Role of MRI T2-DRIVE in the assessment of pituitary stalk abnormalities without gadolinium in pituitary diseases

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Abstract

Objective: To investigate the role of T2-DRIVE MRI sequence in the accurate measurement of pituitary stalk (PS) size and the identification of PS abnormalities in patients with hypothalamic–pituitary disorders without the use of gadolinium.

Design: This was a retrospective study conducted on 242 patients who underwent MRI due to pituitary dysfunction between 2006 and 2015. Among 135 eligible patients, 102 showed eutopic posterior pituitary (PP) gland and 33 showed 'ectopic' PP (EPP).

Methods: Two readers independently measured the size of PS in patients with eutopic PP at the proximal, midpoint and distal levels on pre- and post-contrast T1-weighted as well as T2-DRIVE images; PS visibility was assessed on pre-contrast T1 and T2-DRIVE sequences in those with EPP. The length, height, width and volume of the anterior pituitary (AP), PP height and length and PP area were analyzed.

Results: Significant agreement between the two readers was obtained for T2-DRIVE PS measurements in patients with 'eutopic' PP; a significant difference was demonstrated between the intraclass correlation coefficient calculated on the T2-DRIVE and the T1-pre- and post-contrast sequences. The percentage of PS identified by T2-DRIVE in EPP patients was 72.7% compared to 30.3% of T1 pre-contrast sequences. A significant association was found between the visibility of PS on T2-DRIVE and the height of AP.

Conclusion: T2-DRIVE sequence is extremely precise and reliable for the evaluation of PS size and the recognition of PS abnormalities; the use of gadolinium-based contrast media does not add significant information and may thus be avoided.

Introduction

The advent of magnetic resonance imaging (MRI) has led to a major improvement in the understanding of the pathogenesis of disorders affecting the hypothalamic–pituitary (HP) axis (1, 2, 3); MRI is currently the gold standard for the evaluation of sellar region because of its inherent tissue contrast, direct multiplanar capability and lack of invasiveness (4, 5, 6). Pituitary stalk (PS) evaluation is a crucial part of the assessment of HP dysfunction including precocious puberty, central diabetes insipidus (CDI) and hypopituitarism where the correlation of PS...
phenotypes with pituitary deficits is extremely useful for appropriate diagnosis, management and long-term follow-up (7, 8, 9, 10, 11, 12, 13, 14).

The standard sellar region MRI evaluation normally includes 2–3-mm thick, T1- and T2-weighted images on sagittal and coronal planes. Conventional spin-echo (SE) techniques are usually employed for T1-weighted imaging, whereas turbo/fast spin-echo (TSE) sequences are obtained for T2-weighted imaging; gadolinium-based contrast agents (GBCAs) administration is usually recommended and thin-slice (2–3-mm thick) contrast-enhanced T1-weighted sequences should be obtained on sagittal and coronal planes (5). High-resolution heavily T2-weighted images (including driven equilibrium (DRIVE), constructive interference in steady state (CISS), and fast imaging employing steady-state acquisition (FIESTA) sequences) acquired at sub-millimetric thickness provide excellent contrast between cerebrospinal fluid (CSF) and adjacent parenchymal structures (15, 16). These sequences have traditionally been used in the assessment of cerebellar pontine angle lesions, inner ear structures and the internal auditory canal (17), but can also be acquired for a detailed evaluation of other structures surrounded by CSF (such as the suprasellar compartment), whenever routine MRI sequences do not provide the desired neuroanatomical information (15, 16, 17).

Recently, concerns about the use of GBCAs have been raised both in adults and children due to possible gadolinium deposition within neuronal cells despite a normal hepatobiliary function and intact blood–brain barrier. Specific brain regions (i.e. dentate nucleus and globus pallidus) have been found to demonstrate distinct MR signal changes attributed to cumulative gadolinium deposition, which appears to follow a dose-dependent trend with preferential accumulation in the dentate and deep gray nuclei and occurs independently of patient age; therefore, a judicious use of GBCAs in pediatric population has been recommended (18, 19, 20, 21, 22).

