Movement Disorders

Assessment of Axial Postural Abnormalities in Parkinsonism: Automatic Picture Analysis Software

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ABSTRACT: Background: Software-based measurements of axial postural abnormalities in Parkinson's disease (PD) are the gold standard but may be time-consuming and not always feasible in clinical practice. An automatic and reliable software to accurately obtain real-time spine flexion angles according to the recently proposed consensus-based criteria would be a useful tool for both research and clinical practice. Objective: We aimed to develop and validate a new software based on Deep Neural Networks to perform automatic measures of PD axial postural abnormalities.

Methods: A total of 76 pictures from 55 PD patients with different degrees of anterior and lateral trunk flexion were used for the development and pilot validation of a new software called AutoPosturePD (APP); postural abnormalities were measured in lateral and posterior view using the freeware NeuroPostureApp (gold standard) and compared with the automatic measurement provided by the APP. Sensitivity and specificity for the diagnosis of camptocormia and Pisa syndrome were assessed.

Results: We found an excellent agreement between the new APP and the gold standard for lateral trunk flexion (intraclass correlation coefficient [ICC] 0.960, IC95% 0.913–0.982, P < 0.001), anterior trunk flexion with thoracic fulcrum (ICC 0.929, IC95% 0.846–0.968, P < 0.001) and anterior trunk flexion with lumbar fulcrum (ICC 0.991, IC95% 0.962–0.997, P < 0.001). Sensitivity and specificity were 100% and 100% for detecting Pisa syndrome, 100% and 95.5% for camptocormia with thoracic fulcrum, 100% and 80.9% for camptocormia with lumbar fulcrum.

Conclusions: AutoPosturePD is a valid tool for spine flexion measurement in PD, accurately supporting the diagnosis of Pisa syndrome and camptocormia.

Axial postural abnormalities, including excessive forward and lateral trunk flexion, are common motor symptoms in Parkinson's disease (PD) and atypical parkinsonism.^{1,2} These symptoms, largely resistant to dopaminergic therapy in PD patients, proved to be associated with higher motor dysfunction, falls, autonomy loss, and reduced quality of life.^{1,2} The lack of a common classification and measurement methods for these symptoms led to uncertainty in their epidemiology, pathophysiological features, and therapeutic approaches.^{1–4} Recently, axial postural abnormalities have been classified by the International Movement Disorders Society (MDS) Task Force on Postural Abnormalities in Parkinsonism in different types, according with diagnostic cut-offs (ie, angles and fulcra) of spine flexion based on patients' pictures captured in standing position, both in frontal and sagittal plane.⁵ In this consensus, the authors used a free software-based measurement tool (NeuroPostureApp - UKSH, Kiel University, Kiel, Germany) for the

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semi-automatic calculation of the angles of trunk flexion.⁶ This approach is easy, reliable but somewhat time consuming, requires a minimal operator training or experience, and may have an interand intra-rater variability due to the manual placement of the points of interest on the reference bones for the degree calculation. Software platforms based on deep learning have been implemented in the field of artificial intelligence to perform automatic assessments from RGB-D images.7 These platforms can offer automatic and more reliable measures of spine flexion, avoiding the manual placement of the points of interest and saving time for raters.^{8,9} Therefore, we developed and validated a state-of-the-art platform for human pose estimation (HPE) based on Deep Neural Networks (DNNs) extended with key features to accurately obtain, in real-time, the spine flexion angles and fulcra calculated according to the MDS Task Force criteria.⁵ This software, called AutoPosturePD (APP), would allow a prompt assessment of axial postural abnormalities in patients with PD, which can be used both for clinical practice and research purposes.

Methods

In this study, we present the development and pilot validation of a software for an automatic assessment of the fulcrum and degrees of axial postural abnormality in PD. The software was developed to automatically detect from standard RGB patients' pictures the landmarks and trunk flexion measurements considered the clinical gold standard for the postural abnormalities assessment in PD and recently recommended by the MDS Task Force on Postural Abnormalities in Parkinsonism.⁵

The study was approved by the Verona institutional review board (1655CESC) and all patients provided their written informed consent.

