informative than means, and standard deviations are not as indicative markers of spread (24). In my dataset, all continuous variables had skewness or kurtosis values outside of ±1.0, and/or normality plots that deviated. Consequently I will present descriptive data with medians, give maximum and minimum levels as indicators of spread, and use non-parametric methods for analysis.

Correlation analysis between continuous variables were made with Spearman's correlation coefficient, because the variables validates one or more of the assumptions for using Pearson's correlation coefficient (26); they were not normally distributed and there were several outliers. When relevant outliers are present, Spearman's correlation is preferred as it is relatively robust against outliers (26).

I did correlation analysis between the following parameters:

- To analyse correlations between abscess growth and infection markers, symptom duration, and aetiology:

Size of abscess growth	*CRP level at admission*
	Leucocyte count at admission
	Maximum CRP level in hospital
	Maximum leucocyte count in hospital
	CRP increase
	Leucocyte increase
	Aetiology

- To analyse factors correlating with the haste to perform surgery:

Hospital days before surgery	*Abscess volume*
	CRP level at admission
	Leucocyte level at admission

- To analyse the relationship between symptom duration before admission, abscess size and systemic response:

Duration of symptoms	*CRP level at admission*
	Leucocyte count at admission
	Maximum CRP level in hospital
	Maximum leucocyte count in hospital
	Abscess volume
Abscess volume	*CRP level at admission*
	Leucocyte count at admission
	Maximum CRP level during hospitalisation
	Maximum leucocyte count in hospital

Wilcoxon Signed Rank Test was used to analyse change over time in abscess volumes, CRP, and leucocyte values. This is the non-parametric alternative to a repeated measures t-test (24). Again, my choice of non-parametric analysis was due to the lack of normal distribution, as well as the relatively small sample size (24).

Results

Epidemiology

The 42 patients in this study were among 250 patients treated for brain abscesses at Oslo University Hospital during 2011-2018. The catchment area for their neurosurgical department comprises the South East region of Norway, with a population of about 3 million people. This gives an incidence of 1 per 100 000 people per year. The largest proportion of the patients were male (Figure 1). Age varied from one to 85 years old (Figure 2). At the time of data gathering, nine of the 42 patients had deceased. Of these, only one died as a direct consequence of the brain abscess, which gives a mortality rate of 2.3%.

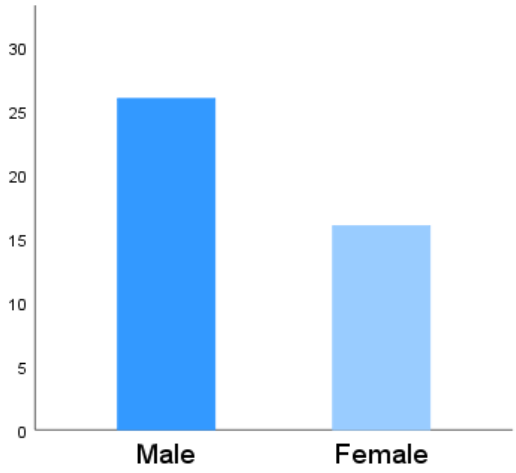


Figure 1: Gender distribution among brain abscess patients. Of the 42 brain abscess patients in this study, 26 were male (62%), and 16 female (38%).

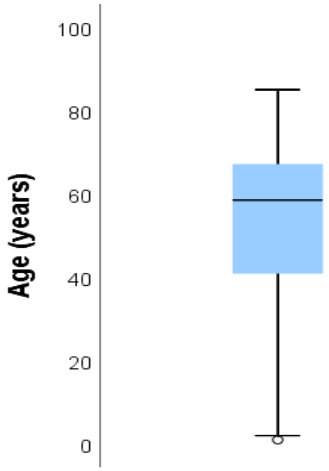


Figure 2: **Age distribution among brain abscess patients.** Boxplot of age distribution among this study's 42 brain abscess patients. The box represents the two middle interquartile ranges, with 50% of the patients, from 41 to 67 years old. The vertical line is the median age of 58.5 years. The whiskers represents the minimum and maximum age of 1 and 85 years.

Abscess volume and growth

A CT or MRI head scan were performed shortly after admission for most patients, but not immediately. Imaging was secured for 12 patients on the day of admission, and within 3 days for 36 patients. The longest time interval before an abscess was located on a head scan was 26 days after admission. This patient had been admitted with a brain infarction and was hospitalized for a long time before an abscess developed in the infarction zone. Apart from this patient, the longest time interval between admission and radiological investigation was 8 days. The first head scans made showed a great variety in abscess size, ranging from 0.6 cm^3 to 63 cm^3 (Figure 3). The median volume was 16.4 cm^3.

Among the 14 cases evaluated for abscess growth, a significant increase in volume (more than 20%) was found in all but one (93%) (Table 1). One abscess was found to decrease in volume. The decrease was below the significance level of 20% volume change. The abscess volume increase varied from 0.4 to 22.6 cm^3 (Figure 3, Table 1). The abscess growth was found to be significant (Z = -3.17, r = 0.60, p = 0.002).

