Keywords
Spontaneous Spinal Cerebrospinal Fluid Leaks, spontaneous intracranial hypotension, computer-aided diagnosis, mathematical morphology, biomedical image processing

Summary
Background: Spontaneous Spinal Cerebrospinal Fluid Leaks (SSCFL) is a disease based on tears on the dura mater. Due to widespread symptoms and low frequency of the disease, diagnosis is problematic. Diagnostic lumbar puncture is commonly used for diagnosing SSCFL, though it is invasive and may cause pain, inflammation or new leakages. T2-weighted MRI imaging is also used for diagnosis; however, the literature on T2-weighted MRI states that findings for diagnosis of SSCFL could be erroneous when differentiating the diseased and control. One another technique for diagnosis is CT-myelography, but this has been suggested to be less successful than T2-weighted MRI and it needs an initial lumbar puncture.

Objectives: This study aimed to develop an objective, computerized numerical analysis method using noninvasive routine Magnetic Resonance Images that can be used in the evaluation and diagnosis of SSCFL disease. Methods: Brain boundaries were automatically detected using methods of mathematical morphology, and a distance transform was employed. According to normalized distances, average densities of certain sites were proportioned and a numerical criterion related to cerebrospinal fluid distribution was calculated. Results: The developed method was able to differentiate between 14 patients and 14 control subjects significantly with p = 0.0088 and d = 0.958. Also, the pre and post-treatment MRI of four patients was obtained and analyzed. The results were differentiated statistically (p = 0.0320, d = 0.853). Conclusions: An original, noninvasive and objective diagnostic test based on computerized image processing has been developed for evaluation of SSCFL. To our knowledge, this is the first computerized image processing method for evaluation of the disease. Discrimination between patients and controls shows the validity of the method. Also, post-treatment changes observed in four patients support this verdict.

1. Introduction
Protection of the brain and spinal cord from external shocks is provided by the skull, the three layered membrane system (namely the meninges) and specifically also by the cerebrospinal fluid. The layers of meninges are called the dura mater, arachnoid and pia mater, from the outer to inner levels respectively. Cerebrospinal fluid (CSF) existing between the arachnoid and pia mater acts as a damper by dispersing local shocks to the entire surface of the pia mater. In a healthy person, the pressure and constituents of the CSF are maintained at certain levels [1]. If one or more tears occur on the dura mater, CSF leaks out. This situation is called a “Cerebrospinal Fluid Leak” [2]. If there is no known reason for these leakages, such as surgery or trauma, the disease is described as a “spontaneous” one. Such tears are usually seen in spinal sites of the dura mater instead of cerebral sites. This is most likely because of the higher pressure of the CSF in lower areas and the higher mobility of the dura at spinal sites. If tears occur at a spinal site, the disease is said to be a “spinal leak” rather than a “cranial leak”. Although tears occur at spinal sites, the brain is affected as well. In the disease, “Spontaneous Spinal Cerebrospinal Fluid Leaks” (SSCFL), usually CSF pressure decreases due to leakages. Although the disease is sometimes named “spontaneous intracranial hypotension”, CSF pressure may be within a normal range and therefore the name “intracranial hypotension” does not cover all cases. By the loss of CSF, the brain, which normally floats in CSF, tends to sag. If the disease progresses, this sagging can be detected using Magnetic Resonance Imaging (MRI) by a physician who is familiar with the disease.

Genetically connective tissue disorders or a sudden movement are thought to lead to tears on the dura, but certain cause of the disease is unknown. Although the disease is becoming better understood, it is not yet easy to obtain an accurate diagnosis [3–7]. The main problems with the diagnosis are the low frequency of the disease and the wide spectrum of symptoms [4,5]. It is sometimes misdiagnosed as a hypertension-triggered headache, meningitis,
migraine, psychological disorder (malingering) and sometimes other diseases [3, 8]. The most specific sign is an orthostatic headache which is relieved when lying down [9] though this is not necessarily a sign of SSCFL [10]. The likely cause of this headache is sagging of the brain and traction on pain sensitive structures such as the meninges or blood vessels. Additionally, increased pressure at the inferior sites of the brain due to the sagging can cause ataxia, hearing problems, and other functional problems related to the brain [11]. Though this disease is known to be a benign one, due to the increase in diagnosis of disease, it has been observed to cause serious and varied problems [12], [13], and [14]. Once it is diagnosed, treatment can usually be carried out by epidural autologous blood injection; but if it is not diagnosed properly, it can cause death [5]. While the frequency of the disease is estimated to be 1 per 50,000 according to a study done in 1998 [15], a newer study claims the frequency to be 5 per 100,000 [16]. Schievink et al. states that the frequency of the disease is actually more than estimated [16]. According to a study, 94% of diagnosed patients are initially misdiagnosed and their average diagnosis time is 13 months [3]. Also it is stated in another study that patients are never correctly diagnosed in the Emergency Department [16]. These observations show that diagnosis of the disease is problematic.

