Pituitary Deformation in High Altitude Immigrants and the Correlation with Headache：A Preliminary Study.

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Research

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Abstract

Aim: To investigate pituitary gland deformation (PGD) in high altitude (HA) immigrants and determine if a correlation exists between PGD with headache and the ratio of brain volume to total intracranial volume (BV/TIV), and to investigate whether PGD can be used as an objective indicator of headache in HA immigrants.

Methods: A total of 34 male HA immigrants and 60 age- and gender-matched sea-level (SL) residents were enrolled in this study. 3D T1 weighted brain MRI scans and headache scales were acquired. HA participants were classified into headache positive (HA[+]) and headache negative (HA[-]) subgroups. PGD was graded visually on mid-sagittal images of the pituitary gland. All continuous variables and categorical variables were compared using Student's t-test or Mann-Whitney test and the χ^2 or Fisher exact tests, respectively. Kendall's tau rank correlation coefficient and Spearman's rho were used to investigate the relationship between PGD and headache or BV/TIV, respectively. Receiver operating characteristic (ROC) analysis was used to evaluate whether PGD can be used as an objective indicator of headache in HA immigrants.

Results: A higher proportion of HA participants had PGD (54.8%) than SL residents (23.3%) (p=0.005). The proportion of HA(-) participants with PGD (68.2%) was higher than that of HA(+) participants (22.2%) (p=0.044). PGD was negatively correlated with headache (Kendall's tau=-0.323, p=0.0097) and positively correlated with BV/TIV (r=0.454, p=0.010). The presence of PGD was an indicator of headache in HA immigrants (area under the ROC curve=0.712, p= 0.038, sensitivity=0.778, specificity=0.682).

Conclusion: A greater proportion of HA immigrants had PGD, which is an adaptation to chronically altered ICP or compliance. The presence of PGD indicated a restoration of spatial compensatory capacity and compliance of intracranial system, leading to headache relief. PGD is a potential indicator of headache in HA immigrants.

Introduction

Headache is a highly prevalent condition among populations living at high-altitude (HA). Approximately 60% of healthy Chinese Han males who migrated to the Qinghai-Tibetan plateau reported headache [1], and in patients with chronic mountain sickness (CMS), the prevalence of headache exceeds 80%[1, 2]. Headache constitutes the largest proportion of disease burden of CMS [3]. Hence, headache in HA immigrants is an issue of public health. Headache is an important component in the diagnosis of high-altitude deterioration (HAD) and CMS. Traditionally, it was assessed by the headache score scale depending on subjective feelings [1, 2, 4]. Objective indicators for diagnosis of headache in HA immigrants are missing.

Despite its high prevalence, very little is known about the pathogenesis of headache in HA immigrants. In studies of acute mountain sickness (AMS), in which headache is the core symptom, one of the accepted

mechanisms is the “tight-fit” hypothesis proposed by Ross in 1985[5]. The “tight-fit” hypothesis states that individuals with smaller intracranial and intraspinal capacity and limited compliance would not tolerate hypoxic brain swelling and would suffer from AMS. In subjects exposed to HA or hypoxia, studies revealed brain edema in AMS subjects, and suggested that brain swelling is associated with severity of AMS[6–8]. Further, brain edema was reported in subjects after a thirty-day HA exposure[9] and in CMS patients[10], indicating that mild brain edema may exist in populations exposed to HA even after a long-term adaption. Brain edema will lead to deterioration of intracranial compliance (ICC) or elevation of intracranial pressure (ICP) [11], and thus to headache and morphometric changes on brain MRI [12].

In clinical scenarios, chronically elevated ICP can be revealed by morphological changes of the pituitary gland detectable by MRI [13, 14]. The concavity of the superior aspect of the pituitary and empty sella are regarded as features of chronic elevation of ICP [14]. Additionally, the brain to total intracranial volume ratio (BV/TIV) is a surrogate marker of the extent of intracranial system “tight-fit” [15]. Combining the pituitary measurement and the ratio of BV/TIV might provide information regarding ICP in HA immigrants. However, this has not yet been investigated.

