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ORIGINAL ARTICLE

The evaluation on neural status of cervical spinal cord in normal and Hirayama disease using diffusion tensor imaging

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Abstract

Purpose To explore the changes in diffusion tensor imaging (DTI) parameters in cervical spinal cord in Hirayama disease (HD) patients and healthy volunteers and to compare these parameters between cervical flexion and neutral positions in HD patients.

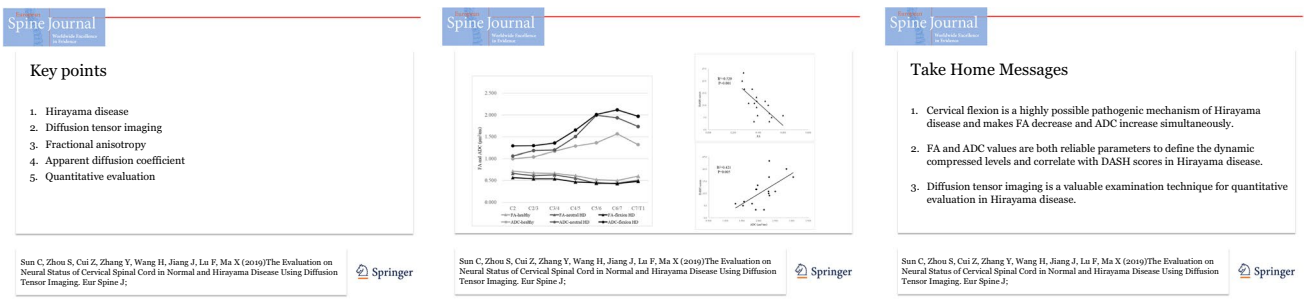
Methods Seventeen male patients with HD and eleven healthy young males were included to receive DTI scans in cervical flexion and neutral positions. The FA and ADC values of different levels were measured based on the region of interest drawn on the mid-sagittal plane. The dynamic compressed level's parameters were defined as the lowest and the second lowest FA and the highest and the second highest ADC, respectively. The clinical assessment of patients was obtained using their disabilities of the arm, shoulder and hand (DASH) scores.

Results For the HD patients, the FA values in the cervical flexion position were lower and the ADC values were much higher than those in the cervical neutral position. Compared with the controls, the ADC values were significantly higher in the lower levels (C5/6-C7/T1) and the FA values obviously lower at C7/T1 in HD patients in cervical neutral position. The FA and ADC values of the dynamic compressed level in HD patients deviated significantly from the average of the lower levels in controls. Both the FA and ADC values of the dynamic compressed level correlated with the DASH scores (FA, $R^2 = 0.520$, $P = 0.001$; ADC, $R^2 = 0.421$, $P = 0.005$).

Conclusions DTI parameters can support a hypothesis of dynamic cervical flexion compression and noninvasively reveal the neural status of HD patients.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.



Chi Sun and Shuyi Zhou are co-first authors: Chi Sun and Shuyi Zhou have contributed equally to this work.

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Extended author information available on the last page of the article

Keywords Hirayama disease · Diffusion tensor imaging · Fractional anisotropy · Apparent diffusion coefficient · Quantitative evaluation

Introduction

Hirayama disease (HD), also known as juvenile spinal muscular atrophy of the distal upper extremities, is a benign and self-limiting neurological disease that usually affects young males [1]. First discovered in 1959 by Hirayama in Japan, the disease has become familiar in the past 20 years. There have been large-sample studies in Asia [2–5], but an increasing number of cases are being reported in western countries [6–10], indicating that HD should not be neglected in the white pediatric population. This disease usually causes muscular weakness and wasting in the forearm and hand. Due to the serious consequences of muscular atrophy, Hirayama disease has gradually attracted attention in recent years.

The exact pathogenic mechanisms of HD remain unclear; however, the hypothesis that repeated cervical flexion causes dynamic compression on the spinal cord has come to be widely accepted [2–4]. Clinically, electromyography and conventional cervical flexion MRI are essential for diagnosis and assessment by showing specific manifestations, but precise quantitative evaluation of the spinal cord in HD patients is unrealized [11–13]. Our team conducted a series of studies on HD from diagnosis, assessment, and treatment to prognosis [11, 14–17]. Though an abnormal motor cortex activation pattern in HD has been found [18], it is still important to determine the neural status of the spinal cord.