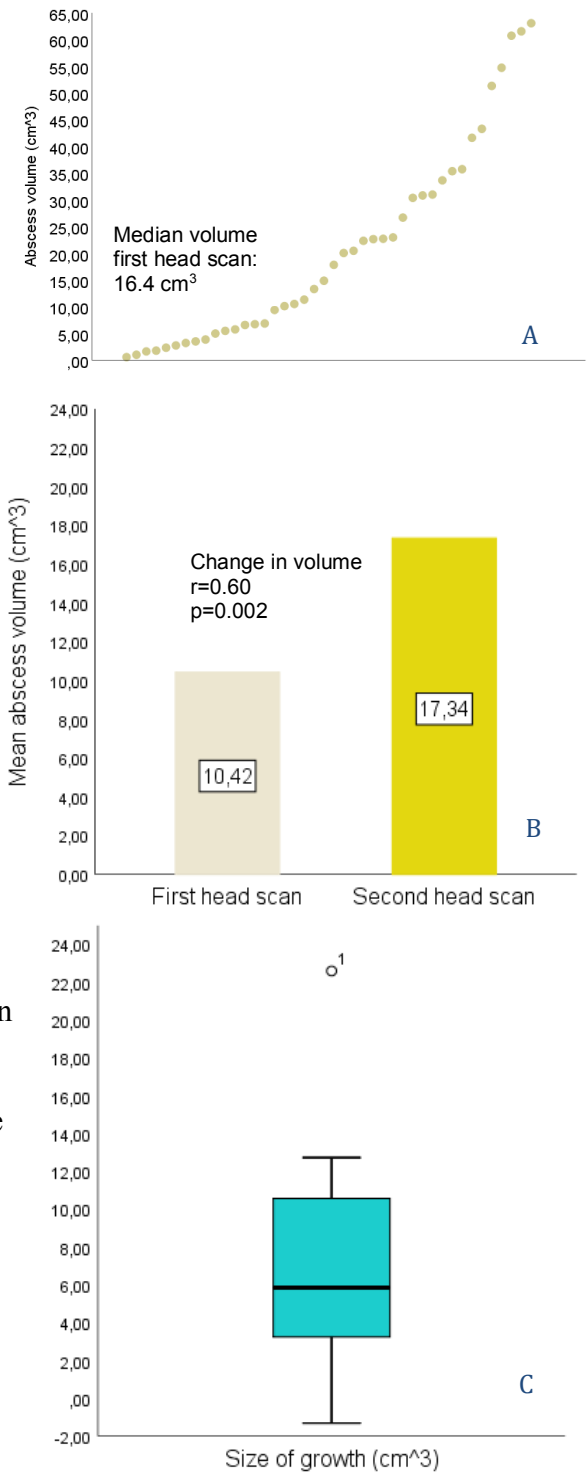


Figure 3: Abscess volumes and growth. **3A**: The first head scan suspecting an abscess in 42 patients showed a wide range of abscess sizes. The x-axis represents the brain abscesses arranged by increasing volume. The abscesses range in volume from 0.59 to 63.1 cm^3. **3B, C:** 14 patients had two available head scans within a week after admission. The time interval between the two scans range from 1 to 7 days. Abscess volume was measured in both scans, to evaluate volume change over time. **3B:** Histogram displaying the change in mean abscess volume from first to second head scans. **3C:** Boxplot demonstrating the spread of the demonstrated abscess volume change (cm^3). The box shows 50% of the cases, representing growth between approx. 3 and 11 cm^3. The vertical line shows a median size increase of 5.8 cm^3. The bottom whisker shows the minimum increase of -19.2 cm^3. The top whisker protrudes to the maximum growth within 1.5*Interquartile range. The circle above shows an outlier that had the largest growth of 22,6 cm^3.

Table 1: **Overview of 14 brain abscesses measured at two time points, with volume changes**. 14 patients had two head scans available from the first week of hospitalisation. Abscess volume was measured in both scans. A change in volume was considered significant if exceeding 20% of the original size. Significant volume change was found in 13 of 14 cases, all displaying a volume increase, marked with green background. The largest growth in cm^3 was an increase of 22.6 cm^3, which happened over 5 days. The largest change in percentage was an increase of 1060% over 6 days, with the fastest average increase per day of 176.7%. The smallest volume change was a decrease of -1.31 cm^3. Abscess growth was found to be significant (r=0.6, p=0.002). Five patients were not originally planned for surgery, but surgery was performed as the abscesses grew. These cases are marked with blue background. Patients treated with antibiotics between the two scans are marked with orange in the identification column to the left.

Gender, age	Localisation	Aetiology	Volume 1	Days between	Volume 2	Volume change cm^3	Volume change %	Change per day %
M, 85	Occipital lobe	*S. Milleri*	35.4	5	58	22.6	63.9%	12.8%
M, 60	Parietal lobe	*H. Parainfluenza*	2.8	5	9.1	6.3	229%	45.7%
M, 81	Cerebellum	*S. Milleri*	14.9	2	23.3	8.5	56.9%	28.4%
M, 26	Multiple	*S. Intermedius, S. Aureus*	22.7	5	35.5	12.7	56.0%	11.2%
M, 25	Frontal lobe	*Fusobacterium. nucleatum*	26.7	1	37.3	10.6	39.6%	39.6%
M, 72	Basal ganglia	*S. Intermedius*	3.9	4	7.2	3.3	85.8%	21.4%
F, 31	Temporal lobe	*A. Aphrophilus*	1.8	2	2.2	0.4	20.9%	10.4%
F, 43	Parietal lobe	*S. Intermedius*	1	6	11.9	10.9	1060%	177%
M, 67	Temporal lobe	*S. Pneumonia*	1.7	4	3.5	1.8	109%	27.3%
M, 62	Parietal lobe	*S .Intermedius, A. Aphrophilus*	3.5	3	6.8	3.3	92.1%	30.7%
M, 60	Temporal lobe	*Streptococci, uncertain*	6.9	7	11.6	4.7	68.4%	9.8%
F, 41	Parietal lobe	*S. Intermedius*	6.8	4	12.1	5.4	79.6%	19.9%
M, 59	Temporal lobe	*S. Milleri*	11.3	2	19.1	7.7	68.1%	34%
M, 70	Occipital lobe	No culture obtained	6.6	4	5.3	-1.3	-19.9%	-5,0%

10 out of 13 cases exhibiting growth were treated with antibiotics in the period between the two head scans. Five of these were not planned for surgery, but surgery was performed as the abscesses grew during antibiotic treatment. No correlations were found between the volume change and the time span between the two scans, infection marker values at admission, or the change in infection markers during hospitalisation. There was a tendency between maximum CRP in hospital and volume increase ($r = 0{,}576$, $p = 0{,}082$). There was no correlation between the aetiology and the volume increase.