Phase 1: Software Development

At the state of the art, standard HPE platforms (eg, OpenPose, PoseNet, MoveNet) extrapolate, from any RGB image, a set of key-points (Fig. 1A). Each key-point corresponds to a human joint and is numerically represented through the 2D or 3D spatial coordinates. Even though the number and types of key-points vary with the adopted DNN model (eg, Densnet, Resnet, etc.) all platforms provide a common subset to represent shoulders, elbows, wrists, pelvis, knees, and ankles. Common key-points include face points such as nose, eyes, and ears. Although the extrapolated coordinates allow for motion analysis such as gesture recognition or gait analysis, they are not sufficient for the assessment of axial postural abnormalities according to the MDS criteria.⁵ What is missing, in particular, are the key-points that identify the last vertebra of the cervical section (C7), the last vertebra of the lumbar section (L5), the point between the two ankles (MA) for both the frontal and sagittal views and the point most distant from another line between C7 and L5 (FC) for the sagittal view. Since no HPE platform at the state of the art includes any of these points, we implemented a post-processing software application (APP) that, starting from the key-point



FIG. 1. Set of key-points extrapolated from the standard human pose estimation platforms for coronal images. (A) total body; (B-D) key points and error estimation of ears and shoulders (B), hips and knees (C), and ankles (D).

information provided by the HPE software, it automatically identifies the missing anatomical points of interest.

Spinal Bone Landmarks: Lateral Trunk Flexion

Using manual palpation, an experienced movement disorders expert identified and marked the C7 spinous processes, through an assisted movement of the cervical spine into extension, as a protuberance around the end of the neck along the vertebral column.¹⁰ APP geometrically identifies this point as the intersection of two segments connecting the shoulder key-points to the ear key-points in the opposite side (Fig. 1B). We measured the difference between the spatial coordinates of the spinal process C7 identified by APP and the spinal process C7 manually identified by a movement disorders expert with 20 subjects. Figure 1B shows the results, which quantify the error between two measurements, in average, below 5% of the subject's trunk length (ie, 2.3 cm).

Using manual palpation, an experienced movement disorders expert identified and marked the spinous processes L5, as the first spinal process under an imaginary line connecting the two iliac crests.¹⁰ To enrich the original HPE output with this point, APP first identifies the middle point (MH) between the left hip (LH) and the right hip (RH). Starting from MH, it traces a vertical segment and identifies L5 at a distance $DIST_{MH-L5} = K_1\%$ (avg[(LH – LK), (RH – RK)]). The distance corresponds to a parametric percentage (K₁%) of the average left and right leg length, where each leg length corresponds to the distance between the hip key-point (LH and RH for the left and right



FIG. 2. Example of the angles calculated by the APP throughout the automatic identification of the patient's reference bones. APP, AutoPosturePD.

hip, respectively) and the knee key-point (LK and RK for the left and right knee, respectively) (Fig. 1C). With $K_1 = 20$, we observed an estimation error of measurements that, in average, is below 11% of the subject's trunk length (ie, 4.9 cm) (Fig. 1C).

MA is the point between the two ankles. Using a visual estimation, an experienced movement disorders expert identified and marked the MA, as MH between a line connecting the heel of the right and left foot. To enrich the original HPE output with this point, APP calculates MA as the MH between the keypoints provided by HPE that identify the left ankle and the right ankle (Fig. 1D). For this point, we measured an error that is negligible for the most subjects (ie, below 4% of the subject's trunk length—1.8 cm) and, in any case, within 11% of the subject's trunk length (4.9 cm) (Fig. 1D).

Finally, Figure 2 shows as an example of the angles calculated by the APP throughout the automatic identification of the patient's reference bones C7, L5, and MA. On the top left side, the picture indicates the measurement error between the angle calculated by the APP and the key-points identified manually by the clinical rater.

Spinal Bone Landmarks: Anterior Trunk Flexion

When the image is taken from the sagittal side, the HPE software identifies the key-points close to the center of the body joints. To measure the angle for the camptocormia with upper and lower fulcrum,⁵ we need the position of the anatomical C7 and L5, which are located *at the edge* of the subject silhouette. The match of subject underwear and background colors, as well as the environment light, can strongly impact the accuracy of the subject edge extrapolation. To reduce such an accuracy loss, APP first implements an image segmentation phase that extracts the *regions of interest* and applies the graph cut algorithm (Fig. 3A).¹¹ This allows the software to sensibly reduce false negative pixels and, thus, to increase the accuracy in the extrapolation of reference bones C7, L5, FC, and MA.