Based on these considerations, and because a sagittal T2-DRIVE sequence has been part of our institutional routine sellar MRI protocol since 2006, in addition to conventional SE T1- and TSE T2-weighted imaging, the objectives of this study were to evaluate the potential diagnostic role and sensitivity of T2-weighted DRIVE sequence in PS identification and measurements in patients with HP disorders. In particular, we first tested the degree of agreement and reliability between standard pre- and post-contrast T1-weighted images and T2-DRIVE in a large group of patients with pituitary dysfunction of different etiologies; then, we compared the diagnostic information collected with T2-DRIVE and T1-weighted sequences in subjects with anatomic abnormalities of the pituitary gland and PS.

Subjects and methods

Patients

We examined our institutional MRI database and performed a text search for pituitary MRI reports using ‘T2-DRIVE’ between 2006 and 2015. A total of 242 patients were found and were divided into two groups based on the position of the posterior pituitary (PP) lobe: ‘eutopic’ (i.e., located within the pituitary fossa, posterior to the anterior pituitary lobe (AP)) (189 patients)) and ‘ectopic’ (i.e., above the pituitary fossa, either at the median eminence (ME) or along the PS) (53 patients)). Among eutopic PP patients, only studies including sagittal 3-mm thick T1-weighted images acquired before and after contrast material administration in addition to sagittal T2-DRIVE images were included for analysis. This study was approved by the local ethics committee and consent was obtained from all caregivers or patients at the time of diagnosis. In addition, informed consent was obtained as part of current procedures and regulations before gadolinium administration.

Among those with ‘ectopic’ PP gland, only those with T1-weighted sagittal images and T2-weighted coronal images (3 mm thick) were enrolled. All MRI scans were performed with a 1.5 T MR system (Intera Achieva 2.6; Philips). The T2-DRIVE sequence was acquired on the sagittal plane with a slice thickness of 0.6 mm (25 slices) and a scan time of 2 min and 32 s, using a 3D technique with isotropic voxels (0.6 × 0.6 × 0.6 mm) that allows multiplanar reformatting with no geometric distortion. Subjects with incomplete imaging studies (n = 25), low-quality images due to movement artifacts (n = 13), brain tumor masses that compressed or modified the HP district anatomy (n = 51) and those who underwent sellar/suprasellar surgical sequelae (n = 15) were excluded, yielding 104 excluded patients. One hundred and thirty-five patients (81 females and 54 males; age range, 1 month to 29 years, median: 9.5 years) were eligible: the group with ‘eutopic’ PP gland included 102 patients with pituitary dysfunction of different etiologies, while the group with ‘ectopic’ PP gland consisted of 33 patients with AP defects (Fig. 1).
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N=135: F=81 (60%); M=54 (40%)
Age at MRI
Median: 9.5 years (1\textsuperscript{st}-3\textsuperscript{rd} quartile: 7.3-12.0 years)

Eutopic Posterior Pituitary
N=102: F=67 (65.7%); M=35 (34.3%)

Ectopic Posterior Pituitary
N=33: F=14 (42.4%); M=19 (57.6%)

Number of Pituitary Defects
1, N=8 (24.24%)
2, N=8 (24.24%)
3, N=12 (36.36%)
Panhypopituitarism, N=5 (15.15%)

Posterior Pituitary Position
Median eminence, N=28 (84.85%)
Proximal third of pituitary stalk, N=2 (6.06%)
Middle third of pituitary stalk, N=2 (6.06%)
Distal third of pituitary stalk, N=1 (3.03%)

Endocrine Disorders
Precocious Puberty, N=61 (59.80%)
Central diabetes insipidus, N=25 (24.50%)
Growth hormone deficiency, N=3 (2.95%)
Multiple Pituitary hormone deficiencies, N=3 (2.95%)
Growth hormone deficiency caused by Langerhans cell histiocytosis, N=2 (1.96%)
Other conditions associated with growth failure and/or short stature, N=8 (7.84%)

Figure 1
Patients with endocrine disorders who performed T2-DRIVE MRI and were enrolled in the study.

