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Research Article

Evaluation of interpeduncular angle values according to age and gender by magnetic resonance imaging

Manyetik rezonans görüntüleme ile yaşa ve cinsiyete göre interpedünküler açı değerlerinin değerlendirilmesi

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Abstract

Aim: This study aimed to evaluate the prognostic significance of the systemic immune-inflammation index (SII) in patients with nasopharyngeal carcinoma (NPC).

Material and Methods: This retrospective study included 42 patients diagnosed with NPC between January 2014 and January 2020. Clinical data, hematological parameters, and survival outcomes were collected. Disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System. Pre-treatment SII values were calculated using complete blood count data (platelets × neutrophils / lymphocytes).

Results: The mean patient age was 54.0 ± 13.8 years, with a male predominance (66.7%). Most patients presented with advanced disease (AJCC Stage III–IV). Higher pre-treatment SII values were significantly associated with poorer overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis confirmed that elevated SII independently predicted reduced OS (HR: 1.06; 95% CI: 1.02–1.09; $p < 0.001$). ROC analysis identified optimal SII cut-off values of >610 for OS (sensitivity: 73.9%, specificity: 60.0%) and >580 for PFS (sensitivity: 75.0%, specificity: 57.1%). Kaplan–Meier analysis demonstrated significantly lower OS and PFS in patients with elevated SII (log-rank $p < 0.001$).

Conclusion: Elevated SII is a strong and independent prognostic marker for poor outcomes in NPC patients and may guide personalized clinical management.

Keywords: nasopharyngeal carcinoma, systemic immune-inflammation index, prognosis, survival analysis, inflammation

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Öz

Amaç: Bu çalışma, sağlıklı yetişkin bir popülasyonda manyetik rezonans görüntüleme (MRI) kullanarak interpedünküler açı (IPA), pontomesensefalik açı (PMA) ve pontomedüller açı için normatif, yaşa ve cinsiyete göre tabakalandırılmış referans değerleri belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2018 ile Aralık 2020 arasında beyin MRI'ı çekilen 290 sağlıklı yetişkin hasta (124 erkek, 166 kadın; ortalama yaş: 43,1 ± 16,7 yıl) dahil edildi. IPA, PMA ve pontomedüller açılar, standartlaştırılmış aksiyel ve orta sagital T1 ağırlıklı spin-eko MRI dizilerinde ölçüldü. Sınıflandırma şu şekildeydi: 18-24 yaş (genç yetişkinler), 25-33 yaş (yetişkinler), 34-48 yaş (erken orta yaşlı), 49-64 yaş (orta yaşlı), ≥65 yaş (yaşlı).

Bulgular: Ortalama IPA 75,5° ± 10,2, PMA 57,0° ± 10,2 ve pontomedüller açı 133,8° ± 10,6 idi. Erkek ve kadınlar arasında herhangi bir açısal ölçümde anlamlı bir fark gözlenmedi ($p > 0,05$). Ancak, özellikle orta yaşlı ve yaşlı gruplarında, ilerleyen yaşla birlikte IPA değerlerinde anlamlı bir artış gözlendi ($p < 0,001$). IPA yaşla orta düzeyde pozitif bir korelasyon gösterdi ($r = 0,372$; $p < 0,001$), PMA ve pontomedüller açı ise yaşla anlamlı bir korelasyon göstermedi. Üç açısal parametre arasında anlamlı bir korelasyon bulunamadı.

Sonuç: IPA değerleri yaşla birlikte önemli ölçüde artarken, PMA ve pontomedüller açılar yetişkinlik boyunca nispeten sabit kaldı. Bu bulgular, beyin sapı açısal ölçümleri için normatif, yaşa ve cinsiyete göre sınıflandırılmış referans verileri sağlar ve bu da klinik tanılamada, özellikle spontan intrakraniyal hipotansiyon ve nörodejeneratif sendromlar gibi durumlarda, bunların kullanımını artırabilir.