We hypothesize that the “tight fit” of the intracranial system and sub-edema in HA immigrants could result in chronically elevated ICP or deterioration of ICC, leading to headache and pituitary gland deformation (PGD). Therefore, our study aimed to investigate PGD in HA immigrants, and identify possible correlations between the extent of PGD and either headache or the ratio of BV/TIV in HA immigrants. Additionally, we determined whether PGD can be used as an objective marker of headache in HA immigrants.

Materials And Methods

The protocol was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army, and conformed to standards set by the Declaration of Helsinki. Written informed consent of all participants was acquired.

Participants

Apparently healthy male subjects who had relocated to Lhasa (3658 m) from plain districts for more than 2 years were recruited from communities by word-of-mouth. The high-altitude immigrant subjects (HA group) were screened for the following criteria: (1) permanent residence before relocating to HA at less than 1500 m; (2) no history of ischemic hypoxic encephalopathy as infants; (3) no serious brain injuries that resulted in loss of consciousness; (4) no tobacco or drug abuse or alcohol addiction; (5) no chronic or genetic diseases; (6) Qinghai score < 6 to exclude chronic mountain sickness; (7) a willingness to participate in the study and sign the informed consent form; (8) male; (9) right-handed; (10) 20 to 40 years; (11) immigrated to HA after reaching 18 years of age.

A group of sea-level-resident healthy male subjects (SL group) were included as a control group. SL subjects were recruited from communities near our hospital, and the screening criteria were the same as the HA group except for (6). The age of SL subjects was matched to HA subjects. Exclusion criteria consisted of contraindication for MRI.

Headache assessment

Because headache can occur intermittently and its severity can change over time, the participants were asked to recall and rate the presence and extent of headache according to four levels (no headache, mild, moderate, and severe headache) during the past month. The headache score was defined as follows: 0, no headache; 1, mild headache; 2, moderate headache; 3, severe headache. According the headache score, the HA group was divided into two sub-groups: the subjects with a headache score of zero were classified as the non-headache group (HA[-]), and the subjects with a headache score greater than zero were classified as the headache group (HA[+]).

MRI

All participants were imaged on two identical 3.0T MR scanners (Discovery MR 750, GE Healthcare, Milwaukee, WI, USA) in the General Hospital of Tibet Military Region (Lhasa, 3658 m, HA group) and the First Medical Center of the General Hospital of the Chinese People's Liberation Army (Beijing, 50 m, SL group), respectively, by using two identical 8-channel head coils. Magnet hardware and software remained unchanged during the study. Given the time difference, the imaging of HA group was performed between 3:00 pm and 6:00 pm Beijing time, and the imaging of SL group was performed between 1:20 pm and 4:20 pm Beijing time, to minimize the influence of physiological rhythms. Participants abstained from alcohol, caffeine, tea (including Tibetan buttered tea), strenuous exercise, gluttony, and any medication for at least 24h before the MRI scan to minimize potential confounding effects on brain volume and ICP. The three-dimensional fast spoiled gradient recalled echo (3D-fSPGR) sequence was used to acquire high resolution structural images. The parameters were as follows: repeat time=6.9ms, echo time=3.0ms, bandwidth=±31.25kHz, field of view=25.6cm, slice thickness=1mm, matrix =256 × 256, number of excitations=1, number of slices=192, acquisition time=4 min 47s.

Pituitary gland assessment

3D-fSPGR sagittal images of the pituitary gland were corrected for head tilt or rotation using a three-dimensional multiplanar reconstruction tool on the GE Advantage Workstation (AW) system. Pituitary gland height (PGH) was measured on mid-sagittal T1 images as the maximum orthogonal distance from the upper surface of the pituitary gland to the sella floor (Figure 1). PGD was assessed visually using the following grading scale modified from a previous report [14]: normal appearance (convex and flat dome of the pituitary gland, 0 points); mild PGD (loss of pituitary height h ≤ □ of the sella height, 1 points); moderate to severe PGD (loss of pituitary height h >□ of the sella height to empty sella, 2 points) (Figure 2).