A common method used in diagnosis is lumbar puncture [17]. Lumbar puncture is a method used for treatment or diagnosis in which the physician sticks a needle under the dura mater and reaches the CSF. Although the contents of the CSF can be informative, pressure of the CSF is commonly regarded as helpful for diagnosing SSCFL. Low pressure can be a sign of the disease whereas the pressure can be normal or too low to measure [18]. Since the lumbar puncture is an invasive procedure, it is painful and may cause inflammation, injury of the spinal cord or new leakages [19].

A noninvasive alternative technique for diagnosis of SSCFL is MRI. MRI is regarded as the most appropriate modality for examining soft tissues. Diagnosis of SSCFL has been improved through the widespread use of MRI [20]. Since the early 1990s, well-documented studies have been published about MRI signs of this disease and these studies have led the disease being understood better [21]. MRI signs include subdural fluid collections, pachymeningeal enhancement, sagging of the brain and pittuitary hyperemia. Although these signs in advanced phases of the disease can be detected by physicians who are familiar with the disease, if the signs are mild, diagnosis is hard by pure visual inspection [3]. This leads to misdiagnosis and the application of incorrect treatments [3, 8, 16].

CT-myelography is another imaging tool that is used for diagnosis. However it includes an invasive procedure using a contrast dye (agent) injection. Moreover, it is claimed to be less sensitive compared to T2-weighted MR imaging [22, 23].

Many studies related to imaging signs of the disease have been published to date, but they have been carried out by physicians and based on visual inspections. Our literature survey resulted in no study in which computerized image processing methods were used for evaluation of the disease. In this study, we aimed to develop an algorithm that generates a numerical feature related to SSCFL disease, so that the disease can be evaluated quantitatively via computerized image processing methods. It is obvious that such an objective, reproducible numerical criteria could be used for management of the treatment process, graduation of phases and discrimination of mild symptomatic cases from healthy subjects, especially for physicians unfamiliar with the disease. After encouraging findings of our preliminary research [24], the study was continued to confirm the effectiveness of our method statistically on a larger group of subjects.

2. Materials and Methods

2.1 Materials

Magnetic Resonance Imaging is usually considered as the best modality to examine anatomical structures of the brain since it has high contrast resolution in soft tissues and does not use ionizing radiation as in Computerized Tomography. Also, its spatial resolution is higher and it is easy to penetrate the skull compared to Cranial Ultrasound. By changing the timings of radio frequency pulses and magnetic gradients in MRI, it is possible to obtain different modes, each having different sensitivities for different types of tissues [25]. T1 weighted, T2 weighted and proton density weighted modes are examples of these modes. The T1 scan mode is sensitive to body tissues that contain more fat while the T2 scan mode is sensitive to body tissues that contain more water. Since CSF is a fluid with high water content, it is more reasonable to use T2 weighted MRI images for the SSCFL investigations. T2 weighted routine MR scans are performed with a 1.5 Tesla MR scanner device. The thicknesses of the slices are 5 mm. To easily eliminate the tissues that are not of interest, such as those of the mouth, jawbone, and skull; axial images were used. Since the undermost images among axial scans include structures such as the mouth or jawbone which are not related to disease, they are excluded from automatic examination. Similarly, the uppermost images do not include enough brain tissue to determine fluid distribution. Also they have widely dispersed skin tissues which obstruct segmentation. Regarding these circumstances, the middlemost image and three neighboring images above it were chosen for examination.

This study was approved by the Ethical Committee on Research of Fatih University (No: 22/01). Subjects were informed and their consent was obtained. Twenty-eight subjects were included in this study. Half of them were patients diagnosed with SSCFL while the others were healthy volunteers who were recruited as controls. Patients were selected from the Cerrahpasa Medical Faculty who had been diagnosed with SSCFL. Control subjects were selected from healthy persons who didn’t have any brain-related or systemic disease. Also post-treatment images of four patients were obtained and evaluated. There were no post-treatment images for the controls.

The ages (mean ± standard deviation) of the SSCFL patients and control group were 38.9 ± 19.6 and 38.7 ± 20.9, respectively. Six of the subjects in the SSCFL diseased patients group were male while four of the controls were male.
Processing of MR images was done by MATLAB® software. Broad libraries and detailed documentation were cause of preference in the use of this software.