Anahtar Kelimeler: interpedinküler açı, pontomesensefalik açı, pontomedüller açı, manyetik rezonans görüntüleme, beyin sapı morfolojisi, normatif veriler

Introduction

The interpeduncular angle (IPA) is a neuroanatomical measurement defined as the angle formed between the cerebral peduncles of the midbrain on axial magnetic resonance imaging (MRI) (1). In particular, spontaneous intracranial hypotension – a syndrome of low cerebrospinal fluid pressure - is associated with downward displacement of brain structures ("brainstem slumping") that markedly narrows the IPA (2). Although recent studies have shown that IPA is lower in patients with intracranial hypotension compared to healthy individuals, it appears to be elevated in patients with idiopathic normal pressure hydrocephalus (iNPH) and comparable in those with progressive supranuclear palsy (PSP) (3).

In addition to the IPA, other quantitative brainstem angular measurements - such as the pontomesencephalic angle (PMA) - offer further insight into midbrain and pontine anatomy. The configuration of subarachnoid cisterns - shaped in part by arachnoid membrane attachments - may influence multiple brainstem angular measurements, including both the PMA and the pontomedullary angle (4). The PMA is defined at the junction of the midbrain and pons, formed by the anterior surface of the midbrain and the superior surface of the pons. This angle also decreases in pathological states such as spontaneous intracranial hypotension (5). On the other hand, the pontomedullary angle, a sagittal measure between the pons and medulla (6), remains under-characterized in the literature.

Although clinical interest in brainstem morphometry has grown in recent years, there remains a notable lack of well-established reference values or nomograms for angular brainstem measurements in routine MRI interpretation. This absence is particularly evident in the case of the IPA, for which no large-scale normative data exist across the adult lifespan. Preliminary observations suggest that IPA values may be influenced by demographic factors such as sex, with males potentially exhibiting higher angles than females (7). These findings are consistent with broader studies of brainstem structure that have documented age- and sex-related variations in other angular metrics, including the PMA (8). However, comprehensive age- and sex-specific reference values for the IPA, PMA, and pontomedullary angle have yet to be systematically established.

To address this gap, this study aimed to provide age- and sex-stratified reference values for multiple brainstem angular measurements - including the IPA, PMA, and pontomedullary angle - in a healthy adult population.

Material and Methods

This retrospective study was conducted using cranial MRI scans obtained between January 2018 and December 2020 from adult individuals who had presented to Adana Yüreğir State Hospital for various non-neurological reasons. The study was approved by the Cukurova University Non-Interventional Clinical Research Ethics Committee (Date: 05.11.2021, Decision No: 2021/116-60) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, a total of 290 patients who had undergone cranial MRI were retrospectively evaluated. Patients with known neurological disease, radiologically confirmed brainstem pathology, or inadequate image quality due to motion artifacts or technical limitations were excluded. The exclusion process was conducted by an experienced neuroradiologist with over 20 years of experience, who also confirmed the suitability of each case for angular measurements.

Study Protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. MRI images were retrieved from the hospital's digital archive, and subject eligibility was determined through radiological screening. For subgroup analysis, participants were stratified into six age groups based on predefined age ranges to examine age-related variations in brainstem angular measurements (9, 10). The classification was as follows: 18–24 years (young adults), 25–33 years (adults), 34–48 years (early middle-aged), 49–64 years (middle-aged), ≥65 years (elderly).

MRI Acquisition

MRI examinations were performed using a 1.5-Tesla scanner (GE Signa Excite HD; GE Medical Systems, Milwaukee, WI, USA). The routine cranial MRI protocol included axial and mid-sagittal T1-weighted spin-echo sequences. Axial images were acquired with repetition time (TR) of 1173 ms, echo time (TE) of 8.9 and 35.5 ms, a slice thickness of 5 mm with a 0.4 mm interslice gap, and a matrix size of approximately 320 × 224. Mid-sagittal images were obtained using comparable parameters optimized for anatomical clarity. No intravenous contrast was administered.