PGH measurements were performed by two radiologists (J. F. and X. Y., with 12 and 3 years of imaging experience, respectively). First, images were opened by X.Y. and were anonymized; then, PGD and PGH were assessed by J. F. Two weeks later, the two raters exchanged roles and PGH was assessed again. Image reformation and head position correction were independently performed by each radiologist to prevent any bias introduced by the other radiologist. Radiologists were blinded to clinical data and each other's measurements during PGH assessments. The averaged value of PGH measured by the two radiologists was used for statistical calculations. Until the PGH measurements were completed, the extent of PGD was assigned points by consensus interpretation according to the PGD by the two radiologists. Disagreements were reviewed until consensus was achieved.

Brain to intracranial volume ratio calculation

Brain to intracranial volume ratio of HA group was calculated to assess the "tight fit" extent of intracranial system. All brain structure images were converted to NIFTI files using MRIcroN software (University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com). The intensity of brain structure images was corrected using the N4 algorithm[16]. SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was employed to segment the brain images into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using default parameters. Using the quantifications of gray matter volume (GMV), white matter volume (WMV), and total intracranial volume (TIV), BV/TIV was calculated as BV/TIV = (GMV+WMV)/TIV.

Statistical Analysis

Data analysis was performed using MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). We report statistical significance and descriptive statistics. Continuous variables were assessed using mean ± standard deviation or median (IQR), and categorical variables were summarized with percentages. A two-tailed critical α was set to reject the null hypothesis at 0.05. The intraclass correlation coefficient (ICC) was used to assess the reliability of PGH measured by a single rater and different raters (J. F. and X. Y.). The ICC of the HA and SL groups were evaluated separately. The independent samples t-test or Mann-Whitney test was used to compare the differences between groups. The Cochran-Armitage test for trend was used to quantify whether there was a linear trend of the proportions of participants with PGD among SL, HA+ AND HA- groups. Fisher's exact test was used to perform pairwise comparisons of proportions of participants in each group. In addition, Kendall's tau rank correlation was used to investigate the relationship between PGD and the headache, and Spearman's rho was used to calculate the correlation between PGD and the ratio of BV/TIV. Receiver operating characteristic (ROC) analysis was performed to evaluate whether PGD is a potential indicator of headache in HA immigrants.

Results

Participant Characteristics

Thirty-four participants completed all of the examinations. Two of them were excluded on the basis of age (older than 40 years), and one was discarded due to poor image quality. A total of 31 participants were enrolled in the HA group (30[29,34] years, residing in HA for 8.16±3.05 years), and 60 participants were enrolled in the SL group (29[27,34.5] years). Nine participants were HA(+) (29.03%), and the rest were HA(-) (70.97%). None of the SL participants reported headache. Demographics are summarized in Table 1.

Pituitary Gland Height and Deformation

The mean PGH of the HA group was 5.13±1.44 mm compared with 5.75±1.35 mm for the SL group (p=0.043). The mean PGH of the HA(-) group was 4.93±1.23 mm compared with 5.61±1.85 mm for the HA(+) group (p=0.238). Excellent single and average rater agreement and intraclass correlations (with 95% confidence intervals, [95% CI]) were observed both in the HA group (single and average rater agreement, 0.92 [95% CI: 0.85, 0.96] and 0.95 [95% CI: 0.92, 0.98], respectively) and the SL group (single and average rater agreement, 0.96 [95% CI: 0.92, 0.97] and 0.98 [95% CI: 0.96, 0.98], respectively). Qualitative analysis showed that PGD was present in 17 of 31 (54.8%) HA participants and 14 of 60 (23.3%) SL participants (p<0.005). At the sub-group level, two of 9 (22.2%) participants in the HA(+) group had PGD and 15 of 21 (68.2%) participants in the HA(-) group had PGD (p=0.044). The HA(-) group had a larger proportion of participants with PGD than the SL group (p<0.001). The proportions of participants with PGD showed a linearly increasing trend among SL, HA(+), and HA(-) groups (χ^2=13.09, p<0.001). Details are provided in Table 2 and Figure 3.