2.2 Preprocessing

An important artifact encountered in MRI is noise. To eliminate the noise in the images to be examined, a Gaussian filter of $3 \times 3$ size with 0.5 standard deviation ($\sigma$) was used. Thus, high frequency random noise was filtered out.

Since image pixel values can have particular ranges due to a number of factors including subject and machine dependence, intensity normalization was performed to achieve consistency in the dynamic range. Normalization coefficients were chosen so that all images consisted of real numbers in the range of (0, 1).

2.3 Elimination of Non-brain Tissues

SSCFL disease directly affects the distribution of CSF in the axial images. Due to this fact, it was decided to extract the criterion according to CSF distribution. Firstly, tissues in the images except the brain were eliminated, since they did not include CSF. To distinguish different tissues, normalized images were converted to binary images by thresholding with the value 0.3. This value was chosen regarding the analysis on histograms of images. After the conversion, objects (with 8-connected neighborhood) smaller than five pixels were discarded so that small specks originating from noise and located around the head could be eliminated. A T2 weighted sample image and its thresholded form can be seen in Figure 1.

In the binary image, a skin object surrounds the brain while there are some small objects between them (see Figure 1). These small objects are pixels of the same bone tissue in fact, but MR imaging does not show bones well and therefore they seem to be discontiguous. To choose the outer object, i.e. the skin, the smallest convex polygon surrounding the objects was determined. All objects touching this polygon were chosen and morphologically dilated three times by $3 \times 3$ flat structure element. Also, the smallest convex polygon was chosen after application of morphological dilation seven times by a $3 \times 3$ structure element. By combining these two, a new mask was obtained. This mask was used for elimination of skin objects in a grayscale image (Figure 2). Only pixels inside this mask were kept and thresholded with the value 0.21. In the resulting binary image, the largest object was selected, and was considered to be brain tissue (Figure 2). To obtain a more robust mask, sharp edges of the mask were smoothened by morphological closing and opening operations using a disk shaped structure element, seven pixels in diameter. Additionally, gaps smaller than one tenth of the image were filled. Eventually, the obtained mask is loci of the brain tissue (Figure 2).

2.4 Extraction of Original Quantitative Features

By the extraction of brain tissue, the brain boundary was obtained as well (Figure 3). Since it is hypothesized in this study that SSCFL changes the brightness distribution between the inner and outer sites of a brain image, a distance trans-

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In this study, in order to quantitatively analyze T2-weighted MRI, using a feature that could reflect the changes in the CSF distribution was suggested and confirmed statistically. For this aim, 112 T2-weighted MRI slices of 14 SSCFL patients and 14 controls were automatically evaluated by our algorithm.

In Figure 5, the x axis shows normalized depth from the brain boundary to the center, and the y axis shows the averages of intensity values of pixels located in each bin. As seen in this figure, a numerical value is obtained by proportioning the sums of two ranges. Figure 7 shows these sums more clearly. These ratios are proposed to be correlated with illness since they directly reflect the CSF distribution. To verify this, a t-test was done for the diseased and control groups, after confirming that their distributions matched normal distribution using Jarque-Bera and Shapiro-Wilk tests. The difference was significant (p = 0.0088), with a standardized mean difference of 0.958.

We obtained pre-and post-treatment values of four patients as well. These values were compared using a paired sample t-test. A significant change from pre-to post-treatment was observed (p = 0.0320) with standardized mean difference 0.853. This difference between pre-and post-treatment cases, as well as difference between diseased and control was mainly because of fluid accumulation in distal sites.

3. Results

Previous studies have shown that diagnosis of SSCFL can be hard or erroneous in most cases. This issue of diagnosis of SSCFL affects the type of treatment method offered in clinics and its success. The main reasons for this difficulty in diagnosis are widespread symptoms, the relatively lower frequency, and the difficulty in seeing imaging findings on visual inspection of MRI or CT images.
and fluid lack in central sites. Since the fluid contains water, this directly causes pixel values in T2 images to increase.

Showing all plots belonging to all subjects here is inconvenient, but mentioning one of them would be illustrative. In Figure 8, two lines are seen; one of them belongs to the pre-treatment case while the other belongs to the post-treatment case of the same patient. The curve pattern is very similar for two lines. This similarity exhibits reproducibility of depth graph. However, the reason for the differences, as seen in the increase and decrease in certain sites, is the effect of the disease on CSF distribution. A remarkable change in the same subject proves that CSF intensity distribution graph, thus the numerical feature is illness-dependent instead of being subject dependent.

4. Discussion

Issues concerning the diagnosis of the disease make it an interesting topic; hence, medical literature has well documented studies. But to our knowledge, there is no study using computerized image processing methods in diagnosis or graduation of SSCFL, though studies do exist in which computerized image processing methods are used to examine the brain.