Symptoms and signs

The patients presented themselves with a range of different symptoms. Headache was by far the most common symptom, afflicting 73% of the patients before or at admission (Table 2). The second most frequent symptom was focal neurological symptoms. Other common symptoms were nausea with/without vomiting, reduced consciousness, reduced general condition, and seizures, all affecting around 30% (Table 2). Seizure was the primary symptom for some patients, but it could also occur later in the symptomatic phase, after a period of headache or feeling unwell, often after the patient was hospitalised. Fever was somewhat less common – reported in only 22% (Table 2). The triad of fever, headache and focal neurological symptoms appeared in only 2 patients. The time from symptom onset, to the patients were admitted to their local hospital, varied from immediate admittance to a month (Figure 4). More than half were admitted within one week, while a few had a long symptomatic phase before hospitalisation. Patients who were admitted late had less distinct neurological symptoms, and more diffuse disease signs up until admittance.

Table 2: Symptomatology of brain abscess patients. As outlined in methods, symptoms and sigs are divided into nine categories based on likely affected brain areas or functions. Almost all patients experienced symptoms within more than one category. One patient had no reported symptoms, as the abscess was an incidental finding. This left a total of 120 symptoms reported on 41 patients. The first column shows how often a symptom within each category was reported. The second column gives each symptom category in percentage of the total symptom burden. The third column shows the percentage of patients who experienced symptoms of each category.

	Number of patients experiencing a symptom/sign	Percent a symptom category constitutes of all reported symptoms	Percent of patients experiencing a symptom/sign
Focal neurological symptoms: sensory, motoric and loss of vision	15	13%	37%
Aphasia or dysphasia	8	6.7%	20%
Dizziness, reduced balance or ataxia	6	5.0%	15%
Headache	30	25%	73%
Nausea with or without vomiting	14	12%	34%
Reduced consciousness	12	10%	29%
Reduced general condition	13	12%	32%
Fever	9	7.5%	22%
Seizure	13	11%	32%
Total	120	100%	293%

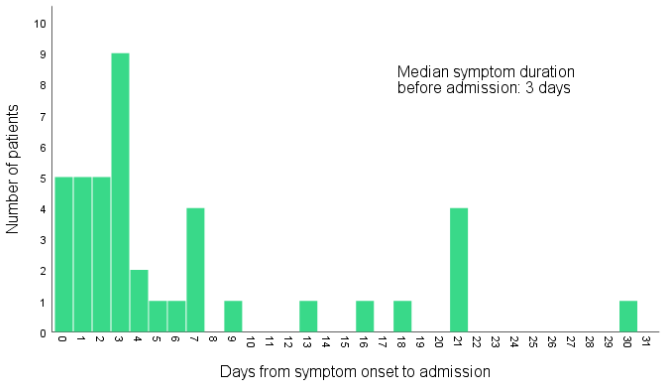


Figure 4: Symptom duration before admission for 41 brain abscess patients: Histogram showing number of days from symptom onset to admission (x-axis) for 41 of 42 patients in the dataset (one was already in hospital when the abscess arose). Median symptom duration before admittance was 3 days. 78% of the patients were admitted within a week after symptom debut, while the remaining 22% had long delays, up to 30 days for the longest.

Timing of surgery

In three patients, antibiotics were the main treatment, and the abscesses were not treated surgically. The remaining 39 patients underwent surgery at Oslo University Hospital, mostly by stereotactic aspiration. Only two patients had surgery within the same day as admission to local hospital, following a quick transfer. The majority of patients had surgery within the first week after admission, while a few patients experienced a long delay before surgery (Figure 5A). One patient had no surgery performed before 31 days of hospitalisation had passed, due to a complicated medical history and unstable condition.

The time from admission at local hospital to transfer to neurosurgical department at Oslo University Hospital varied. Within two hospital days, more than 50% of patients were transferred, but the remaining could spend 1-2 weeks in local hospital before being transferred, the most extreme delay being 31 days (Figure 5B). After transfer to neurosurgical department, surgery followed quickly (Figure 5C). 85% were operated within the same or next day. The first consulting call, or referral from the local hospitals to the neurosurgical department, concerning brain abscess or possible differential diagnosis, mostly resulted in a swift transfer. 22 patients were transferred the same day as contact was made. 12 were transferred the following day. Consequently, most patients were transferred to neurosurgical department quickly after the neurosurgical department received information about the patient, but not all. In a few cases, the neurosurgical department advised the local hospitals to wait and observe, not recommending surgery.

The number of preoperative hospital days correlated negatively with the leucocyte count at admission ($r= -0.53$, $p= 0.004$). No correlation was found between preoperative hospital days and CRP level, or abscess volume at admission.