Association of PGD and BV/TIV

PGD-score had a negative correlation with the headache-score in HA immigrants (Kendall's tau=-0.323, p=0.0097) and a positive correlation with the ratio of BV/TIV (r=0.454, p=0.010).

PGD as a Biomarker of Headache in HA Immigrants

The area under the ROC curve (AUC) was 0.712 (95%CI, 0.522 to 0.860, p=0.381). Sensitivity was 0.778 (95%CI, 0.400 to 0.972), NPV was 0.882 (95%CI, 0.581 to 0.963), specificity was 0.682 (95%CI, 0.451 to 0.861), and PPV was 0.500 (95%CI, 0.331 to 0.669) based on the cutoff value of PGD-score≤0 (normal pituitary) (Figure 4).

Discussion

By comparing age- and gender-matched HA and SL participants, the present study revealed that a much larger proportion of HA participants had lower PGH (p = 0.043) and more prevalent PGD (p = 0.005) than the SL group, and a greater proportion of non-headache HA participants had PGD than HA participants experiencing headache (p = 0.044). PGD correlated with headache (Kendall's tau=-0.323, p = 0.0097) and the ratio of BV/TIV (r = 0.454, p = 0.010), and has a potential use for predicting headache or relief from headache (AUC = 0.712, p = 0.381).

To our knowledge, this is the first study on PGD in HA immigrants. No previous studies have provided comparable PGH data specific to HA immigrants. Therefore, we compared SL data with previous studies on SL residents. PGH changes dramatically with age, reaching a peak towards the first half of the third decade[17]. In a previous report, the mean PGH of 15-19-year old Han males was 6.41 ± 2.01 mm[18], which was higher than the PGH reported by Kato[17]. Therefore, the higher PGH (5.75 ± 1.35 mm) of SL group reported in our study than that of 20–39-year-old males reported in the study by Kato et al is reasonable. This difference might be attributed to differences in age and ethnicity. Given the excellent reliability of PGH assessments, the lower PGH in the HA group is unlikely to be a result of measurement error. About 23% of SL participants showed a concave superior aspect, similar to the study by Kato et al (22%). In the HA group, 54.8% of the participants had a concave superior aspect of pituitary gland, while in the study by Kato et al, such a high incidence of concavity was only observed in males older than 50 years[17].

There are many potential causes of PGD, such as chronic pituitary apoplexy[19, 20], chronic pituitary inflammation[21], panhypopituitarism[22], severe traumatic brain injury or repetitive chronic head trauma, and idiopathic intracranial hypertension[23]. However, these conditions are rare in Chinese patients and only have been reported as case reports in HA residents. Therefore, they cannot explain the large proportion of participants with PGD. Normal circulating pituitary hormones were reported in acclimatized lowlanders who resided at high altitude for 3 to 12 months[24]. Therefore, the endocrine alterations induced by hypoxic stress are unlikely to be the cause of PGD. All the participants were staff at the hospital, and none of them had a history of chronic or severe head trauma.