To obtain the spinal process C7, APP first identifies A as the $K_2\%$ MH between the shoulder and ear key-points (Fig. 3). Starting from A, it identifies C7 as the last point of the mask within the line perpendicular to the segment connecting the ear and shoulder, passing via A. With $K_2 = 40$, we observed an estimation error that is negligible for most subjects and, in any case, is below 6% of the subject's trunk length (ie, 2.2 cm) (Fig. 3B).

To extrapolate the spinal process L5, APP implements two phases. First, it extrapolates L5 with the same approach used for L5 in the frontal view. Then, starting from L5, it implements a search process to find the last segmented pixel of the subject silhouette (Fig. 3C). With the same value $K_1 = 20$ as for the frontal view, we observed an estimation error that, in average, is below 14% of the subject's trunk length (ie, 5.8 cm) (Fig. 3C).

FC is the point used in the evaluation of camptocormia with upper fulcrum. This point is defined as the contact of the tangent to the back parallel to the line between C7 and L5, as depicted in Figure 3D. The software extrapolates this point starting from



FIG. 3. Set of key-points identified by APP for sagittal images. (A) total body; (B–D) key points and error estimation of spinal process C7 (B), spinal process L5 (C), FC–contact of the tangent to the back parallel to the line between C7 and L5– (D), and ankles (E). APP, AutoPosturePD.

the segment C7-L5 and moving perpendicularly backward to the edge of the subject. Figure 3D shows the obtained results, which underline an average estimation error below 2 cm.

For the sagittal view, APP maps MA in the HPE key-point that identifies the ankles (Fig. 3E). The direct mapping leads the

software to an estimation error below 8% of the subject's trunk length (3.7 cm) at most (Fig. 3E).

Finally, Figure 4 shows, as examples, the angles calculated through the reference bones C7, L5, MA and C7, FC, and L5. The figure on the top left side reports the error of measurement between the angle calculated by the APP and through the keypoints identified manually by the clinician $(0.3^{\circ} \text{ and } 2.6^{\circ} \text{ for lower and upper camptocormia, respectively}).$

Phase 2: Pilot Validation

Study Participants

Seventy-six pictures from 55 PD outpatients taken in standing position in two different planes (sagittal and coronal) were used for the analysis. Demographic and clinical features of patients included in the study are reported in Table 1.

Procedures

Seventy-six pictures of undressed PD patients (with underwear) with different degrees and fulcrum of axial postural abnormalities were analyzed and used for the analysis of the bending angles: 25 were in frontal plane and used for the analysis of lateral trunk flexion and 51 were in sagittal plane and used for the analysis of anterior trunk flexion with thoracic and lower fulcrum, as per the recent recommendation of the MDS Task Force on Postural Abnormalities in Parkinsonism.⁵ Accordingly, each picture was analyzed using the NeuroPostureApp[®] (https://www. neuroimaging.uni-kiel.de/NeuroPostureApp/, UKSH, Kiel University, Kiel, Germany),⁶ a software-based measurement tool provided by the Kiel University, for the calculation of the following angles: (1) thoracic fulcrum anterior trunk flexion, defined as the external angle between two lines, one passing from the fulcrum of the spine flexion and L5 vertebra process, the second one passing from the fulcrum of the spine flexion and the C7 vertebra process; (2) lumbar fulcrum anterior trunk flexion, defined as the external angle between two lines, one passing through the L5 vertebra process and the lateral malleolus and the second one passing through the L5 vertebra process and the C7 vertebra process; (3) lateral trunk flexion, the external angle between two lines, one passing through the midpoint of the feet and the L5 vertebra process and the second one passing through the L5 vertebra process and the C7 vertebra process.6

Statistical Analysis

To assess the validity of the automatic software against the current gold standard method of postural angle calculation, we performed the following analyses: (1) Bland-Altman mean differences and 95% limits of agreement; (2) intraclass correlation coefficient (ICC) and standard error of measurement;¹³ and (3) Cohen's kappa. Bland & Altman plots were used to investigate the existence of any systematic difference between the automatic software measurements and the manual software-based gold standard and to compute 95% limits of agreement for each





comparison. The 95% limits of agreement were calculated as [mean of the differences \pm (1.96 × SD)], in which SD is the standard deviation of mean of the differences.¹² Mean differences are the average difference between the gold standard and the

automatic software, while the limits of agreement are the random error or variation between instruments. ICC estimates and their 95% confident interval were calculated to investigate agreement between pairs of observations (automatic software and gold

