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Cortical Gray Matter Thickness to Pons Ratio: A Novel Diagnostic Index for Alzheimer's Disease

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Abstract: *Introduction:* Alzheimer's disease is a chronic neurodegenerative disease that is being diagnosed more and more commonly in neurology clinics. Physicians are familiar to see brain atrophy definition in the MRI reports of these patients. To aid physicians in the diagnosis, we aimed to find a novel radiological diagnostic index for Alzheimer's disease by making MRI-based specific measurements. *Materials and Methods:* Fifty-three patients diagnosed with typical Alzheimer's disease and fifty-five healthy control cases were enrolled in our study. Demographic data containing age, gender, and medical history were recorded. Non-contrast 1.5T brain magnetic resonance images of all participants were collected. Measurements of the prefrontal and precentral sulcus cortical gray matter thickness, as well as the area of the pons, were done by a radiologist. The cortical thickness to the pontine area ratio was calculated and compared between the two groups. Finally, a ROC curve analysis was done to find a certain index value. *Results:* In the patient group, prefrontal and precentral gray matter thicknesses were significantly lower than in the control group. Also, the ROC curve analysis revealed a crucial ratio of prefrontal gray matter thickness to the pontine area. This novel radiological index ratio distinguished Alzheimer's disease atrophy from healthy variances with a sensitivity of 21% and a specificity of 97%. *Conclusion:* The radiological ratios that we found in our study can not be caught by the human eye. Calculating and reporting our suggested index ratio in brain MRI reports may provide additional information for physicians diagnosing Alzheimer's disease.

Keywords: Alzheimer's Disease, Alzheimer Dementia, Brain Imaging, Dementia, Novel Diagnostic Index, Prefrontal Cortex to Pons Ratio

1. Introduction

Alzheimer's disease is a progressive chronic condition in which the acquired abilities fade slowly, usually starting from cognitive functions. Other vital functions like breathing and swallowing keep their integrity until the very last stages of the disease. These functions mostly rely on brainstem structures. No doubt, having efficient functionality means that there should be healthy neural structures. This relative sparing of brainstem functions and clinical deterioration order during brain atrophy in Alzheimer's disease brings the opportunity of using pons as a reference point in determining the value of cortical atrophy seen in Alzheimer's patients.

In many local studies carried out in Turkey, prevalence rates of dementia were calculated to be around 15-20% which of whom composed mainly of Alzheimer's disease (AD) [1, 2]. Other studies from developed countries state similar rates for Alzheimer's disease and estimations of future rates are increasing [3]. Neuropathologic and histopathologic diagnosis of the disease relies on the presence of neurofibrillary tangles and beta-amyloid plaques (amyloid-β (Aβ)) in brain specimens [4]. The deposition of these substrates results in cellular dysfunction and final neuronal loss. Clinical manifestation depends on the degree and localization of this involvement. The findings may vary from mild cognitive impairment to complete cognitive loss and immobility. In the end, it is well known that the death of a patient with severe Alzheimer's disease is mostly expected to be from infectious diseases. Thus, death reports usually don't contain AD as a cause of death. Researches prove this dilemma right. Many studies reveal higher mortality rates due to AD than officially reported [5, 6]. Eventually, this

uptrend in disease prevalence and mortality rates also increases the significance of early diagnosis and disease management. We think that the early diagnosis of the disease may be possible with a new radiological indicator.

In our study, we tried to catch a diagnostic clue from a novel perspective by looking into pontine and cortical imaging measurements of Alzheimer patients. With our findings, we hope to increase early diagnosis rates of the disease.

2. Materials and Methods

2.1. Case Selection and Procedures

Fifty-three patients diagnosed with typical Alzheimer's disease and fifty-five healthy control cases were enrolled in our study. All of the patients were considered new patients and the diagnosis of Alzheimer's disease was re-established through clinical interviews and neuropsychological testing. The standardized mini-mental test (SMMT) was used for this purpose. Their medical history, medication usage information, and demographic data were collected. Also, brain magnetic resonance images were taken from the hospital database.

On the other hand, we enrolled fifty-five healthy cases into the control group. They were chosen from the patients who applied to our neurology clinic with complaints like extremity pain or headache indicating temporary insignificant situations other than chronic neurodegenerative diseases. The SMMT applied to all the healthy participants as well. Individuals who failed in the SMMT were excluded from the study. We looked up all the healthy participants' medical history to be sure that these participants had no neurodegenerative disease or condition interacting with cerebral volume. Also, the medication usage information, magnetic resonance images, and demographic data containing age, gender, and medical history were collected.