A reduction in pituitary height is commonly regarded as a surrogate marker of chronic intracranial hypertension[12, 25]. It is accepted that chronically increased ICP leads to an arachnoid herniation downward from the diaphragma sellae and to a decrease in PGH[14]. HA immigrants might experience chronic brain sub-edema[9, 10], which leads to a mild increase in brain volume. According to the Monroe-Kellie doctrine, volume increase of one component (arterial blood, brain parenchyma, venous blood and CSF) must be compensated by volume decrease of another component or increased ICP[11]. The intracranial spatial compensatory reserve is dominated by CSF volume[26]. Ross proposed the “tight fit” hypothesis to explain inter-individual differences in susceptibility to AMS [5]. Individuals who have inadequate compensatory capacity and compliance to tolerate increased brain volume are thought to be more likely to suffer from AMS when they ascend to high altitude [5]. The core symptom of AMS is headache. Here, we speculate that headache in HA immigrants is also attributed to the “tight fit” intracranial system. The ratio of BV/TIV is an indicator of the extent of “tight fit”, in that a greater ratio of BV/TIV indicates a more “tight fit” intracranial system. Therefore, the positive correlation between PGD and BV/TIV in HA participants suggested that individuals with a “tight fit” intracranial system have more severe PGD. In a “tight fit” intracranial system, the compliance of the intracranial system approaches the “knee” of the exponential pressure-volume index compliance curve (PVI curve)[26] and the intracranial system is more sensitive to brain swelling induced by hypoxic exposure, leading to ICC deterioration and

ICP elevation. The same increase in volume will result in a more significant increase in ICP in a “tight fit” brain, leading to headache. Repeatedly and chronically elevated ICP results in PGD.

However, there seems to be a contradiction in that most subjects with PGD did not suffer from headache. We speculate that there might be at least two reasons for this. First, chronic elevation of ICP is associated with bony enlargement of the sella turcica, which contributes to a partially empty sella[27]. However, whether the total intracranial volume (TIV) increased or not in HA immigrants is not clear. Increased TIV was reported in astronauts with a chronically elevated ICP and PGD[25]. An enlarged TIV tolerates brain swelling better[5]. Secondly, an empty sella is considered a late manifestation of elevated ICP, while mild and moderate concavity of the pituitary gland superior aspect are considered earlier manifestations[14]. Meanwhile, a longer duration of symptoms can lead to a decrease of CSF outflow resistance and release of symptoms[28].

The mismatch of PGD and headache in HA immigrants, or in other words, the unexpected greater PGD in non-headache HA participants, and the linear increasing trend of the proportion of participants with PGD in the SL, HA(+), and HA(-) groups suggested that the headache symptom in HA immigrants might antedate the “normal” state. If this is true, then, along with altitude acclimatization and the prolonged duration of symptoms, headache would have disappeared in some of the HA immigrants, leaving an unrecoverable PGD. Thus, the presence of PGD has potential as a diagnostic tool to predict headache or the release of headache.

Limitations

This study has several limitations that should be mentioned. The first limitation is the relatively small sample size of the HA group and especially the HA(-) subgroup. Despite the small sample size, strong statistical significances were found for the differences in PGH and the proportion of PGD. Although a larger sample is not likely to change the conclusion in this study, it can offer a more detailed grade of PGD and description of the correlation with headache. Another limitation was that the present study only enrolled male subjects aged 25–40 years. Extrapolating the conclusions to male subjects in other age groups and to female subjects should be done carefully. According to previous reports, males older than 40 had highly variable PGH[17]; here, two subjects older than 40 were excluded to minimize the multifactorial influences on PGH.

Conclusions

Long-duration HA exposure was associated with a high prevalence of headache and PGD, while PGD correlates negatively with headache, and greater PGD is associated with a more “tight fit” intracranial system. We speculate that headache in HA immigrants is caused by the “tight fit” intracranial system compounding brain sub-edema, which leads to chronic elevation of ICP and PGD, and that headache release is due to symptom duration-related spatial compensation capacity and ICC restoration, leaving an unrecoverable PGD. Future longitudinal studies will be needed in a cohort of HA immigrants, pre- and

post-long-term HA residence, to investigate whether ICP elevation and symptom duration-related compensatory capacity restoration contribute to the occurrence and relief of headache in HA immigrants, as hypothesized in our study.

Declarations

Ethical Approval and Consent to participate

The protocol was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army (Registry NO. S2015-014-02), and conformed to standards set by the Declaration of Helsinki. All of the participants were informed of the potential risks and experimental procedures, and informed written consent was obtained.