MRI procedures

Eutopic posterior pituitary gland group
In this group, we measured the PS size in the sagittal plane, drawing a line perpendicular to the axis of the major stem at three levels: proximal PS (just below the ME), midpoint and distal (near its insertion on the pituitary gland). Measurements were achieved on our Picture Archiving and Communicating System (Vue PACS workstation, Carestream Health, Rochester, NY, USA), on the sagittal pre-contrast T1-, T2-DRIVE and post-contrast T1-weighted sequences. Each measurement was performed independently by two readers: an experienced neuroradiologist (GM, 10 years of experience) and a pediatric resident (EG, 1 year of training). Before each measurement and in order to perform each assessment at the same level, the two readers agreed and indicated with an arrow the three levels (proximal, midpoint and distal) of the PS where to perform the measurements on the three different sequences; measurements were made independently thereafter. The workstation’s electronic calipers were used to measure the size of the PS.

Ectopic posterior pituitary gland group
All images were examined by two pediatric neuroradiologists (AR, 24 years’ experience and GM, 10 years’ experience) and evaluated for PS visibility on sagittal pre-contrast T2-DRIVE and T1-weighted images. PS visibility on post-contrast T1-weighted images was also evaluated (12 out of 33 patients). In addition, the position of the PP, length, height and width of the AP, volume of the AP (length×height×width/2), height and length of PP and AP area (height/2×length/2×3.14) were evaluated. The heights and lengths of the AP and PP were measured on sagittal pre-contrast T1-weighted images, whereas AP width was measured on T2-weighted coronal image (6, 23, 24). Patients were classified according to the presence
or the absence of PS visibility on sagittal T1-weighted, T2-DRIVE and post-contrast T1-weighted images (when available).

### Statistical analysis

Categorical variables were described in terms of absolute frequencies and percentages. Quantitative variables were reported in terms of means, standard deviations (s.d.) and minimum and maximum values. The associations between two categorical variables were evaluated using the Fisher’s exact test. Since the main objective of the study was to investigate the level of agreement between the different readers by measuring the PS diameters on sagittal pre- and post-contrast T1-weighted and T2-DRIVE images, the intraclass correlation coefficient (ICC) was firstly selected as a reliability indicator and its 95% confidence intervals were calculated and reported. The ICC values were compared using a z-test as all observations were greater than 50 units. Subsequently, for the interpretation of the ICC values, the following classification was used: <0.4 = poor agreement; 0.4–0.74 = moderate agreement; ≥0.75 = good agreement. Furthermore, the agreement was also assessed by the Bland–Altman method (25). According to this method, a plot of the difference between the two readers (y-axis) with respect to the mean (x-axis) was drawn and the limits of 95% (mean value ± 1.96 × s.d.) were added to the plot. There is a general consensus in accepting only 5% of observations outside the limits of the agreement. The mean difference between the two readers is called ‘bias’ and should be as close to zero as possible. Cohen’s kappa coefficient was then used to evaluate the chance-correct concordance for the case between two different sequences that are expressed in the form of categorical data (26).

All statistical tests were 2-sided, and P values <0.05 were considered to be statistically significant. The software ‘Statistica’ (release 9.0, StatSoft Corporation, Tulsa, OK, USA) was used for descriptive and bivariate analyses, and Stata software, version 7 (Stata), was used for Cohen’s kappa calculation.

### Results

#### Eutopic posterior pituitary gland group

The mean values and s.d. of PS sizes measured at proximal, midpoint and distal PS levels from the two observers in 102 patients are shown in Table 1.

### Agreement between the two readers

The agreement between the measurements of the two readers in the same sequences showed that the ICC in the T2-DRIVE sequence was 0.96 at the proximal level of the PS, 0.99 at the midpoint level and 0.97 at the distal level. In pre-contrast T1-weighted sequence, the ICC was 0.89 in the proximal part, 0.85 in the midpoint and 0.76 in the distal part. Finally, on the post-contrast T1, the ICC was 0.88 at the proximal, 0.87 at the midpoint and 0.79 at the distal PS levels. A significant difference between the ICC on the T2-DRIVE and the pre-and post-contrast T1-weighted sequences was demonstrated (Table 2). No significant differences emerged between the ICC calculated on the pre-contrast and post-contrast T1-weighted sequences.