2.2. Exclusion Criteria

The patients and control cases having various causes of brain atrophy were excluded from the study. Structural abnormalities like gliosis, cerebrovascular disease, or encephalomalacia were considered reasons for exclusion. Fazekas staging was used for the classification of the MRIs containing gliosis. The patients having gliotic foci more than the Fazekas 0 stage were not enrolled in the study. Other causes of dementia (Parkinson's disease, frontotemporal dementia, vascular dementia, etc.) and other neurodegenerative diseases were considered exclusion criteria. All of the cases were assessed with the hospital anxiety and depression scale, and the cases having depressive symptoms were excluded to eliminate pseudodementia. Additional attention was paid to match the patient and the control group as gender and age-similar as possible.

2.3. MR Image Processing and Device Specifications

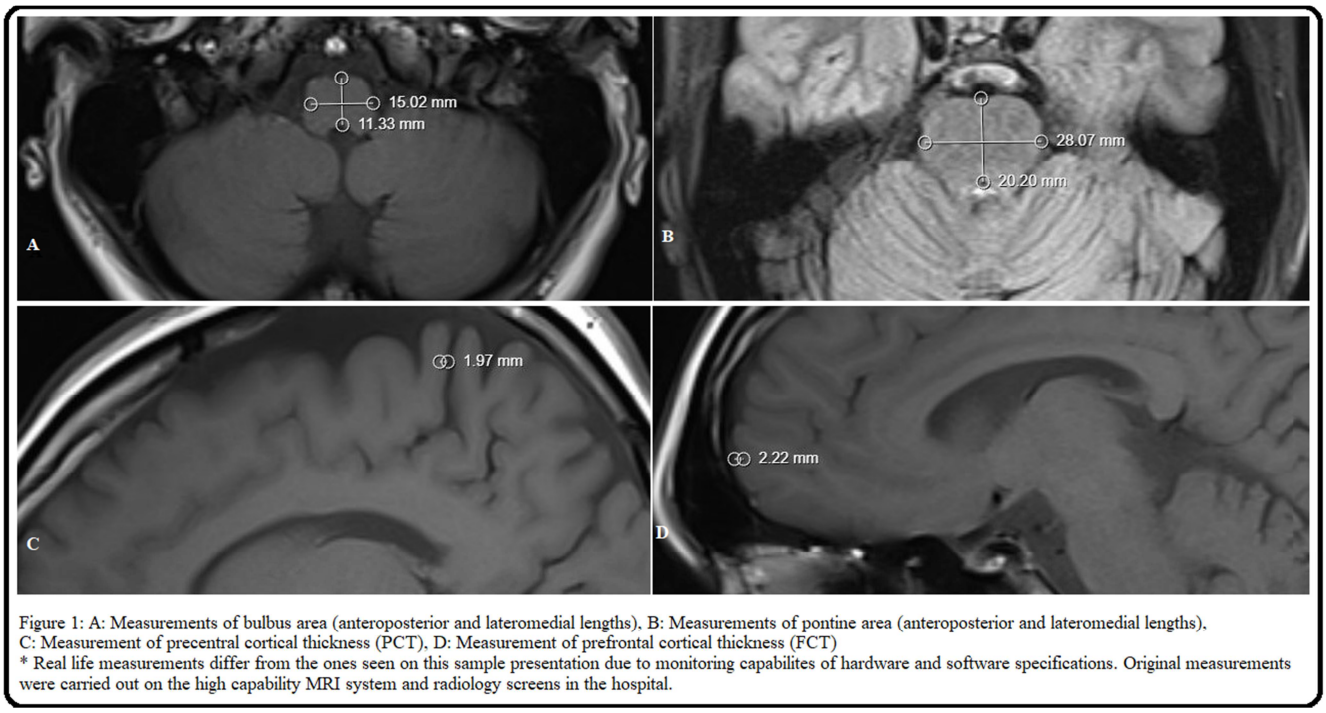

Figure 1: A: Measurements of bulbus area (anteroposterior and lateromedial lengths), B: Measurements of pontine area (anteroposterior and lateromedial lengths), C: Measurement of precentral cortical thickness (PCT), D: Measurement of prefrontal cortical thickness (FCT)
* Real life measurements differ from the ones seen on this sample presentation due to monitoring capabilites of hardware and software specifications. Original measurements were carried out on the high capability MRI system and radiology screens in the hospital.