In order to examine the symptoms of a disease in a medical image, tissues should be segmented and identified. The most common segmentation method used by physicians is manual segmentation [26]. However, it has some drawbacks. For instance, to segment manually, physicians who are expert in that field are needed since manual segmentation is based upon visual and clinical experience. Another disadvantage of manual segmentation is its changeability for every expert, i.e. it is not reproducible. Therefore, many different automatic segmentation methods have been proposed, to date. The basic idea behind these methods is to assign each pixel to the correct tissue class. With a simple approach, if each pixel is simply assigned according to its intensity value, this procedure is called thresholding [27]. But optimum threshold values may change from one image to another, and for more generalizability, pixel values are fitted to statistical models. For instance, in [28], Kovacevic et al. used the Expectation Maximization algorithm to model local and global histograms of pixels as four overlapped normal distributions, after brain extraction using proton density and T2 weighted scans. In another study, Matsumae et al. obtained positron density and T2 weighted images. Using these images they made a scatter plot of brain tissues, then classified these by two-dimen-
sional separation methods [29]. Finally, they made a semi-automatic correction.

Another approach in segmentation is to take into account the regional properties of pixels. One of the most promising regional approaches is use of the Probabilistic Brain Atlas [30]. In this method, a prior probability density map is used which is based on a database including previous manual segmentations carried out by experts. For example, the Expectation Maximization and Probabilistic Brain Atlas approaches are used together in [29, 31]. But to perform segmentation by this method with high precision, many images have to be manually segmented accurately in order to prepare the database. In addition, examining a disease by using an atlas that is prepared for healthy subjects will be misleading, since the aim of the study is to find whether the disease causes changes in tissue morphologies. If the disease causes such changes, the probabilistic density atlas may not match with the patients. Diseased patients should be used to generate a new prior probability atlas database. Studies that contain many manual segmentations can be done by large crews consisting of many experts as in [32].

The features extracted by our approach can be affected by morphological variations in the brain like a brain tumor or hemorrhage. Nevertheless, patients needing differential diagnosis of SSCFL will probably have diseases such as hypertension, meningitis, migraine, or malingering [3, 8]. And morphological variations in the brain are limited in these diseases. As a future work, it is planned to apply our proposed algorithm to groups having such diseases and SSCFL.

Although the t-test shows a significant difference between groups, to specify the boundaries of the numerical features of the two groups more accurately, the number of
subjects should be increased. If this is achieved, specificity and sensitivity comparisons to standard methods, even graduation of phases can be carried out. But this needs more time since the diagnosis of SSCFL is rare. To assess the diagnostic power of the algorithm, an ROC curve of the diseased vs. the control group is provided (Figure 9). Sensitivity and specificity measures are balanced at the values 77% and 71% respectively. The area under the curve is found as 0.75.

To discuss the success of our algorithm, especially on patients without apparent symptoms in visual MRI inspection, a distribution graph of such a subject is drawn against the control group (Figure 10). This patient was described as "without apparent symptoms in visual inspection of Cranial MRI" by the neuro-radiologist in our research team. As seen, the plot of the patient is increased in distal sites and decreased in mid-central sites, resulting in a higher numerical value of quantitative features. This encourages us to believe the proposed algorithm will be helpful for diagnosis of SSCFL in challenging cases. As mentioned in the last paragraph of the methods section, proportioning areas are selected as the range (0.9) and (10.69) while the range (70,100) is ignored. The reason for ignoring these areas is that there are great deviations in this range, probably due to the irregular morphology of the ventricle in different slices. To overcome this issue and obtain more accurate results, we plan to obtain three-dimensional T2 weighted images in future work. With the aid of this three-dimensional data, each depth range might be weighted individually regarding its relevance to the disease, thus the range (70,100) might be taken into account. Moreover, as the next logical step, a medical decision support system is planned. To train the classifier, features extracted from three-dimensional T2 weighted images as well as additional features based on the "normalized depth vs. average density" curve may be used. Also, other modalities such as T1 weighted images may be used in combination with T2 weighted images for better segmentation of the brain.

5. Conclusion

In this study, a computerized image processing algorithm was developed and applied to SSCFL disease for the first time according to our literature survey. A quantitative numerical feature which has a strong relation with SSCFL was extracted. This relation and therefore the reliability of the algorithm are verified by t-tests and effect size analysis. Although analyzing 3D T2 weighted MRI would be more robust, 3D scans are not routinely acquired, so this would require additional image acquisition processes. After obtaining our results, we decided to apply our method to 3D MR images in future work.

Our algorithm for both extracting the brain in images by eliminating non-brain tissue and analysis of CSF distribution was originally developed by us and has never been used before. Application to other problems may be considered.

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References