Less than 5% of measurements at the proximal PS were outside the 95% concordance limits (both 4.9%) in the T2-DRIVE and in the post-contrast T1-weighted sequences.

### Table 1

<table>
<thead>
<tr>
<th>Pituitary stalk</th>
<th>Observer EG</th>
<th>Observer GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 pre-contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>2.82 (0.74)</td>
<td>2.76 (0.70)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>2.39 (0.75)</td>
<td>2.16 (0.82)</td>
</tr>
<tr>
<td>Distal</td>
<td>1.78 (0.61)</td>
<td>1.61 (0.52)</td>
</tr>
<tr>
<td>T1 post-contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>2.84 (0.72)</td>
<td>2.76 (0.65)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>2.45 (0.73)</td>
<td>2.21 (0.77)</td>
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<tr>
<td>Distal</td>
<td>1.77 (0.66)</td>
<td>1.57 (0.54)</td>
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<tr>
<td>T2-DRIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>2.35 (0.62)</td>
<td>2.40 (0.61)</td>
</tr>
<tr>
<td>Midpoint</td>
<td>1.79 (0.70)</td>
<td>1.80 (0.70)</td>
</tr>
<tr>
<td>Distal</td>
<td>1.28 (0.54)</td>
<td>1.28 (0.51)</td>
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### Table 2

<table>
<thead>
<tr>
<th>Pituitary stalk</th>
<th>ICC (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>T1 pre-contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>0.89 (0.83–0.92)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Midpoint</td>
<td>0.85 (0.78–0.89)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Distal</td>
<td>0.76 (0.66–0.83)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>T1 post-contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>0.89 (0.83–0.92)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Midpoint</td>
<td>0.85 (0.78–0.89)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Distal</td>
<td>0.76 (0.66–0.83)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>T2-DRIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>0.96 (0.94–0.97)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Midpoint</td>
<td>0.99 (0.98–0.99)</td>
<td>&gt;0.005</td>
</tr>
<tr>
<td>Distal</td>
<td>0.97 (0.96–0.98)</td>
<td>&gt;0.005</td>
</tr>
</tbody>
</table>

*indicates P < 0.001
sequences (Fig. 2). The agreement was acceptable for measurements at midpoint of the pre-contrast T1 (3.9%) and T2-DRIVE (4.9%), and it was not possible to reach an acceptable agreement at the distal level of the PS.

Analysis of bias in each sequence showed that it was very small in T2-DRIVE (0.055 proximally, 0.012 at the midpoint, and 0.003 distally). The bias analysis of the T1 pre- and post-contrast measurements showed that this bias was always greater than the one observed in T2-DRIVE at proximal, midpoint and distal PS (Fig. 2).

Ectopic posterior pituitary group

The percentage of PS identified by T2-DRIVE was 72.7% (22/33 clearly visible + 2/33 barely visible), while it was 30.3% on pre-contrast T1-weighted images (6/33 clearly visible and 4/33 barely visible) (Table 3). There was a complete concordance in 15 out of 33 patients (45.5%, observed agreement). In 6 out of 33 patients (18.2%), the PS was clearly visible both on pre-contrast T1-weighted and on T2-DRIVE sequences, and for 9 out of 33 patients (27.3%) PS was not visible either on T1-weighted or on T2-DRIVE.

In 18 out of 33 patients (55.5%), there was no agreement between T2-DRIVE and T1-weighted pre-contrast sequences. In 12 cases, the PS was clearly visible on T2-DRIVE but not visible on pre-contrast T1-weighted images; in 4 cases, the PS was clearly visible on T2-DRIVE, whereas it was barely visible on the pre-contrast T1; finally, in 2 cases, the PS was visible with uncertainty (barely visible) on T2-DRIVE but not visible on pre-contrast T1-weighted image (Table 3). The chance-corrected Cohen’s $\kappa = 0.20$.

Table 3 Identification of pituitary stalk on T2-DRIVE as compared to T1-weighted pre-contrast evaluation in 33 patients with EPP.