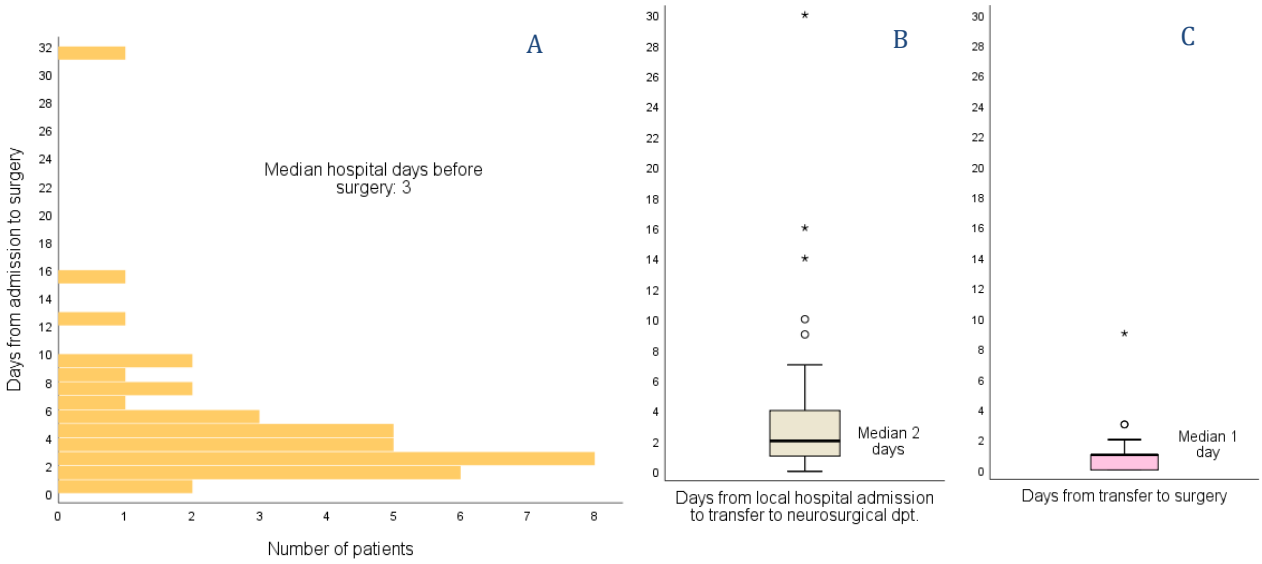


Figure 5: Days spent in hospital before brain abscess surgery for 39 brain abscess patients.

39 of 42 patients in this study underwent surgical treatment for the brain abscess they suffered from. **5A:** Histogram of hospital days from admission to surgery for 39 patients, including days in local hospital and in neurosurgical department, Oslo University Hospital. The majority of patients had ten or less preoperative hospital days. **5B and C:** Boxplots of preoperative hospital days in local hospital (5B) and neurosurgical department, Oslo University hospital (5C). Boxes represent 50% of cases. Horizontal lines show median values. Bottom whiskers show minimum preoperative days before (5B) and after transfer (5C). Top whiskers show 1.5 Interquartile ranges (IQR) above median number of days. Circles and stars are outliers above 1.5 IQR. Stars are extreme outliers. These outliers represent single individuals that had a significant delay from admission to surgery. 5B and C show that the largest proportion of preoperative hospital days was spent in local hospitals. After arrival in neurosurgical department, most patients were operated within 2 days.

Bacterial aetiology

Samples for culturing was collected in 40 of 42 patients. The two remaining patients were both conservatively treated with antibiotics, and no abscess aspiration was done (The third patient who was not treated surgically, as mentioned in the last section, did undergo a surgical procedure to obtain a pus sample for culturing. Due to this patient having multiple brain abscesses, whereof the rest were not targeted surgically, this study regards this individual at *not* treated surgically). 32 cultures were monobacterial, 8 were polybacterial (Figure 6). The most frequently isolated bacteria was *Streptococcus intermedius* (Figure 6). Streptococci was cultured in more than half of the samples. Bacteria from the *S. Anginosus* group were the most frequent bacteria. Apart from these, a great many different bacteria proved to be abscess forming (Figure 6).

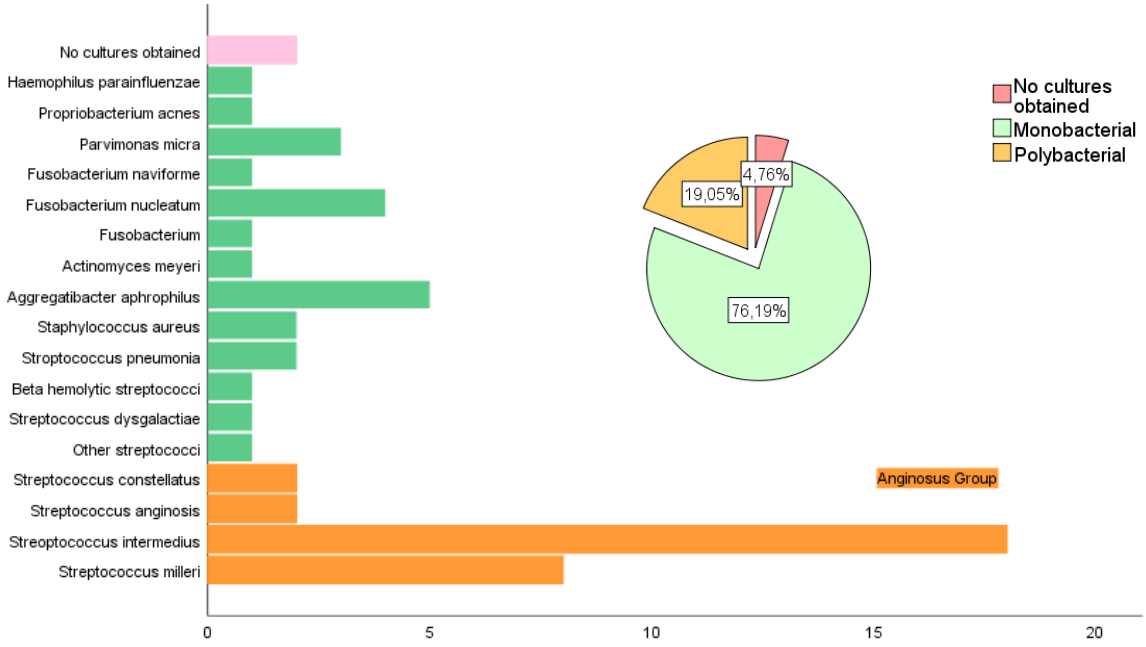


Figure 6: Overview of bacteria identified in pus from 40 brain abscesses.