TABLE 1 Demographic and clinical characteristics of the PD patients

Sample features	Total of patients	LTF (pictures)	U-ATF (pictures)	L-ATF (pictures)
Patients, no	55 ^ª	25	25	26
Gender, M/F		17/8	19/6	19/7
Age, mean (SD), yrs		70 (8)	71(8)	72 (8)
Disease duration, mean (SD), yrs		8 (5)	8 (5)	8 (5)
UPDRS total, mean (SD)		65 (24)	67 (24)	66 (23)
UPDRS III score, mean (SD)		37 (14)	37 (14)	37 (13)
H&Y stage, mean (SD)		3 (1)	3 (1)	3 (1)

^aThe total number of patients: this value does not correspond to the sum of each category (LTF, U-ATF, L-ATF) because the same patient may present one or more axial postural abnormality and therefore has been evaluated twice.

Abbreviations: LTF, denotes patients with Parkinson's disease and Lateral Trunk Flexion; U-ATF, denotes patients with Parkinson's disease and anterior trunk flexion with upper fulcrum; L-ATF, denotes patients with Parkinson's disease and anterior trunk flexion with lower fulcrum; SD, standard deviation; yrs, years; M, Male; F, Female; H&Y, stage Hoehn and Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale; subitem of UPDRS scale part III.

standard) based on a single-rater, absolute agreement, two-way mixed-effects model.¹³ The standard error of measurement was calculated for each measurement modality. This was calculated as described by Atkinson and Nevill¹⁴ as standard error of measurement = $SD\sqrt{(1 - ICC)}$, in which SD is the standard deviation. The resulting value of standard error of measurement is expressed in degrees (the highest the worst). From the dataset, we calculated the average and frequency of underestimation, overestimation, and perfect estimation of automatic software measures compared to the gold standard. We calculated Cohen's kappa¹⁵ sensitivity and specificity for diagnosis of Pisa syndrome, camptocormia with thoracic fulcrum, and camptocormia with lumbar fulcrum, using the manual software-based measurements as the gold standard. The reliability of the newly developed automatic software is 100% since by definition each picture analyzed provides exactly the same results (same input = same output). All P values reported are 2-tailed, and a P < 0.05 was considered statistically significant. Data were analyzed using the Statistical Pack- age for the Social Sciences (SPSS version 27 for Mac [IBM Corp., Armonk, NY]). Data collected and used for the study are available upon reasonable request. All patients involved in the project provided written informed consent for participation.

Results

A total of 76 pictures from 55 PD patients were used for the validation analysis of the new automatic APP, developed according to the methodology reported in the previous sections, against the current gold standard based on manual picture analysis using the angles proposed by the MDS Task Force and here calculated by means of the NeuroPostureApp[©].⁶ Main demographic and clinical data of PD patients included are summarized in Table 1. According to the gold standard, we included 11 patients with diagnosis of Pisa syndrome and 12 with diagnosis of camptocormia, of which nine at the thoracic fulcrum and 3 at the lumbar fulcrum.

Discrepancy of the Estimated Measures between the Gold Standard and the New Software

Based on ICC, we found an excellent agreement between the APP and the gold standard for lateral trunk flexion (ICC 0.960, IC95% 0.913–0.982), anterior trunk flexion with thoracic fulcrum (ICC 0.929, IC95% 0.846–0.968) and anterior trunk flexion with lumbar fulcrum (ICC 0.991, IC95% 0.962–0.997) (Table 2). Bland-Altman plots showed a systematic bias between methods only for camptocormia at the lumbar level, with a mean difference of $-0.6 \pm 3.1^{\circ}$ for the lateral trunk flexion, $-0.3 \pm 2.5^{\circ}$ for the anterior trunk flexion with thoracic fulcrum, and $-1.3 \pm 1.8^{\circ}$ for the anterior trunk flexion with lumbar fulcrum (Fig. 5). Considering an error cut-off of 0.49°, the automatic software perfectly estimated the lateral trunk flexion in 32% of cases, overestimated it in 24% of cases by a mean of 3.3° and underestimated it in 44% of cases by a mean of 3° . For the anterior thoracic flexion with thoracic fulcrum, the automatic software perfectly estimated the lateral trunk flexion in 20% of cases, overestimated it in 32% of cases by a mean of 2.2° and underestimated it in 48% of cases by a mean of 2.2°. For the anterior thoracic flexion with lumbar fulcrum, the automatic software perfectly estimated the lateral trunk flexion in 4% of cases, overestimated it in 16% of cases by a mean of 1.8° and underestimated it in 80% of cases by a mean of 1.9° (Fig. 5).