Figure 1. *Measurement areas of the study.*

An experienced radiologist performed measurements of mainly prefrontal and precentral cortical gray matter thickness as well as pontine and medulla oblongata area. During this procedure, non-contrast 1.5 Tesla, T2, T1, and, Flair sagittal and axial brain MRI sequences were all interpreted together. Bilateral hemispheric measurements were averaged to get a single value for each location. Echo time (TE) and repetition time (TR) were 79,0 ms and 4590,0

ms, respectively. Measurement locations are shown in Figure 1. From these raw values, prefrontal cortical gray matter thickness to pontine thickness (anteroposterior and lateromedial thickness) ratio (FCT/P1-2 ratio), and precentral cortical gray matter thickness to pontine thickness ratio (PCT/P1-2 ratio) were generated. Also, these ratios were calculated again for the pontine area which was calculated as anteroposterior thickness multiplied by the lateromedial width of the pons. The nomination of these ratios will be called Pa/FCT and Pa/PCT, respectively. Putting pons to calculations as a value of the area was aimed to get a more consistent estimation of pontine condition. As stated before, pons develops far before the brain cortex, and as the clinical progress of an Alzheimer's disease patient shows us, its functions fade at the very last stages of the disease. So, this area may be taken as a reference point in interpreting cortical atrophy and the disease progress.

2.4. Statistical Analysis

The measurements and all the collected data were transferred to the IBM SPSS Statistics v25 program. Analyzes were done to reveal whether there were statistically significant differences between the patient and the healthy control group. While doing calculations, bare measurement values like prefrontal gray matter thickness, and pontine thickness and ratios like prefrontal cortical gray matter thickness to pontine area were compared separately. In summarizing the data, continuous variables were mean ± standard deviation, while categorical variables were age, gender, and disease severity. Independent Samples T-test was used for the comparison of the groups in terms of measured values and suggested ratios. In the examination of the relationships between categorical variables, Pearson chi-square or Likelihood ratio tests were used depending on the distribution of the data, and the Pearson correlation coefficient was calculated for continuous variables. ROC (Receiver Operating Characteristic) analysis was done to detect a cut-off value for any measured value. A p-value equal to or lower than 0.05 was considered statistically significant.

3. Results

The summary of the demographic data of the participants are listed in Table 1.

Comparisons of prefrontal cortical thickness (FCT), precentral cortical thickness (PCT), pontine area (Pa), and bulbus area (Ba) means by gender revealed no significant differences among healthy cases (males and females) and patients (males and females).

We expected to find relatively minor or no atrophy in the pons rather than heavy atrophy in the prefrontal cortex. To clarify this suggestion we analyzed the raw pontine values. Pontine anteroposterior measurement value (P1) was similar (p=0,327) between the patient (20,90 ± 1,37) and the control group (21,17 ± 1,49). However, we found a significant difference (p=0,022) in pontine lateromedial measurement value (P2) between the patient (27,86 ± 3,89) and the control group (29,30 ± 2,40). This finding supported our idea of using pontine area rather than anteroposterior or lateromedial measurement alone. Performed raw measurements and generated areas of pons and bulbus are stated in Table 2. Area calculations are made by multiplying anteroposterior and lateromedial measurements of the pons and the bulbus. All values and generated ratios were compared between the patient and the control group, as well as the mild and severe disease groups.

In the pontine area to prefrontal cortical thickness ratio (Pa/FCT) calculation, in other words, while creating this novel index, we expected to find higher values in the patient group since the pontine area would be divided by smaller cortical thickness value of the patient due to cortical atrophy in Alzheimer's disease. Table 3 summarizes the statistical comparison of measurements and generated index values between the patient and the control group. According to these data, there were significant differences between these groups in the measurements of the prefrontal cortical thickness, precentral cortical thickness, pontine area, and bulbus area. Since we aimed to determine the relative atrophy of the cortex to the pons, we calculated the Pa/FCT ratio, our suggested new index for the early diagnosis of Alzheimer's disease. We showed that there was a statistically significant difference between the patients and the healthy cases. Although the precentral cortical thickness and pontine area were statistically different between the groups, there was no statistically significant value in Pa/PCT. This finding directed us towards using FCT as a part of the index rather than PCT. Also, another significant result of the calculations was to find a similar pontine area to bulbus area ratio in the patient and the healthy control group.