Histogram showing bacteria identified in cultures from brain abscess pus. Bacteria was identified in samples from 40 of 42 cases. A 43rd case was excluded due to fungus aetiology. In two cases, no samples for culturing was obtained. The orange bars represents the *Streptococcus anginosus* group. The bar *S. milleri* is included among these, and may refer to any species within the *Anginosus* group, as these names frequently are interchanged by convention. Streptococci from the *Anginosus* group was identified 30 times. *S. intermedius* was the most frequent bacteria, identified in 18 cultures. The pie chart shows the proportion of mono- and polybacterial cultures. 32 of 40 cultures were monobacterial.

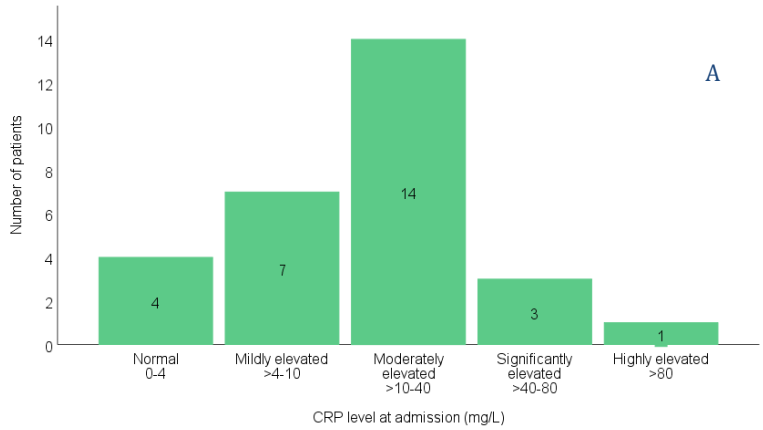
Laboratory infection parameters

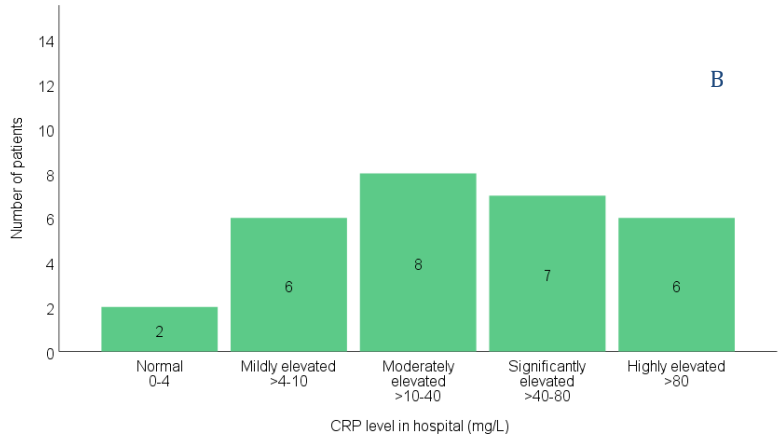
CRP and leucocyte values varied among patients (Table 3). 4 patients were admitted with normal CRP values. Most patients had a mild to moderate CRP increase between 4 and 40 mg/L at admission (Figure 7). About half of the patients had normal leucocyte values at admission (Figure 7). During the early hospital stay, infection markers changed. CRP and leucocytes could increase or decrease, but most patients experienced an increase (Table 3, Figure 7). The change in CRP had no statistical significance, but there was a significant increase in leucocyte counts ($z = -2.273$, $r = 0.42$, $p = 0.001$).

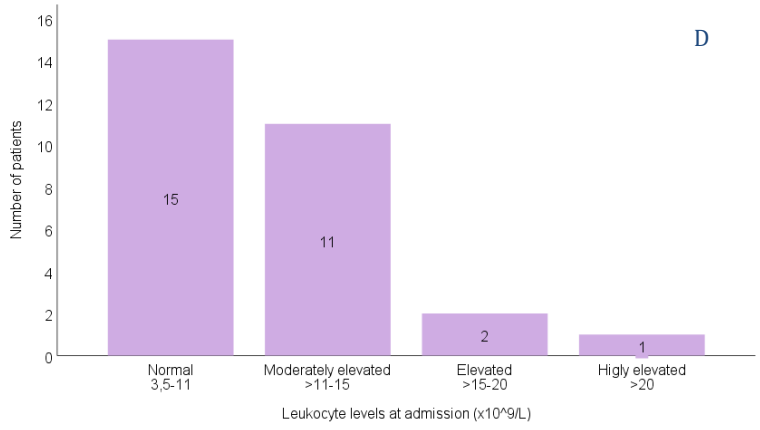
Table 3: Infection parameters in blood from 29 brain abscess patients at admission and during hospital stay.