Discrepancy in the Diagnosis of Pisa Syndrome and Camptocormia between the Gold Standard and the New Software

The automatic software showed a perfect agreement with the gold standard in the diagnosis of Pisa syndrome (k = 1; P < 0.001), an almost perfect agreement in the diagnosis of camptocormia with thoracic fulcrum (k = 0.83; P < 0.001), and a substantial agreement in the diagnosis of camptocormia with lumbar fulcrum (k = 0.69; P < 0.001). Sensitivity and specificity were 100% and 100% for detecting Pisa syndrome, 100% and 95.5% for camptocormia with thoracic fulcrum, 100% and 80.9% for camptocormia with lumbar fulcrum.

Caveats

The relevant disagreements in the measurement of the degree and fulcrum between the APP and the gold standard NeuroPostureApp was mainly due to three main technical aspects related to the patients' pictures: (1) the environment in which the picture was taken; (2) the body patient's exposure and (3) the position of camera while taking the picture. Considering that patient's picture should be taken with the patient undressed to reduce the possibility of measurement error, it is also important that (1) the patient is positioned in front of a background as uniform as possible, and (2) that there is a sufficient chromatic contrast between the background color and the patient's skin color

TABLE 2	Agreement	between	the	APP	and	the	gold	standard
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Measurement	ICC	95% CI	P value
Lateral trunk flexion	0.960	0.913 to 0.982	< 0.001
Anterior trunk flexion with thoracic fulcrum	0.929	0.846 to 0.968	<0.001
Anterior trunk flexion with lumbar fulcrum	0.991	0.962 to 0.997	<0.001

Abbreviations: APP, AutoPosturePD; ICC, intraclass correlation coefficient; CI, confidence interval with lower and upper bound.





(and the patient's underwear color in case it is maintained while taking the picture). Finally, the camera should be well positioned in front of the patient and photographs should be taken horizontally from a distance of at least 3 to 5 m with the lens approximately at waist height. It is important that the photograph displays the patient in a screen-filling way.⁶



FIG. 6. Examples of outliers with the errors due to (A) improper camera position or (B) inadequate clinical setting.

We reported in Figure 6 two examples of our outliers, with the errors due to (A) improper camera position or (B) inadequate setting, consisting of an inadequate chromatic contrast between the color of patient's skin and underwear and with the background (B).

Discussion

In this study, we showed the development and validity of the new APP for automatic, quick and reliable assessment of axial postural abnormalities in patients with PD, according to the criteria proposed by the MDS Task Force on Postural Abnormalities in Parkinsonism.⁵ We found an almost perfect agreement in the degree measurement between the new APP and the current gold standard NeuroPostureApp.⁶ Such an excellent agreement has been reached for both lateral trunk flexion degrees and anterior trunk flexion degrees at lumbar and thoracic level. Moreover, we found that the APP shows a sensitivity of 100% for the diagnosis of Pisa syndrome and camptocormia with upper and lower fulcrum.⁵ The specificity is also 100% for the diagnosis of Pisa syndrome, and high for the diagnosis of camptocormia (95.5% for thoracic fulcrum and 80.9% for lumbar fulcrum). Such results are extremely relevant for the clinical practice since

movement disorders experts and other healthcare figures working with PD patients (ie, neurologists, physiatrists, physiotherapists) need a reliable, yet easy and time-saving tool, for the early detection and diagnosis of axial postural abnormalities, as well as for their monitoring over time according to the changes of medical or not medical interventions.⁵