Consent for publication

Not applicable.

Availability of supporting data

Data are the property of the authors and can be obtained by contacting the Principal Investigator: Dr. Jie F; e-mail: 13920449779@163.com

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J F and X Y performed data analysis and wrote the first draft of the manuscript. W M performed data analysis. L M conceived the study, J F, X Y, W L and J L contributed to data collection and analysis, and edited the manuscript.

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Competing financial interests:

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Tables

Table1 Demographic and physiological information

	HA	SL	p
Age (y)	30(29,34)	29(27,34.5)	0.230
Years immigrated to HA (y)	8.16±3.05	-	-
Height (cm)	172.77±4.48	174.13±3.73	0.128
Weight (kg)	69.58±7.36	71.50±10.02	0.349
BMI (kg/m^2)	22.99(22.47,24.10)	23.64(21.67,25.88)	0.439
SpO_2 (%)	90.39±1.94	-	-
HCT (%)	52.24±3.88	-	-

Table 2 Trend analysis of the proportion of subjects with PGD among three groups

PGD	SL	HA (+)	HA(-)	χ^2 for trend	p
PGD-	46	7	7	13.092	0.0003
PGD+	14	2	15		

PGD-, normal pituitary gland; PGD+, pituitary gland deformation.

Figures

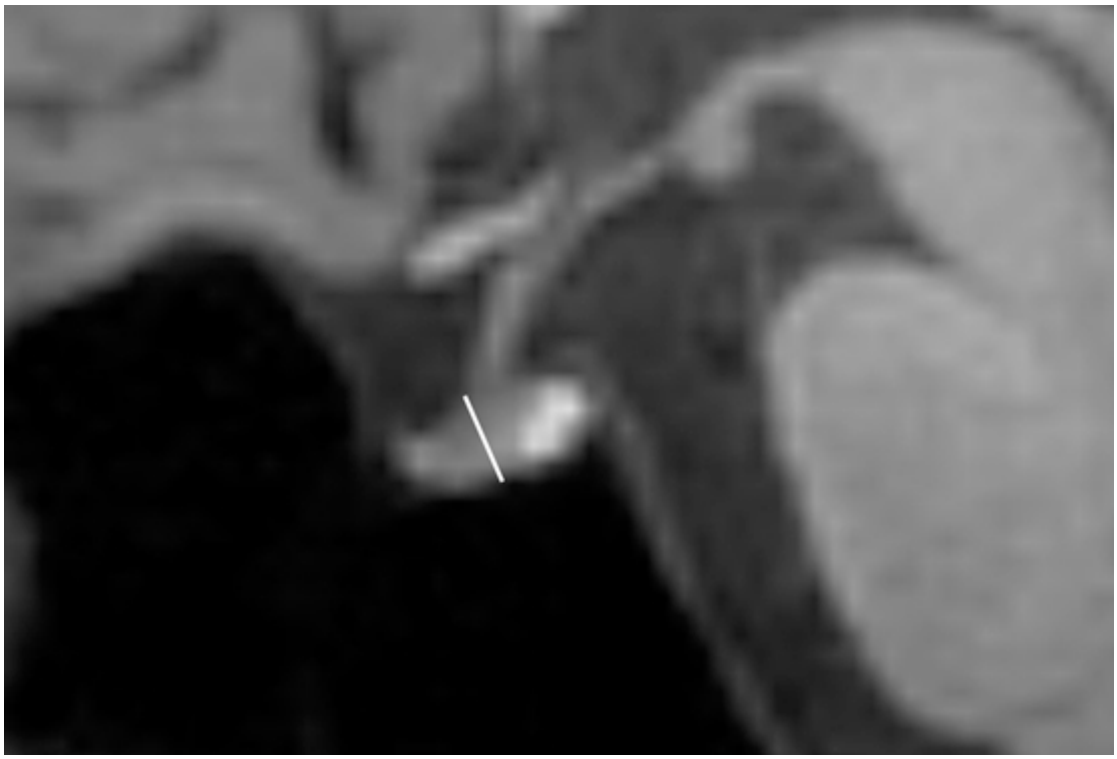

Figure 1

Schematic diagram of pituitary height measurement

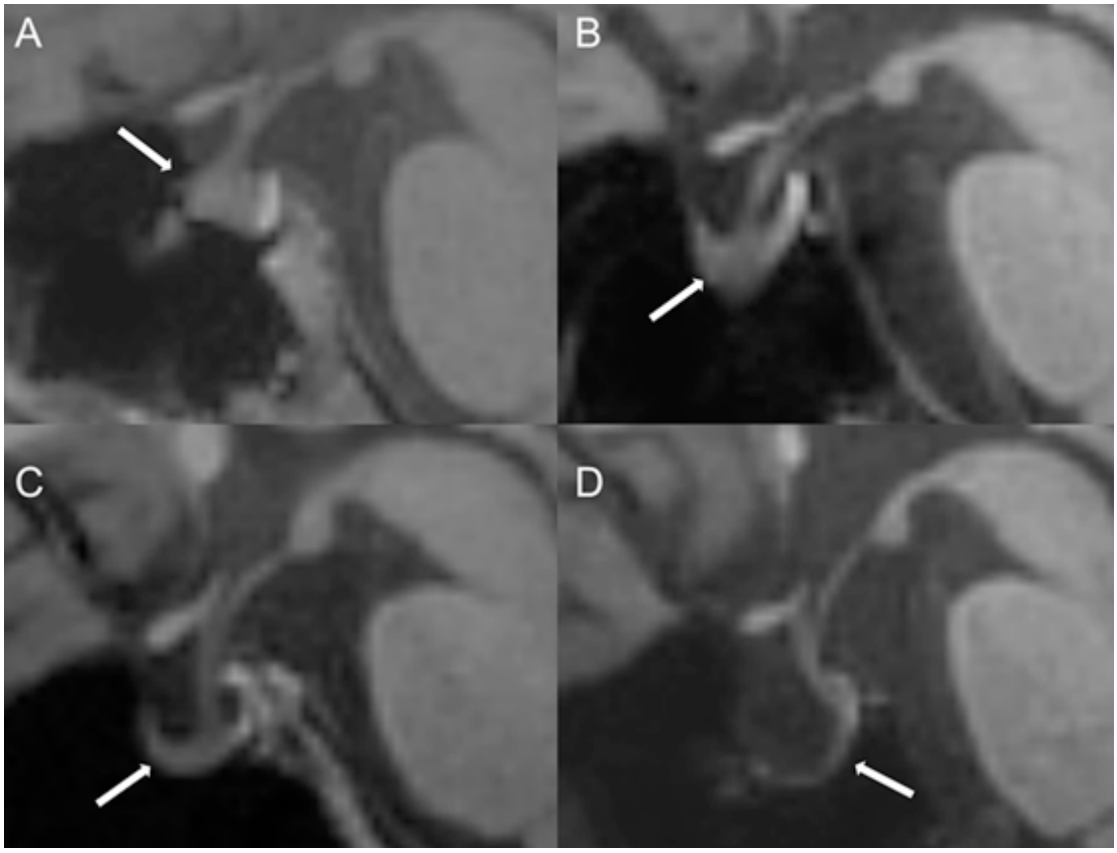

Figure 2

Schematic diagram of pituitary deformation (PGD) assessment. Normal pituitary with a convex superior aspect (A, PGD-score=0); mild PGD (B, PGD-score=1); moderate to revere PGD (C and D, PGD-score=2)