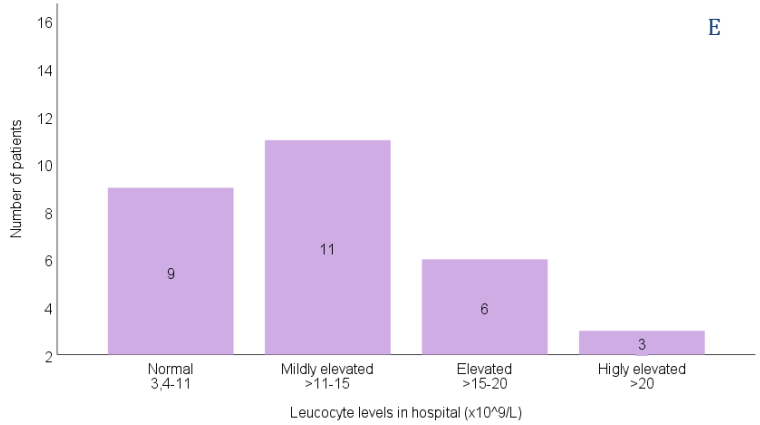
The in hospital values represent the maximum value among values sampled around the time of radiological investigation. The column "change" displays the median, minimum and maximum change in CRP and leucocyte values from admission to the in hospital value. The leucocyte increase was found to be statistically significant (r=0.42, p=0.001)

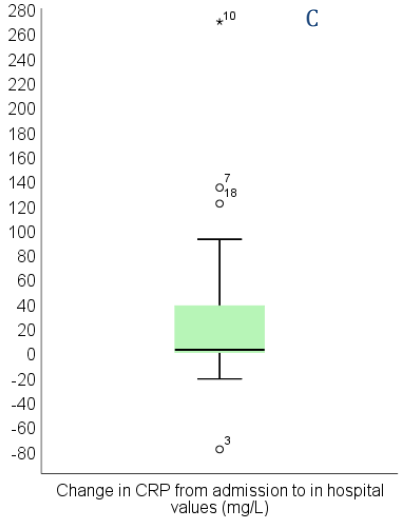
		At admission	In hospital	Change
CRP (mg/L)	Median	16	28	2
	Minimum	1	2	-79
	Maximum	141	270	269
Leucocytes (x9^10/L)	Median	11	12.7	1
	Minimum	6,5	6,8	-5
	Maximum	22.2	28	13











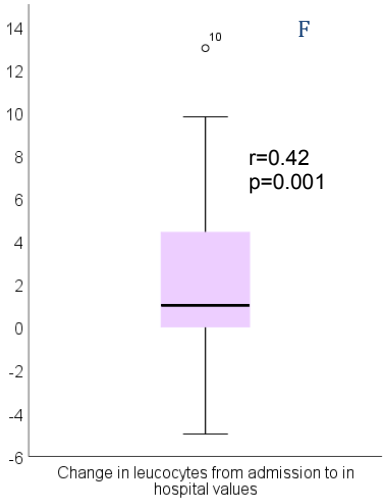


Figure 7: Infection parameter values in blood from brain abscess patients. Histograms shows distribution of CRP (7A,B) and leucocyte (7D,E) levels among 29 patients at admission and in hospital. In hospital values represent highest sampled value at the time of first radiological investigation or transfer to Oslo University Hospital, which happened close in time. Boxplots show change in CRP (7C) and leucocyte (7F) values from admission to the in hospital value. Boxes represent mid 50% of cases' change. Horizontal lines show median change of 2 mg/L for CRP and $1x10^9$/L for leucocytes. The whiskers, circles and stars show the variety in change.

Correlations between symptom duration, abscess volume and systemic response

There were no significant correlations between symptom duration and leucocytes at admission, in hospital CRP values, or in hospital leucocyte values. Also, no correlation was found between abscess volume and CRP or leucocyte values during hospitalisation. Positive correlations were found between symptom duration and CRP at admission, between symptom duration and abscess volume, and between abscess volume and CRP, and leucocyte values at admission (Table 4).

Table 4: Correlation analysis between symptom duration, infection markers, and brain abscess volumes. This study contains 42 brain abscess cases. Numbers of patients included in each analysis are shown in column N. All analysis including infection markers have 29 participants, as data on infection parameters was excluded from 13 patients who suffered from another infection or received strong immunosuppressive therapy/chemotherapy at the time of admission. In one patient, the brain abscess was an incidental finding. Therefore, symptom duration was recorded in 41 patients. The abscess volumes used in the correlation analysis are measured from the first radiological head scans showing a brain abscess after admission. Significant correlations are highlighted with a blue background.

Variable 1	Variable 2	r	N	p-value
Symptom duration	CRP at admission	0.40	29	0.03
Symptom duration	Leucocytes at admission	0.025	29	0.90
Symptom duration	CRP during hospitalisation	0.19	29	0.32
Symptom duration	Leucocytes during hospitalisation	-0.21	29	0.28
Symptom duration	Abscess volume	0.41	41	0.008
Abscess volume	CRP at admission	0.49	29	0.006
Abscess volume	Leucocytes at admission	0.37	29	0.05
Abscess volume	CRP during hospitalisation	0.12	29	0.53
Abscess volume	Leucocytes during hospitalisation	-0.08	29	0.67

Discussion

Brain abscesses grow after they have been diagnosed

This study is the first to show that brain abscesses grow after they have been diagnosed. Growth was demonstrated over a short time span after admission, proving that abscesses can multiply in size within less than a week. One abscess grew from 1 cm^3 to 11.9 cm^3 in six days – which is more than a thousand percent increase. Almost all abscesses that increased in size did so in the presence of antibiotic treatment, showing that antibacterial treatment does not halt brain abscess growth.

Why do brain abscesses grow?

The observation that brain abscesses grow despite antibiotic treatment might implicate that the bacteria's role in abscess growth is inferior to other mechanisms. I propose two mechanisms for abscess growth that are complementary: 1) brain tissue destruction by leucocytes, and 2) ballooning of the encapsulated abscess resulting from water diffusion into the cavity, due to a high osmotic pressure in the abscess content.