In the last few years, a rising attention has been pointed on axial postural abnormalities, being a relatively frequent and highly invalidating motor symptom of PD and other parkinsonisms.² The attention of the research community on these symptoms highlighted the lack of common and practical assessment tools, nowadays based on subjective rater-dependent evaluations.^{6,16} Only recently, a few studies aimed at developing technological solutions for an objective and automatic measurement of posture. In one study,¹⁷ authors applied a deep learning-based pose-estimation algorithm to sagittal pictures of patients with PD for the measurement of the anterior trunk bending angle, defined as the angle between the vertical reference and the lines connecting the hip joint and shoulder joint, and the dropped head angle, defined as the angle between the lines connecting the hipacromion and acromion-ear. Although reaching an excellent agreement with manual labeling methods, the data about anterior flexion angle were not confirmed with manual calculation with malleolus method, and the pose-estimation algorithm was not able to detect the fulcrum of camptocormia.¹⁷ A recent review reported 13 studies about postural disorder assessment with Microsoft Kinect, a motionsensing device for interaction with game consoles and computers. The studies focused specifically on measures to detect postural instability, shoulder position angulation and body joint angles, but the accuracy in the detection of posture disorders was not considered.¹⁸ Another article evaluated the possibility to provide an accurate and automated assessment of axial postural abnormalities in PD patients by Kinect, evaluating the ICC between the angles calculated and the MDS-UPDRS-III 3.13 score.¹⁹ These studies enrich the potential set of tools available for the early detection of axial postural abnormalities but do not consider the recent MDS consensus-based criteria for their diagnosis. Therefore, the development of this new APP following the consensus-based criteria and their rules for the angle measurement⁵ can be useful and quickly integrated into research and clinical practice. In fact, APP has the potential to increase the diffusion of a common way to define and measure axial postural abnormalities in an easy and time-saving way.

Our study is not without technical limitations, which may reduce the applicability of the APP in clinical practice. Possible measurement errors can occur mainly due to (1) inadequate clinical setting, (2) poor environmental light, (3) improper camera position, or (4) an inadequate chromatic contrast between the color of patient's skin/underwear and the background. Therefore, it is important to get the full picture of the patients, possibly without clothes, and with a correct height and distance between the camera and the patient. Moreover, not every place is suitable for taking the picture since a certain degree of chromatic contrast is needed for the maximum reliability of the assessment. The main measurement errors occur only in the assessment of the anterior trunk flexion and when different factors combine during the photo shooting. A software improvement to overtake this limitation is the use of depth information provided by RGB-D camera sensors to implement the human silhouette segmentation. In the case of depth information, the software would be limited to smartphones with depth camera. However, since the presence of these last-generation cameras on smartphones is a trend, the software extension taking advantage of depth information is part of our current work for further software improvement. It is important to note that the current version of the APP cannot be directly included in a smartphone due to the need for a powerful processor-like those of personal computers-to reach this level of accuracy in picture elaboration. However, it would be feasible to use the smartphone to take the pictures, encrypt the images for privacy reasons, send them to a computer (a laptop locally or even in the Cloud), and receive the response on the smartphone.

The camera position and the subject rotation with reference to the camera may also affect the measurement accuracy. These factors also affect the accuracy of the state-of-the-art measurement methods (ie, wall goniometer and NeuroPostureApp) and it would be difficult to assess such an error on single pictures without a ground truth. To overtake such a limitation, we are extending the software to work on sequences of images (ie, video) to provide the corresponding statistics on temporal windows. For the same reason, the role of dyskinesia or other hyperkinetic movements have not been considered in this study being based on a static assessment of posture, according with the current gold standard. Finally, we have validated the software on a small sample of patient pictures provided by two centers with experience in movement disorders and only on camptocormia and Pisa syndrome, excluding antecollis, another invalidating axial postural abnormality. A wider, multicenter validation is therefore recommended before an implementation of the APP into clinical practice.

These limitations notwithstanding, we believe that the new software presented in this study has the potentiality to become an easy-to-use tool fostering the uniformity in the assessment of axial postural abnormalities in research studies and also in clinical practice, to assist healthcarers involved in the assessment and management of PD for the early detection, diagnosis and management of axial postural abnormalities, which deserve prompt management interventions.⁵

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Author Roles

All authors have materially participated in the research and/or article preparation (see roles, below). All authors have approved the final submitted article. This article represents original work by the authors, has not been published elsewhere, and is not under consideration for publication elsewhere.

Research Project: A. Conception, B. Organization,
 C. Execution; (2) Statistical Analysis: A. Design, B. Execution,
 C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

C.A.A.: 1B, 1C, 2A, 2B, 3A. C.G.: 1B, 1C, 2A, 2C, 3A. G.I.: 1C, 2C, 3B. S.C.: 1C, 2C, 3B. S.A.: 1B, 1C, 2C, 3B. L.L.: 2C, 3B. M.T.: 1A, 1B, 2C, 3B. N.B.: 1A, 1B, 2C, 3B.

Disclosures

Ethical Compliance Statement: The patients gave written consent to participate in the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The Verona institutional review board approved the study (1655CESC).

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