In addition to analyzing all the patients as a single patient group, the patient group was divided into mild and severe disease groups so that other calculations could be made to see the difference within the patient group itself. For this purpose, DSM 5 criteria and the clinical findings of the patients were taken into consideration. Practically, the patients using one or no medication for Alzheimer's disease and its behavioral changes were taken into the mild disease group and the other patients were listed under the severe disease group.

Comparison of the ratios between the mild and severe disease groups revealed no statistically significant differences except the slight difference in the pontine area to the bulbus area. This difference in Pa/Ba was considered meaningless since there was no statistically significant difference in Pa/Ba between the patient and the control group. The summary of these calculations is listed in Table 4.

ROC analysis revealed a cut-off value of 3900 mm for the Pa/FCT index with a sensitivity of 21% and a specificity of 97% for the early diagnosis of Alzheimer's disease. This finding suggested that, if present, this index value is significantly related to Alzheimer's disease. On the other hand, FCT itself may be more practical to use in daily practice since it has a cut-off value of 0,187 mm with a sensitivity of 75% and a specificity of 82%. (Table 5)

Table 1. *Demographic data of the patient groups and the healhty control groups.*

Variable	Patient Group (Overall) (Mean ± SD) n=53	Mild Disease Group (Mean ± SD) n=23	Severe Disease Group (Mean ± SD) n=30	Healthy Control Group (Mean ± SD) n=55
Age	70,57 ± 11,33	67,78 ± 13,58	72,70 ± 8,91	64,55 ± 8,63
Gender	Male 64%	Male 78%	Male 53%	Male 36%
	Female 36%	Female22%	Female 47%	Female 64%

Table 2. *Measured raw values and generated estimated area values.*

Variables Measurements	Patient Group (Mean ± SD) n=53	Mild Disease Group (Mean ± SD) n=23	Severe Disease Group (Mean ± SD) n=30	Healthy Control Group (Mean ± SD) n=55
Prefrontal Cortical Thickness (FCT)	0,180 ± 0,034 mm	0,187 ± 0,030 mm	0,176 ± 0,036 mm	0,208 ± 0,027 mm
Precentral Cortical Thickness (PCT)	0,179 ± 0,026 mm	0,179 ± 0,025 mm	0,178 ± 0.027 mm	0,197 ± 0,025 mm
Pontine Anteroposterior Thickness (P1)	20,90 ± 1,37 mm	21,04 ± 1,28 mm	20,79 ± 1,45 mm	21,17 ± 1,49 mm
Pontine Lateromedial Thickness (P2)	27,86 ± 3,89 mm	29,47 ± 3,91 mm	26,64 ± 3,46 mm	29,30 ± 2,40 mm
Pontine Area (Pa)	583,07±93,29 mm^2	619,22 ± 84,18 mm^2	555,36 ± 91,64 mm^2	621,62±75,28 mm^2
Bulbus Anteroposterior Thickness (B1)	11,86 ± 1,00 mm	12,06 ± 1,09 mm	11,71 ± 0,92 mm	12,23 ± 1,23 mm
Bulbus Lateromedial Thickness (B2)	15,29 ± 0,91 mm	15,18 ± 0,92 mm	15,38 ± 0,91 mm	15,62 ± 1,19 mm
Bulbus Area (Ba)	181,64±20,81 mm^2	183,22 ± 21,46 mm^2	180,43 ± 20,58 mm^2	191,08 ± 24,17 mm^2

Table 3. *Suggested ratios and statistical analysis between the patient and the control group.*

Ratios	Patient Group (Mean ± SD) n=53	Healthy Control Group (Mean ± SD) n=55	P Value
FCT	0,180 ± 0,034 mm	0,208 ± 0,027 mm	0,000
PCT	0,179 ± 0,026 mm	0,197 ± 0,025 mm	0,000
Pa	583,07±93,29 mm^2	621,62±75,28 mm^2	0,020
Ba	181,64±20,81 mm^2	191,08 ± 24,17 mm^2	0,032
P1/FCT	119,24 ± 21,87	103,42 ± 15,86	0,000
P2/FCT	158,34 ± 32,51	143,43 ± 24,89	0,008
Pa/FCT	3305,24 ± 683,66	3040,68 ± 577,89	0,032
P1/PCT	119,30 ± 20,49	108,90 ± 16,84	0,005
P2/PCT	158,65 ± 31,84	150,66 ± 23,60	0,141
Pa/PCT	3318,37 ± 716,70	3197,68 ± 579,14	0,337
Pa/Ba	3,24 ± 0,58	3,22 ± 0,60	0,903

Table 4. *Comparison of means between the mild disease and the severe disease group.*