Brain tissue destruction mediated by leucocytes were suggested in a recent proteomics study. This study found that brain abscesses contain a large number of proteins with neurotoxic properties, probably leading to destruction of brain tissue during abscess formation (27). Additionally, the high protein content will contribute to a high osmolality within the abscess cavity. A high osmotic pressure produces an osmotic gradient, leading water from surrounding vessels and extracellular spaces into the cavity. A very high osmotic pressure has been demonstrated in pus from abscesses in other localizations in the body (28). Recent studies on brain abscess pus contents have found a remarkably high concentration of glutamate, aspartate, potassium, ammonia and several trace metals (17-19). Although sodium concentrations in pus approximated serum values, at 140 mmol/L (18), the mean extracellular concentration of other electrolytes were found to exceed serum and CFS concentrations. Mean potassium concentration in brain abscess pus was 10.6 mmol/L – almost four times higher than the potassium concentration in CFS (18). Extracellular concentrations of calcium and magnesium were also found to be higher in pus than in CFS. Pus osmolality was not measured in these studies, but added together, their findings of electrolyte concentrations give a higher osmolality in the abscess pus compared to osmolality in serum and CFS.

Following these findings I suggest a model for growth of brain abscesses: To begin with, bacteria that have found their way into the brain provoke a local immune response with invasion of leucocytes – creating a cerebritis (3). In the absence of a capsule in the early brain abscess stage, neurotoxic proteins secreted by leucocytes spread to surrounding brain tissue. Enzymes and toxic proteins destroy brain tissue (27), and create a space which constitutes an early capsule cavity. Fibroblasts eventually start to form a capsule around this process (3). When the abscess capsule is in place, the break down products of leucocytes, neurons, astrocytes and bacteria create a high osmotic pressure within the capsule. This in turn pulls water into the abscess cavity. Water may be drawn from the capsules' vessels, or diffuse across the capsule wall from surrounding brain tissue. When the cavity fills up with water, the capsule stretches, and the abscess balloons. The growth of the abscess is not halted by antibiotic treatment that targets the bacterial agents, because it is leucocytes that contribute to the formation and growth of the brain abscess, by destroying brain tissue, and creating a high osmotic pressure within the cavity.

Pus and water is kept inside the cavity by the firm, collagenous capsule. However, before encapsulation, the toxic products of leucocyte activity may spread, and damage brain tissue and functions. Of the toxic contents identified in brain abscess pus, glutamate and aspartate may interfere with excitatory neurotransmission and contribute to seizure generation (17). High potassium concentration may give both neuronal inactivation and activation – also a possible contribution to seizures, as well as focal neurological deficits (18). Iron and copper may facilitate formation of reactive oxygen species (18), while free ammonia will have a toxic effect on the brain (19).

Clinical consequences - brain abscess patients should undergo surgery earlier

Guidelines for treatment of brain abscesses are not clear, especially regarding which patients should undergo surgery, and at what time surgery should be performed (2, 12, 13). In this study, 93% were operated, but not immediately. Only two patients had surgery on the day of admission. Most patients had surgery within a week after admission, but some experienced a much longer delay. I suggest that surgery should be performed sooner on brain abscess patients, as I will argue for in this section.

The largest systematic review conducted on brain abscesses states that 16% receive only antibiotic treatment, and no operation (1). Other studies advocate operation for all patients (2, 11). Observations in this study, along with previous articles, give an impression

that brain abscesses are not always treated as emergency operation indications. The choice of not performing surgery may be based on several reasons. Such reasons may be a patient's poor clinical condition (7), with low chances of surviving surgery, an abscess location dangerous to approach surgically (12), or small chances of achieving successful decompression (7), as may be the case with small sized abscesses that are difficult to access precisely with a needle. Delayed or absent surgery may also be due to convention or a lack of clear guidelines. If a choice not to perform surgery is based on a small abscess size, the rapid growth potential shown in this study tells us that we need to monitor the abscess closely in case of growth, and re-evaluate the surgery indication.

We do not know much about the brain damage caused by brain abscesses, but one might assume that the more the abscess expands, the more damage it creates. Knowing that brain abscesses will grow, we should do surgery before they achieve a larger size. This study found that several patients not planned for surgery eventually had to undergo surgery as the abscesses got larger during antibiotic treatment. In cases like these, a faster decision would shorten the disease course for both the patient and the hospital. One study showed that delayed surgery increased the length of hospital stay (9). Earlier surgical intervention would thus be cost saving, by reducing hospital days. The same study also found a tendency of delayed surgery to worsen neurological outcome ($p=0.132$) (9). This finding may reason for surgery to be performed sooner, and could possibly be due to the abscesses' expanding properties.

The largest proportion of preoperative hospital days in this study were spent in local hospitals. After transfer to neurosurgical department at Oslo University Hospital, many were operated immediately, and most had undergone surgery within two days. However, some patients spent several days, or even weeks, in local hospitals before transfer. In many cases, the local hospitals contacted the neurosurgical department for consulting before requesting transfer. In a few cases, the neurosurgical department recommended antibiotic treatment and no surgery. The local hospitals were told to wait and observe, but as the patients' clinical conditions deteriorated, the patients had to be transferred for surgery a few days later. In order to achieve an earlier surgical intervention, I propose that local hospitals need to recognise and refer brain abscess patients more quickly, and that neurosurgeons should take all incoming calls concerning suspected brain abscesses seriously, admit them promptly, and plan for surgery as soon as possible.