Diffusion tensor imaging (DTI) is an MRI technique sensitive to the magnitude and orientation of water diffusion in the tissues [19]. Numerous studies have reported abnormal DTI parameters in cervical spondylotic myelopathy (CSM), most prominent at the maximum compression level, compared with healthy volunteers [20–22]. DTI parameters were also found to correlate with the Japanese Orthopedic Association (JOA) scores of CSM, as reported by Jones et al. in 2013 [22]. HD causes the repeated and continued compression on the cervical spinal cord as in CSM; however, no studies have focused on the evaluation of DTI parameters or have provided a quantitative assessment of chronic spinal cord injury in HD patients, except for a DTI-based study on HD focusing solely on the integrity of the supraspinal cortical-spinal tract [23]. Thus, in the present study, we aim to (1) explore the changes in DTI parameters in different cervical spine levels in HD patients and healthy volunteers and (2) compare the DTI parameters of the cervical spinal cord between cervical flexion and neutral position in HD patients.

Materials and methods

Subject population

We recruited our study subjects in a 1-year period from May 2016 to May 2017. Patients who were clearly diagnosed with HD and age-matched healthy young males as controls were included. The inclusion criteria for healthy young males were as follows: (1) no history of significant neck pain, (2) no symptoms of cervical spine disease in the form of radiculopathy or myelopathy, and (3) no evidence of cervical spinal cord compression on MR images. Those who had previous cervical surgery were excluded. Seventeen male patients with HD (mean age, 18.9 years; range, 15–20 years) and eleven healthy young males (mean age, 19.3 years; range, 17–22 years) were ultimately included in this study. The disabilities of the arm, shoulder and hand (DASH) scoring scale was used for the assessment of dysfunction in the included patients [16, 24]. This study was approved by the institutional review board of our hospital, and informed consent was obtained from all individual participants included in the study.

DTI protocol

All the included subjects received a DTI scan in a supine position using a 3T MRI scanner (Siemens Magnetom Verio, Erlangen, Germany) with a cervical coil. The subjects first received a neutral cervical DTI scan. Then, for 30 min, the patients bowed their heads and assumed a position similar to their daily life when reading or using a cell phone. The patients then were given a cervical flexion DTI scan (flexing the neck until the chin contacts the chest with the support of a specially made pillow). A DTI scan was performed using a single-shot echo-planar imaging (SS-EPI) sequence. The imaging parameters were as follows: b value, 0 and 500 s/mm^2; MPG, 30 directions; TR/TE, 2900/61 ms; sagittal section orientation; slice thickness/gap, 3/1 mm; FOV, 300×300 mm^2; matrix, 128×128; actual voxel size, $3.7 \times 3.0 \times 3.0$ mm^3; and scan time, 8 min 24 s. Sagittal T2-weighted anatomical images were also obtained by using the following protocol: T2 turbo-spin-echo (TSE) sequence with variable flip angle RF excitations (SPACE, sampling perfection with application optimized contrasts using different flip angle evolutions); TR/TE, 3200/411 ms; FOV, 320×320 mm^2; matrix, 128×128; and slice thickness/gap, 3/1 mm.

Postprocessing of DTI data

Data postprocessing, such as determining the independent elements of the diffusion tensor, deriving the corresponding eigenvalues and eigenvectors, and reconstruction, was performed using dedicated software (Neuro 3D, Siemens Healthcare AG). Sagittal T2-weighted anatomical images were overlaid on the DTI data to permit the anatomical correlation. For each subject, FA and ADC values of the cervical spinal cord were measured based on the region of interest (ROI) from C2 to C7/T1. The circular ROIs were drawn manually in the mid-sagittal plane by a spine surgeon and a radiologist. We used the anteroposterior diameter of each level in the cervical spinal cord as the diameter of each ROI. The FA and ADC values could be read immediately in the software after placing the ROI, and the averaged FA and ADC values of each ROI were used for further statistical analysis (Fig. 1). For each patient's DTI parameters in the cervical neutral position, we defined the average of the lowest and the second lowest FA values and the highest and the second highest ADC values as the dynamic compressed level's DTI parameters, respectively.

Statistical analysis

Statistical analysis was performed using STATA (version 14.0, StataCorp LP, Texas, USA). Descriptive statistics were used to assess the trends in variation of the DTI parameters. Continuous variables are presented in the form of mean and standard deviation (SD). Student's t test and a paired t test were used to compare the patients and controls and the cervical flexion and neutral positions, respectively. Spearman's correlation analysis was used to determine correlation between the DTI parameters and DASH scores. $P < 0.05$ was considered statistically significant.