Image Analysis and Measurements

All images were reviewed on the hospital's workstation using Karmed PACS software (Kardelen Software, Türkiye). Each parameter was measured twice, at least two weeks apart, using identical zoom levels, and the arithmetic mean of the two measurements was recorded as the final value for analysis. The IPA was measured on axial T1-weighted images at the level of the corpus mamillare. Lines were drawn along the medial borders of the cerebral peduncles, and the anteriorly converging angle between them was recorded (Figure 1). The PMA was assessed on the mid-sagittal plane as the angle between tangents to the anterior surfaces of the midbrain and pons (Figure 2). The pons-bulbus angle, also referred to as the pontomedullary angle, was measured on the same sagittal image as the angle formed between tangents to the inferior pons and the superior medulla oblongata (Figure 2).

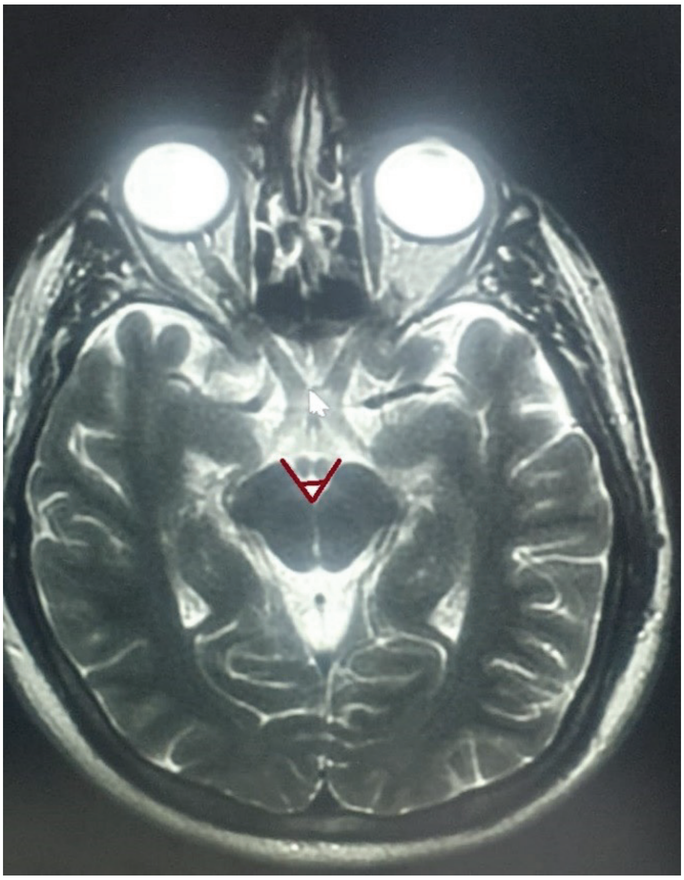

Figure 1. Axial magnetic resonance imaging (MRI) illustrating measurement of the interpeduncular angle (IPA). The red lines indicate the angle formed between the medial aspects of the cerebral peduncles at the midbrain level.