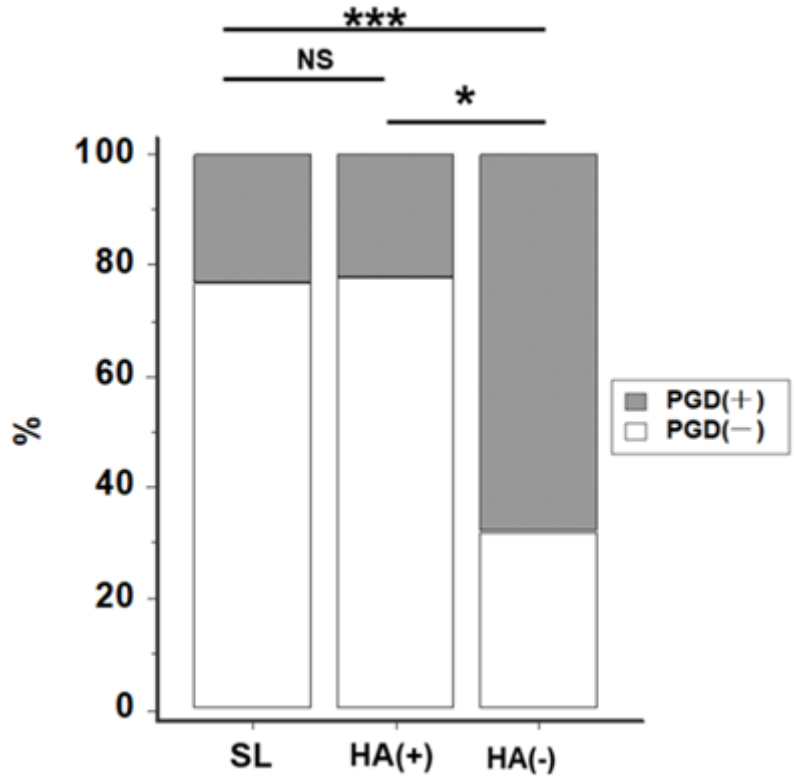

Figure 3

The proportion of subjects with PGD shows a linear increasing trend among SL, HA(+) and HA(-) groups. PGD(+),pituitary gland deformation; PGD(-), normal pituitary gland;***, p<0.001;*, p<0.05.

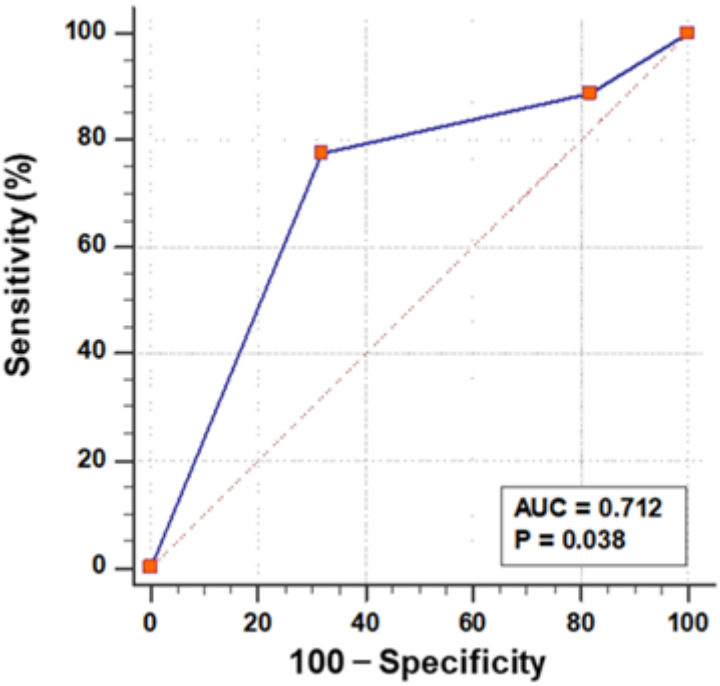

Figure 4

Receiver operating characteristic curve shows PGD-score≤0(normal pituitary gland) having a potential use to diagnosis headache in HA immigrants, with an area under the curve(AUC)=0.712.