Ratios	Mild Disease Group (Mean ± SD) n=23	Severe Disease Group (Mean ± SD) n=30	P Value
P1/FCT	115,02 ± 17,73	122,48 ± 24,38	0.221
P2/FCT	160,55 ± 29,46	156,65 ± 35,07	0,669
Pa/FCT	3373,45 ± 629,58	3252,95 ± 728,61	0,530
P1/PCT	119,73 ± 21,88	118,97 ± 19,74	0,896
P2/PCT	167,20 ± 34,01	152,10 ± 28,94	0,087
Pa/PCT	3516,71 ± 751,02	3166,30 ± 661,85	0,077
Pa/Ba	3,42 ± 0,63	3,10 ± 0,51	0,045

Table 5. *ROC analysis of measured parameters.*

	Value	Sensitivity	Specificity	Likelihood Ratio	AUC	95% CI
FCT	0,167 mm	36%	97%	9,85	0,770	0,675-0,866
FCT	0,172 mm	43%	93%	5,96	0,770	0,675-0,866
FCT	0,187 mm	75%	82%	4,15	0,770	0,675-0,866
PCT	0,147 mm	11%	92%	6,22	0,685	0,586-0,785
Pa/FCT	3911 mm	19%	99%	10,37	0,610	0,503-0,717
Pa/FCT	3900 mm	19%	97%	5,18	0,610	0,503-0,717
Pa/FCT	3841 mm	21%	95%	3,80	0,610	0,503-0,717

4. Discussion

Alzheimer's disease is a chronic neurodegenerative disease. As stated in the definition of the disease, we expect a developed neural structure to be destroyed progressively in time. From this aspect, the developmental stages of the human brain become even more significant. A typical Alzheimer's patient shows mild cognitive impairment at the first clinical stage and then progresses slowly to a complete cognitive decline stage in which the patient becomes confined to bed. Until the very last stages of the disease, the patient keeps vital primitive functions like chewing and swallowing intact. This clinical clue tells a lot about the possibility of different involvement areas of the brain and variable degeneration speed. Starting from this point, we

aimed to use these relative degenerations and involvements of the brain areas in favor to create an MRI-based novel diagnostic index.

Dating back to the 1950's we already knew that the swallowing function of the fetus starts far before the cortical structural development. [7]. Recent studies reveal that substantial swallowing occurs by the 22-24 weeks of gestation [8]. There is no doubt that complex preparation phases like myelination of the corresponding cranial nerves take place earlier. The cranial nerves participating in chewing and swallowing are mainly trigeminal, facial, glossopharyngeal, vagus, and hypoglossal [9]. Most of the nuclei of these nerves are located in the brainstem, which was one of our measurement locations in the study. Not only these cranial nerves but also lots of vital functions rely on the health and integrity of the pons and brainstem [10]. Thus, this important area keeps its functionality and volume till the very last stages of life.

Apart from primitive tasks of the brain, cognition is a kind of learned ability. It is believed that cognitive development has many aspects like memory, representational competence, attention, and processing speed [11]. All these domains maturate in a step-by-step manner after birth. They are all needed for competent cognition.

If we consider cognition and functions of the brain a pyramid of developments, the first brick to fall would be the acquired intellectual abilities like attention, language skills, and memory utilization. Other vital abilities like breathing and swallowing would be the last ones to disrupt. Looking from this perspective, it is no surprise that memory loss rather than swallowing is the most common finding in the early stage of Alzheimer's disease [12]. The clinical findings come from the pathological changes in the brain. Substance accumulation like neurofibrillary tangles and beta-amyloid plaques and consequent loss of neurons are responsible for the outcome.

Atrophy, especially in the prefrontal cortex, is widely reported in studies [13]. To our best knowledge, all the studies of dementia in the literature focus on the cerebral cortex and thalamus rather than the brainstem structures. Specifically, in Alzheimer's disease, it has long been known that the mesial temporal limbic cortex and thalamus are affected [14]. Another volumetric study carried out with dementia syndromes revealed different patterns of grey matter volume loss in temporoparietal and medial temporal regions. [15]. Vascular dementia and Alzheimer's dementia showed a similar cerebral and medial temporal atrophy pattern in a huge sample study [16]. Another study pointed out that the severity of atrophy seen in Alzheimer's dementia might be related to the factors like education level other than the disease itself. This makes the significance of atrophy level individual for each patient and supports our efforts for finding a personalized reference value while interpreting the volume loss in Alzheimer's dementia [17]. In dementia with Lewy body, a study reported caudate nucleus sparing atrophy of the whole brain. [18]. Medial temporal lobe atrophy on MR images was found to have significant discriminatory power for distinguishing Alzheimer's disease from Lewy body dementia [19].