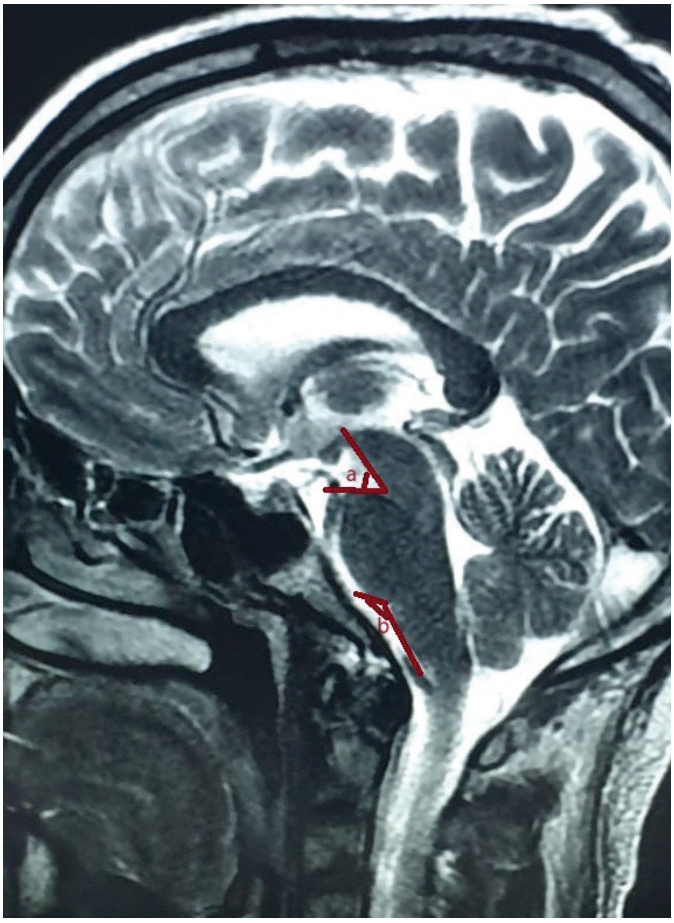

Figure 2. Sagittal magnetic resonance imaging (MRI) demonstrating the measurement of the pontomesencephalic angle (a) and the pontomedullary angle (b).

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range (IQR: 25th–75th percentiles). For comparisons between two independent groups, the Student's t-test was used for normally distributed data, while the Mann–Whitney U test was applied for non-normally distributed data. In comparisons involving more than two groups, one-way ANOVA was used for parametric data, and the Kruskal–Wallis test was employed for non-parametric data. When significant differences were observed, post hoc pairwise comparisons were conducted using the Bonferroni test (for ANOVA) or Dunn's test (for Kruskal–Wallis), as appropriate. The relationships between angular measurements (IPA, PMA, and PBA) were assessed using Pearson's correlation coefficient for parametric variables and Spearman's rank correlation coefficient for non-parametric variables. A p-value < 0.05 was considered statistically significant in all analyses.

Results

The study included 290 patients with a mean age of 43.1 ± 16.7 years, of whom 124 were men (42.8%) and 166 were women (57.2%). The mean IPA was 75.5° ± 10.2, with a range from 46.7° to 99.7°. The PMA had a mean of 57.0° ± 10.2 and values ranging between 30.7° and 96.8°. The pontomedullary angle showed a considerably wider distribution, with a mean of 133.8° ± 10.6, with a range from 102.3° to 158.7° (Table 1).

Comparative analysis of brainstem angular measurements between male and female participants did not reveal any statistically significant differences. The mean IPA was 74.8° ± 10.9 in females and 76.3° ± 9.2 in males (p = 0.202). Similarly, the PMA showed close values across gender, with a mean of 56.8° ± 10.7 in females and 57.3° ± 9.4 in males (p = 0.660). The pontomedullary angle was nearly identical between the two groups (133.9° ± 10.4 in females vs. 133.8° ± 10.9 in males, p = 0.956) (Table 1).

Age-based analysis revealed a statistically significant difference in IPA values across the five age groups. Both the middle-aged and elderly groups exhibited similar IPA values, which were higher on average compared to those of the younger age group (Young adults: 72.3° ± 8.2 vs. Adults: 71.6° ± 10.8 vs. Early middle-aged: 73.8° ± 9.9 vs. Middle-aged: 79.4° ± 9.4 vs. Elderly: 81.4° ± 9.0; p < 0.001). In contrast, IPA values among the younger three groups (young adults, adults, and early middle-aged) remained relatively close, showing no significant differences between them. The mean PMA and pontomedullary angle showed no significant differences among age groups (Table 2).