No symptom triad for brain abscesses is evident

This study showed that the clinical presentation of brain abscesses is varied, as in previous studies. The "symptom triad" of fever, headache and focal neurological symptoms only appeared twice among 42 patients. In Brouwer et al.'s systematic review, this symptom triad was evident in 20% (1), while another study reports only one symptom triad among 49 patients (2). A symptom triad is a collection of three symptoms or signs that are generally associated with a condition, and is useful as a clinical tool when assessing the probability of a disease in a patient. Previous studies and my study show that the symptomatology of brain abscesses is unpredictable, and that the symptom triad of fever, headache and focal neurological symptoms rarely occurs. This makes the symptom triad less relevant as a clinical tool for recognizing brain abscesses.

This study also confirmed that headache is the dominating symptom of brain abscesses (1), while fever is less common (1, 2). Epidemiological findings were also consistent with previous studies, showing an incident of 1 per 100 000 per year, a broad age dispersion, a clear male predominance, and an aetiological pattern dominated by the *Streptococcus anginosus* group (1).

Signs of infection are not always present in brain abscess patients

In this study, a few patients were admitted with no rise in the infection parameters CRP or leucocytes in blood, and most had only a mild to moderate increase. These findings, along with the relatively low proportion of patients with fever, confirm that brain abscess is an infectious disease without the typical signs of infection at presentation. With great symptom variety, without the symptom triad, fever, or infection markers to rely on in diagnostics, brain abscess may be a hard diagnosis to catch without radiological investigation.

Longer symptom duration gives higher CRP levels and larger abscesses

Results from correlation analysis suggest that as the disease course of a brain abscess progresses, the abscess will expand, and the systemic response to the infection may increase, manifested as increased CRP and leucocyte levels in blood.

The CRP and leucocyte values were excluded from my data if the patient suffered from an infection elsewhere in the body, a more widespread brain infection (meningitis, ventriculitis), or underwent immunosuppression or chemotherapy at admission. The remaining infection parameter data should therefore be reliable sources of the patients'

response to the brain abscess solely. The infection parameters data was used to describe the systemic infection response to the brain abscesses, and to explore relationships with symptom duration and abscess volume. Symptom duration correlated positively with CRP at admission. During hospital stay, leucocytes increased significantly, and several patients experienced an increase in CRP. These findings of infection parameters, points towards a trend of increasing systemic response during the disease course of a brain abscess. Both CRP and leucocyte levels at admission correlated positively with brain abscess volume. A possible explanation is that a larger abscess has a greater surface that the immune system reacts to, thereby creating a more pronounced systemic response to the infection.

Abscess volume also correlated positively with symptom duration. This result accords with the study's main finding of abscess growth. Seen together, they suggest that the longer the patient has symptoms, the more the brain abscess expands, and as long as we wait to operate, the abscess will continue to grow.

Limitations and future research

Despite skilled guidance, I gathered most of the data and did the measurements mainly by myself, and did not have a system for blinded measurements of the abscess volumes. I strived to do the measurements in a consistent manner, but it may be considered a scientific weakness to do comparative measurements without blinding the person measuring. In addition, the quality of the head scans were sometimes imperfect, with blurry outlines of the capsules in a few instances. This might give some millimetres inaccuracy when measuring. Small imprecisions may also result from the fact that some patients had CT scans and other MRI scans, not necessarily taken at the same hospital, and thereby with different machines. By using the cut off value of 20% for significant volume change, I hope to have ruled out potential measurement errors.

The clinical condition of the patients is an aspect of the disease courses this study miss consideration of in its analysis. The clinical condition is probably an important factor when planning surgery. Without it, this study found no likely factors that statistically explained the variation in haste to surgery. It is also possible that the clinical condition worsens with both increasing abscess volume and systemic response. This study did not include clinical condition as a variable. A retrospective clinical study deals with clinical information that was given before the research question was formulated. This is not problematic when sampling objective measurements, like lab values. The patients' clinical

condition, on the other hand, is subjectively described by different doctors, not all of them using the same specifications. To make a clinical evaluation of all the patients, I would have to create a scoring system that encompassed signs of clinical condition that is reported repeatedly. A task like that was beyond the scope of this student paper, and would probably require making a scoring system doctors could use as patients are admitted in a prospective study.

An important question for future research is: how does abscess volume relate to short and long term outcome? Do larger abscesses create a more pronounced damage, which gives a larger clinical impact and more extensive long term sequela after treatment? In light of the knowledge of rapid brain abscess growth, a finding of an increased negative impact on outcome, depending on increasing abscess size, would give strength to the argument to prioritize surgery sooner in the disease course.

Conclusion

This study has shown that brain abscesses grow after they have been diagnosed. The growth occurs in the encapsulated stage of the brain abscess, and it happens despite antibiotic treatment. This has implications for the understanding of brain abscess development, and clinical consequences. Not all patients suffering from brain abscesses undergo surgery. This study found a median duration of three days from admission until surgery. Knowing that brain abscesses may grow significantly during this time span, this study concludes that surgery should be performed sooner after patients have been diagnosed.

The symptomatology and laboratory findings of brain abscesses vary and are often not indicative of a brain infection. As a result, a brain abscess may not be suspected initially. The symptom triad of headache, focal neurological symptoms and fever is seldom present, which makes the symptom triad less useful as a clinical tool to recognise brain abscesses. Many patients get admitted with low or moderate increases in infection parameters in blood, but these may increase as the disease progresses. To ensure brain abscess diagnosis at an early stage, radiological investigation should be performed when a brain abscess, or other intracranial pathology, is suspected. If brain abscess is a likely diagnosis, I argue that surgery should be performed quickly, before the abscess grows larger. Future research on the clinical consequences and long term outcomes of brain abscesses dependent on size is required to back up this recommendation.

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