<table>
<thead>
<tr>
<th>T1-weighted pre-contrast</th>
<th>T2-DRIVE</th>
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</thead>
<tbody>
<tr>
<td>Clearly visible</td>
<td>Barely visible</td>
</tr>
<tr>
<td>Clearly visible</td>
<td>6</td>
</tr>
<tr>
<td>Barely visible</td>
<td>4</td>
</tr>
<tr>
<td>Not visible</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
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</tbody>
</table>

EPP, ectopic posterior pituitary.
concordance for the case between the two sequences (T2-DRIVE and T1 pre-contrast) showed very poor values (Cohen’s $\kappa=0.20$), indicating that the two methods are clearly different.

There was no association between MRI results based on the two sequences and the number of pituitary defects ($P=0.40$) (Table 3). When the number of defects was more than or equal to 3, there were still 3 out of 18 patients (16.7%) in whom the PS was visible on both the T2-DRIVE and the pre-contrast T1-weighed sequences, and 8 out of 18 patients (44.4%) in whom the PS was visible on T2-DRIVE (Table 4). Post-contrast T1-weighted images were available for review in 12 out of 33 patients. Presence or absence of the PS on T2-DRIVE was confirmed by post-contrast T1-weighted images in 11 out of 12 patients (in 8 out of 9 patients the PS was clearly visible on both sequences, while in 3 out of 3 patients, it was not visible in either sequence). In 1 of 12 patients, the PS was not visible on post-contrast T1, whereas it was barely visible on T2-DRIVE (Fig. 3).

Multivariate analysis could not be performed as the only two variables that were significantly associated with PS visibility at T2-DRIVE sequence perfectly predicted the outcome. A significant association was found between the visibility of PS on T2-DRIVE and the AP height; in all patients with an AP height greater than 3.3 mm, the PS was visible on T2-DRIVE (10/10; 100%) while when the PS was not visible on the pre-contrast T1-weighed image, it was certainly visible also on T2-DRIVE (10/10; 100%) when the PS was not visible on the pre-contrast T1-weighted images, it was visible on T2-DRIVE in 60.9% of patients (14/23) ($P=0.032$) (data not shown).

**Discussion**

The PS is a funnel-shaped structure connecting the ME of the hypothalamus to the pituitary gland; its disruption can cause anterior and PP dysfunction (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 27, 28, 29, 30, 31, 32). Indeed, a broad spectrum of conditions may affect the PS, including congenital hypopituitarism (1, 2, 3, 4, 5, 6, 10, 11, 12, 13, 14, 30, 31, 32, 33), genetic defects leading to abnormal embryological development of pituitary gland (4, 6, 32, 33), tumors (4, 6, 15, 16), Langerhans cell histiocytosis (LCH) (4, 6, 25, 26, 27), inflammatory (4, 6) and autoimmune and infectious diseases (4, 6). In suspected HP disorders, MRI obtained with 2–3 mm thick T1- and T2-weighted images in the coronal and sagittal planes, provides an optimal amount of information. Ideally, T1-weighted images should also be obtained after administration of GBCAs (4).

Based on our personal experience, we first questioned whether the T2-DRIVE sequence is accurate in measuring PS size in individuals with pituitary dysfunction. Specifically, and in order to standardize the measurement method, we evaluated the degree of concordance and reproducibility of PS measurements between conventional pre- and post-contrast T1-weighted and T2-DRIVE imaging in a large group of patients with endocrine disorders and normal anatomy of PS; we found that the T2-DRIVE sequence was the most reliable method wherever the PS measurements were performed. Furthermore, our data demonstrate that the T2-DRIVE is more accurate than the other two sequences because the ICC values obtained at proximal, midpoint and distal PS were greater than those obtained with pre- and post-contrast T1, indicating a significant

<table>
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<th>MRI findings</th>
<th>Pituitary defects</th>
<th>Total</th>
<th>T1 after contrast</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS visible on T1-weighted pre-contrast and T2-DRIVE only</td>
<td>4* (50%)</td>
<td>3* (42.86%)</td>
<td>3 (16.60%)</td>
<td>10</td>
</tr>
<tr>
<td>PS visible on T2-DRIVE only</td>
<td>3* (37.5%)</td>
<td>3** (42.86%)</td>
<td>8*** (44.50%)</td>
<td>14</td>
</tr>
<tr>
<td>PS not visible on T1-weighted and T2-DRIVE</td>
<td>1 (12.5%)</td>
<td>1* (14.28%)</td>
<td>7** (38.90%)</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>7</td>
<td>18</td>
<td>33</td>
</tr>
</tbody>
</table>

*Clearly or barely visible; Fisher’s exact test: $P=0.40$; *confirmed in 1 patient; **confirmed in 2 patients; ***confirmed in 3 patients by T1 after contrast.
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improvement and a step forward in the correct assessment of PS size.