While age showed a positive correlation with the IPA (r = 0.372; p < 0.001), it was not significantly associated with either the PMA (r = 0.008; p = 0.994) or the pontomedullary angle (r = -0.043; p = 0.468) (Figure 3). No significant correlation was found among the IPA, PMA, and pontomedullary angles (Figure 4).

Table 1. Gender-based comparison of interpeduncular, pontomesencephalic, and pontomedullary angles.

Variables	All population n = 290	Female n = 166	Male n = 124	p
Age, years	43.1 ± 16.7	43.3 ± 16.9	42.8 ± 16.6	0.827
IPA, °				
mean ± SD	75.5 ± 10.2	74.8 ± 10.9	76.3 ± 9.2	0.202
min-max	46.7 - 99.7	46.7 - 99.7	56.5 - 97.7	
IQR	68.0 - 82.7	67.0 - 82.7	69.8 - 83.1	
PMA, °				
mean ± SD	57.0 ± 10.2	56.8 ± 10.7	57.3 ± 9.4	0.660
min-max	30.7 - 96.8	30.7 - 86.9	31.6 - 96.8	
IQR	50.2 - 63.1	49.6 - 62.6	50.7 - 63.8	
PBA, °				
mean ± SD	133.9 ± 10.6	133.9 ± 10.4	133.8 ± 10.9	0.956
min-max	102.3 - 158.7	102.3 - 154.9	106.1 - 158.7	
IQR	126.4 - 141.4	127.3 - 140.8	124.9 - 141.8	

The data are expressed as the mean ± SD, IQR (25th–75th percentiles). IPA, interpeduncular angle; PBA pontomedullary angle; PMA, pontomesencephalic angle.

Table 2. Age-based comparison of interpeduncular, pontomesencephalic, and pontomedullary angles.

Variables	Young adults n = 42	Adults n = 55	Early middle-aged n = 87	Middle-aged n = 70	Elderly n = 36	p
IPA, °						
mean ± SD	72.3 ± 8.2	71.6 ± 10.8	73.8 ± 9.9	79.4 ± 9.4	81.4 ± 9.0	<0.001*
min-max	55.7 – 95.0	46.7 - 96.1	51.1 - 95.3	54.8 - 99.7	59.4 - 98.0	
IQR	67.0 - 78.0	62.2 - 80.9	65.9 - 82.1	73.3 - 86.2	75.7 - 87.2	
PMA, °						
mean ± SD	57.0 ± 10.4	57.3 ± 8.0	57.0 ± 11.0	56.1 ± 10.4	58.4 ± 10.5	0.870
min-max	38.4 - 84.4	39.7 - 72.6	31.6 - 96.8	30.7 - 86.9	38.5 - 78.7	
IQR	53.1 - 60.5	51.9 - 63.6	49.6 - 63.8	49.6 - 62.1	50.6 - 65.8	
PBA, °						
mean ± SD	136.5 ± 10.1	131.4 ± 10.7	133.7 ± 10.1	135.4 ± 10.5	131.9 ± 11.5	0.077
min-max	107.6 - 154.9	102.3 - 150.5	111.9 - 151.8	106.1 - 158.7	107.8 - 154.9	
IQR	130.9 - 143.4	124.1 - 139.4	124.6 - 140.8	127.2 - 142.9	125.3 - 141.0	

The data are expressed as the mean ± SD, IQR (25th–75th percentiles). * P-value <0.05 shows statistical significance. Bold characters show the difference between groups. IPA, interpeduncular angle; PBA pontomedullary angle; PMA, pontomesencephalic angle.

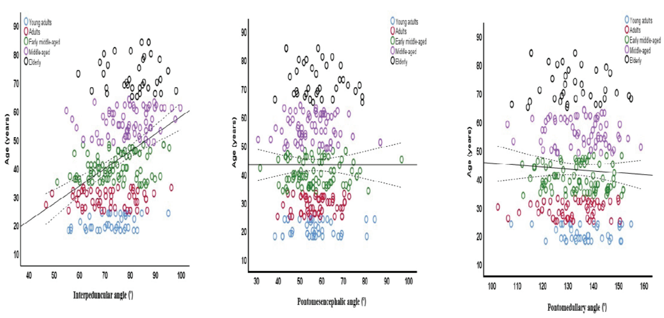

Figure 3. Association of age with ınterpeduncular, pontomesencephalic, and pontomedullary angles.