On the other hand, pontine atrophy has been a research topic of a few studies about spinocerebellar ataxia [20]. Another study further examined the atrophy patterns of the posterior fossa in patients with ataxia and suggested using these imaging patterns to aid the diagnosis [21].

Our study proved significant cortical grey matter degenerations in prefrontal and precentral cortical thickness comparisons. These findings were listed in Table 3.

In a brain volumetric study looking into brain atrophy in Alzheimer's disease, hippocampal atrophy was reported in presymptomatic and mild cases. In that study, prefrontal atrophy was suggested to occur in the later stages of the disease [22]. In our study, we found increased atrophy in the prefrontal region. However, unlike the aforementioned study, statistical analysis revealed no statistically significant differences between the mild and severe disease patient groups. [Table 4] This difference may be due to our age-matched groups rather than the younger control group of the other study.

Another study about brain atrophy in Alzheimer's disease showed a biphasic pattern of atrophy in which accelerated atrophy in mild cases and decelerated atrophy in severe cases were noted [23]. Our findings of statistically similar cortical thickness values in mild and severe disease cases may be compatible with decelerated atrophy rates in transition stages from mild to severe disease.

Unlike intellectual abilities, movement ability is expected to be a rather protected area of functionality in the means of degeneration. Some studies suggest precentral cortical area (primary motor cortex) decrement is a supportive but not a statistically significant indicator for Alzheimer's disease diagnosis [24]. Our data and analysis showed a statistically significant difference in precentral cortical thickness (PCT) between the patient and the control group [Table 3]. Yet, Pa/PCT (estimated pontine area to precentral cortex) ratio difference between these groups was not statistically significant. This finding directed us to use the prefrontal cortical thickness value as a part of our index rather than using the precentral thickness value.

5. Conclusion

Increasing awareness of the disease and prolonging lifetimes will result in increasing numbers of patients with Alzheimer's disease in the coming years. Brain MRI will undoubtedly keep its steady place in supporting physicians during the diagnostic stages. More to add, this precious modality presents us with further information than reporting only gross atrophy. Here, an FCT value of 0,187 mm and a Pa/FCT ratio index of 3900 mm are valuable in the early diagnosis of Alzheimer's disease. With this supportive data, it may be possible to start treatment earlier, which in turn may elongate the physically and functionally self-competent period of the patients. At this period, the patients may still work and live without any financial or physical support. Our index values may contribute

to the prevention of the socioeconomic burden on the patients and their families to some extent by facilitating early diagnosis and treatment, postponing the late stages of the disease that demands heavy physical and financial support. Applying this methodology to other dementia syndromes and Alzheimer subtypes (hippocampal sparing AD, limbic predominant AD, posterior occipital variant, etc.) in large-scale multicenter studies would reveal specific index values for each dementia syndrome.

Abbreviations

AD: Alzheimer's disease, MRI: Magnetic Resonance Imaging ROC: Receiver Operating Characteristic.

FC/P1-2: Prefrontal cortical gray matter thickness to pontine thickness ratio.

PC/P1-2: Precentral cortical gray matter thickness to pontine thickness ratio.

Pa/FCT: Estimated pontine area to prefrontal cortical gray matter thickness ratio.

Pa/PCT: Estimated pontine area to precentral cortical gray matter thickness ratio.

Pa/Ba: Estimated pontine area to estimated bulbus area ratio.

Strengths of the Study

The research is a pioneer study, the first study in the literature to our knowledge, in the field of rationalization of cortical thickness values to pontine values. Sex and age-matched groups make the statistical findings more powerful since Alzheimer's disease is strongly related to aging. Also, the groups are homogenous in every parameter within themselves.

Limitations of the Study

Other dementia syndromes and AD subtypes could not be included in the study due to the small number of specified cases. At this point, multicenter studies with our methodology and a huge number of cases may establish specific index ratios for each dementia entity.

Statement of Ethics

This study was approved by Acibadem University Clinical Research Ethics Committee with the decision number 2021-24/14 on 17.12.2021. Also permission was taken from the chief physician of the hospital in which the data were stored. Written informed consent was obtained for participation in this study.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Consent Statement

All human subjects provided informed consent for the use of MRI and other data.

Conflicts of Interest

The authors declare that they have no competing interests.

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