Despite a recent report on normal diameters and shape of the PS using high-resolution T2-weighted 3T MR imaging (34), our data show that the T2-DRIVE sequence (even when acquired on a 1.5T scanner and with a scan time of 2min and 32s, instead of 11min and 12s of the above mentioned study) can serve as a standard method in evaluating PS size in conditions in which the differential diagnosis of PS thickening represents a challenge. A previous study performed by our group – focused on neuroimaging follow-up of patients with PS involvement in different conditions – showed a wide range of variations in size of the PS, from spontaneous resolution to further enlargement (8). In addition, the most unpredictable neuroimaging features characterized patients with different PS thickness, suggesting that PS biopsy is advisable when MRI reveals a PS thickness widening above 6.5 mm (8, 9, 10, 35, 36, 37). Based on the latter and our current data, accurate PS measurement is crucial indicating that the high spatial and contrast resolution of T2-DRIVE offers appropriate measurements to support clinical decision-making when compared to conventional T1- and T2-weighted images by adding less than 3min to total scan time.

A second question concerned the extent to which T2-DRIVE is equivalent or superior to standard MRI sequences currently used in the diagnosis of HP structural anomalies in hypopituitarism. Although a brain MRI with particular attention to the HP region is advised in any child diagnosed with GHD according to the 2000 consensus statement (38), there is no general agreement on the standard MRI sequences and use of the contrast medium. While post-contrast imaging can be safely omitted in patients with isolated GHD and normal pituitary gland when the anatomical characterization of AP and PS is usually satisfactory (4), the MRI identification of EPP, AP hypoplasia and PS agenesis have a great value in the identification of patients at risk of developing additional hormone deficiencies (3, 11, 12, 13, 14, 31, 32, 33, 39, 40, 41).

Figure 3

Pituitary stalk (PS) visibility in subjects with ectopic posterior pituitary (PP). Left column: sagittal 3-mm-thick pre-contrast T1-weighted images; middle column: sagittal 0.6-mm-thick T2-DRIVE sequence; right column: sagittal 3-mm-thick post-contrast T1-weighted images. (A, B and C) 13-year-old girl with MPHD and lack of visibility of the PS in all sequences (arrows, A, B and C). The PP is located at the level of the median eminence (ME). There is concomitant marked reduction in size of the anterior pituitary (AP). (D, E and F) 11-year-old boy with GHD, TSHD and septo-optic dysplasia spectrum. The distal PS is not visible on the pre-contrast T1-weighted image (arrow, D), whereas it is clearly visible on both T2-DRIVE and post-contrast T1-weighted images (arrows, E and F). The PP is located along the proximal and mid stalk. The AP is hypoplastic. (G, H and I) 1-year-old boy with MPHD. The proximal and mid portions of the PS are not visible on the pre-contrast T1-weighted image (arrow, G), are barely visible on the post-contrast T1-weighted image (arrow, I) and are clearly visible on T2-DRIVE (arrow, H). A tiny PP is located at the level of the ME. There is marked hypoplasia of the AP (J, K and L) 29-year-old girl with GHD, LH/FSHD and CDI. The PS is not visible on pre- and post-contrast T1-weighted images (arrows, J and L). T2-DRIVE sequence allows the detection of a thin structure connecting the ME to the pituitary fossa, likely representing an extremely thinned PS (arrow, K). The PP is located at the level of the ME. The AP is normal.
or permanent defects (12, 13, 14, 32). In our previous studies, the vascular component of PS in patients with EPP was more frequently identified after contrast material administration and those who lacked PS after gadolinium showed a risk of evolution toward MPHD 27 times greater than those in which the PS was visible after contrast, indicating a prognostic functional value of the residual PS and suggesting that a detailed study of PS with GBCAs is recommended (11, 30).