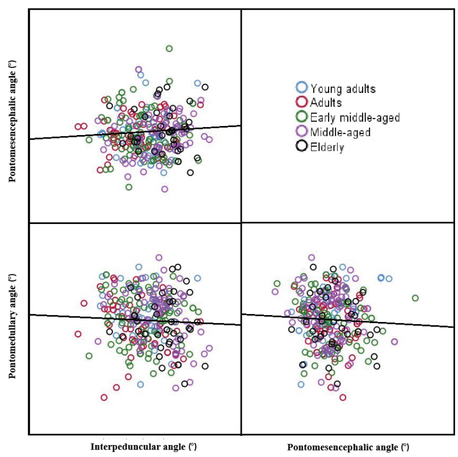

Figure 4. Correlation between interpeduncular, pontomesencephalic, and pontomedullary angles.

Discussion

This study presents one of the largest datasets to date investigating the variation of the IPA, PMA, and pontomedullary angle across age and sex in a healthy adult population. The findings demonstrate that while these angular measurements do not differ significantly by sex, the IPA increases notably in individuals aged 49 years and above. In contrast, PMA and PBA values remain stable across all age groups. The absence of significant correlations among the three angles, along with the age-related constancy of PMA and PBA, suggests a relative anatomical stability of the incisural and pontomedullary cisternal configurations in healthy adults. These results underscore the potential of the IPA as a morphometric marker sensitive to age-related changes, whereas the PMA and PBA appear less influenced by age or sex in the normative population.

In recent years, the IPA has drawn attention as an objective MRI-based indicator of spontaneous intracranial hypotension (7,11). The current literature reports conflicting findings regarding IPA values and their variation with age and sex in healthy individuals. Fatterpekar et al. (12) investigated the role of IPA in diagnosing PSP–Richardson Syndrome and reported an average IPA of 51.2° in the healthy control group. Wang et al. (7) reported that the mean IPA in the control group was approximately 56.3°, with males exhibiting a significantly wider IPA (~64°) compared to females (~53°). However, their study did not evaluate the association between age and the IPA (7). Nevertheless, in a transcranial ultrasound study conducted among adults aged 18 to 50, no significant effect of age or sex on IPA was identified (13). In a large-scale magnetic resonance morphometry study by Debnath et al., the mean IPA was reported as 76.4° ± 9.4, with a gradual widening observed beginning in the fifth and sixth decades of life. The study also noted that females may exhibit IPA values 1–2 degrees higher than males; however, this minimal difference was considered clinically negligible (8). In our cohort, IPA measurements aligned with those reported by Debnath et al., with a noticeable elevation observed in both middle-aged and older adults.

It is known that mild volumetric atrophy occurs in the midbrain (mesencephalon) and brainstem with aging. This condition may lead to a greater separation between the cerebral peduncles, resulting in a relative increase in cerebrospinal fluid (CSF) volume within the interpeduncular cistern (14). Indeed, Wang et al. (7) demonstrated that in cases of intracranial hypotension, the IPA was significantly reduced (from approximately 56° in controls to around 25° in hypotension), and that this reduction in IPA correlated with downward displacement of the brainstem (brain stem slumping). The authors suggested that the angle between the peduncles may be related to the CSF volume in the interpeduncular cistern, indicating that the IPA decreases when the CSF volume is reduced and widens when the volume increases (7). From this perspective, the expansion of the subarachnoid spaces in response to mild brain tissue shrinkage (atrophy) in advanced age may be a factor explaining the increase in the interpeduncular angle. In other words, the age-related increase in the distance between the peduncles is associated with the compensatory expansion of CSF around the brainstem to fill the surrounding space. This may be particularly relevant when distinguishing conditions associated with midbrain atrophy, such as PSP. Indeed, it has been reported that the IPA is significantly widened in PSP patients and demonstrates high sensitivity in differentiating PSP from Parkinson's disease (15). On the other hand, Ugga et al. (16) compared IPA measurements in iNPH, PSP, and control groups, all predominantly composed of elderly individuals. In that study, the average IPA in healthy controls was 75.5°, showing no significant difference compared to PSP patients, but was found to be elevated in those with iNPH (16). Therefore, a larger-than-normal IPA observed in an older individual may not always reflect pathology; the influence of age-related variation should be considered.

In the present study, measurements of both the PMA and the pontomedullary angle demonstrated no statistically significant association with either age or gender. Previous studies have reported a wide range of PMA values in healthy controls, varying between 39° and 65°, and emphasized that PMA does not significantly vary with gender (8, 17). A study involving healthy individuals from the Turkish population showed that the average PMA was greater in females (52°) than in males (56.8°). It was further noted that PMA declined in the 46–65 age group and increased again beyond the age of 65 (18). This apparent variability in PMA across age may reflect underlying anatomical and developmental changes of the brainstem. According to morphometric studies, the PMA tends to be broader in childhood, narrows during adolescence and adulthood as the pons enlarges relatively, and then widens again in older age due to pontine atrophy (8). However, such fluctuations are relatively minor, typically within a 2–4° range. The PMA reflects the curvature at the midbrain–pons junction, which is largely constrained by craniovertebral architecture. Given that the skull base angle remains stable throughout life in healthy individuals, significant age-related variation in PMA is not generally expected. This may explain the lack of correlation between IPA and either the PMA or the pontomedullary angle. Notably, pronounced changes in PMA are observed primarily in pathological conditions, such as severe brainstem compression or anatomical deformities. Similarly, the pontomedullary angle—formed between the pons and medulla—is structurally stable and typically varies only in the presence of marked pathology. For instance, in cases of advanced brainstem atrophy, such as in olivopontocerebellar degeneration, a "flattening" of the pontomedullary angle (i.e., loss of its normally mild curvature) has been described (19).

This study has certain limitations. The retrospective design and single-center data usage introduce classic limitations such as potential selection bias and limited generalizability. Additionally, the sample size may be a limiting factor, particularly in detecting differences within subgroup analyses. A further limitation is that the present study focused exclusively on healthy subjects, thereby excluding the potential influence of pathological conditions. Future research involving various clinical populations could better elucidate the diagnostic and prognostic relevance of these parameters. Lastly, the fact that the measurements were performed manually and based on visual assessment may introduce the risk of interobserver and intraobserver variability. Although the methods used in this study are known to have high reliability, the integration of automated measurement software in future research could provide methodological improvement.

In conclusion, this study provides normative reference values for key brainstem angular measurements (IPA, PMA, and pontomedullary angle) in a healthy adult population and highlights their variation with age. IPA showed a significant age-related increase, while PMA and pontomedullary angles remained relatively stable. No significant sex-based differences were observed. These findings provide valuable diagnostic benchmarks to identify pathological alterations and aid in clinical assessments of neurological and neurosurgical conditions such as spontaneous intracranial hypotension.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Cukurova University Non-Interventional Clinical Research Ethics Committee (Date: 05.11.2021, Decision No: 2021/116-60).

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author, [N.K.Ş.].

Author Contributions: Concept – N.K.Ş., Design- N.K.Ş., H.E. and Y.K.A., Supervision – N.K.Ş., N.B. and Ö.O., Data collection and/or processing - S.T., H.E. and YKA, Analysis and/or interpretation - , Writing – N.K.Ş., Y.K.A., H.E., D.A. and Z.K.B. Critical review- H.E., Y.K.A., S.T., Z.KB., D.A., N.B., and Ö.O. All authors read and approved the final version of the manuscript.

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