Interestingly, on the one hand, the percentage of PS identified with the T2-DRIVE was more than twice higher than that shown by the standard T1-weighted pre-contrast sequence; on the other hand, the poor Cohen’s $\kappa$ obtained indicates that T2-DRIVE is much more sensitive than the T1 sequence and that this result was not corrected by chance but is instead based on the differences between the two MRI sequences. Furthermore, post-contrast T1-weighted images were not superior to T2-DRIVE in the identification of residual PS, indicating that the use of GBCAs could be avoided in the diagnosis of isolated or multiple pituitary hormone deficits (either idiopathic or congenital) and precocious puberty. The latter recommendation is also supported by safety reasons, as emerging evidence of intracranial gadolinium deposits following intravenous administration of GBCAs for routine MRI have raised concerns about their use (18, 19, 20, 21, 22). Although the clinical significance of gadolinium deposition remains undefined, the presence of deposits within the cytoplasm of neurons, particularly within the nucleus, increases the possibility of biological activity of these deposits, probably from the modulation of the activity of the calcium channel or direct interaction with the cellular biomolecules (21, 42). To the best of our knowledge, all these studies have been reported mainly in adults and, despite their small sample sizes, it has not yet been determined whether children would be subject to developing neurotoxicity over time at a higher risk.

While the absence of PS was recognized as a risk factor for MPHD in several studies, this association was not supported by others (13, 14). Our data confirm that the T2-DRIVE sequence is more reliable than the T1 pre-contrast and provide similar or even additional information when compared to post-contrast T1 with regard to the visibility of PS. In addition, the identification of PS by T2-DRIVE sequence in a high number of patients with MPHD raises a question about the real and predictive role of residual PS and suggests that PS itself is not always a hallmark for evolving pituitary hormone defects. It is worth pointing out that our published studies and those reported by others were based on standard T1- and/or T2-weighted sequences before and/or after contrast and not on a highly sensitive sequence such as T2-DRIVE. In addition, the significant association between PS and T2-DRIVE visibility in patients with EPP and AP height represents an interesting new finding in the context of HP structural anomalies.

Despite the fact that not all patients with EPP gland received GBCA is a limitation of our study, the high ICC values obtained on T2-DRIVE and the reproducibility of PS measurements between readers are relevant for the management of patients who need a neuroimaging follow-up. In addition, in patients with EPP who underwent post-contrast imaging, T2-DRIVE provided similar or even additional information (as shown in Fig. 3, visibility of PS was better on T2-DRIVE when compared to post-contrast T1 in 2 subjects).

In conclusion, high-resolution heavily T2-weighted sequences such as T2-DRIVE provide an important framework for a better diagnosis of pituitary gland and PS disorders, allowing precise measurements of the PS and the identification of PS abnormalities. A sagittal T2-DRIVE sequence covering the sellar/supra-sellar compartment and including midline structures takes less than 3 min to acquire; awareness of this sequence and its inclusion into routine sellar MRI protocols is recommended. We suggest that T2-DRIVE may represent a valid alternative to post-contrast imaging, which — also in view of safety issues — may be avoided in subjects with pituitary hormone deficits, central precocious puberty without evident sellar/ suprasellar mass lesions.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

Elisabetta Godano collected data, performed the measurements of pituitary stalk and helped drafting the manuscript. Giovanni Morana designed the study, performed the MRI examinations and the measurements of pituitary stalk and helped drafting and revising the manuscript. Natascia Di Iorgi, Anna Elsa Maria Allegri, Flavia Napoli, Roberto Gastaldi and Annalisa Calcagno are the physicians who take care of patients and critically revised the manuscript. Angela Pistorio was responsible of the entire statistical analyses. Giuseppa Patti, Annalisa Gallizia, Sara Notarnicola, Marta Giacciardi and Serena Noli helped in data collection and follow-up of the patients. Andrea Rossi performed the MRI examinations and critically revised the manuscript. Maricasavina Severino and Domenico Tortora performed the MRI examinations. Mohamad Maghnie designed the
study, participated in drafting and reviewing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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