Results

DTI parameters and their variation trends

The FA and ADC values of the healthy young males are shown in Table 1. From C2 to C6/7, the FA value decreased gradually and then increased at C7/T1. For the ADC value, the trend was the opposite. The DTI parameters of patients with HD in cervical flexion and neutral positions are also

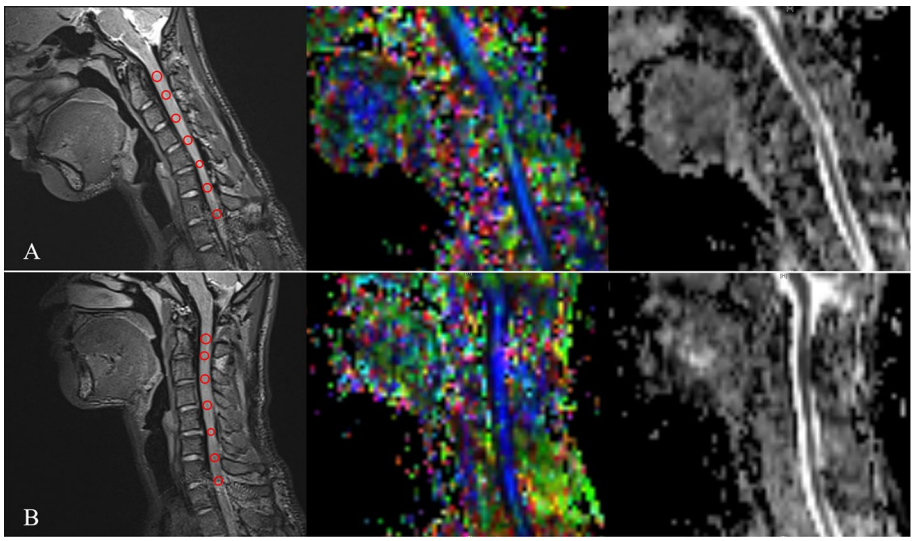

Fig. 1 Measurements of FA and ADC values based on the ROI placed in cervical flexion and neutral positions. In the postprocessing software, FA and ADC values of the cervical spinal cord were measured based on the circular region of interest (ROI). The ROIs were drawn manually in the mid-sagittal plane of cervical flexion (**a**) and neutral (**b**) positions. The diameter of each ROI was defined as the anteroposterior diameter of each level in the cervical spinal cord

Table 1 DTI parameters of the healthy young males and HD patients

DTI parameters	C2	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1
FA healthy	0.717 ± 0.147	0.673 ± 0.085	0.667 ± 0.084	0.614 ± 0.141	0.520 ± 0.085	0.500 ± 0.152	0.600 ± 0.085
ADC healthy	1.001 ± 0.287	1.044 ± 0.207	1.166 ± 0.299	1.288 ± 0.407	1.365 ± 0.277	1.566 ± 0.329	1.322 ± 0.347
FA flexion HD	0.570 ± 0.088	0.542 ± 0.084	0.539 ± 0.083	0.467 ± 0.088	0.451 ± 0.118	0.431 ± 0.117	0.484 ± 0.116
ADC flexion HD	1.290 ± 0.254	1.298 ± 0.181	1.359 ± 0.250	1.654 ± 0.440	2.012 ± 0.615	2.116 ± 0.442	1.970 ± 0.632
FA neutral HD	0.664 ± 0.117	0.613 ± 0.120	0.633 ± 0.121	0.556 ± 0.136	0.434 ± 0.125	0.439 ± 0.117	0.508 ± 0.102
ADC neutral HD	1.063 ± 0.201	1.180 ± 0.266	1.197 ± 0.227	1.508 ± 0.471	1.994 ± 0.552	1.937 ± 0.510	1.737 ± 0.481

Healthy—healthy young males; flexion—cervical flexion position; neutral—cervical neutral position; ADC unit: $\mu m^2/ms$

presented in Table 1. The trends in variation are similar to those of the controls (Fig. 2). The action of cervical flexion decreased the FA values of each level and greatly increased the ADC values in HD patients.

Comparison of DTI parameters between cervical flexion and neutral positions in patients and controls

There were no significant differences in the FA and ADC values between the cervical flexion and neutral positions in most of the cervical spine levels, as shown in Table 2. We speculated that the insufficient time (30 min) for cervical flexion and the small sample size led to this mild difference in values. At the upper levels (C2-C4/5), there were no significant differences in DTI parameters between patients with HD in the cervical neutral position and controls. However, the ADC values were significantly higher at the lower levels (C5/6-C7/T1), and the FA values dropped noticeably at C7/T1 (Table 2). The DTI parameters of the dynamic compressed level in the patients with HD deviated significantly from the average of the lower levels (C4/5-C7/1) in the controls (Table 3).

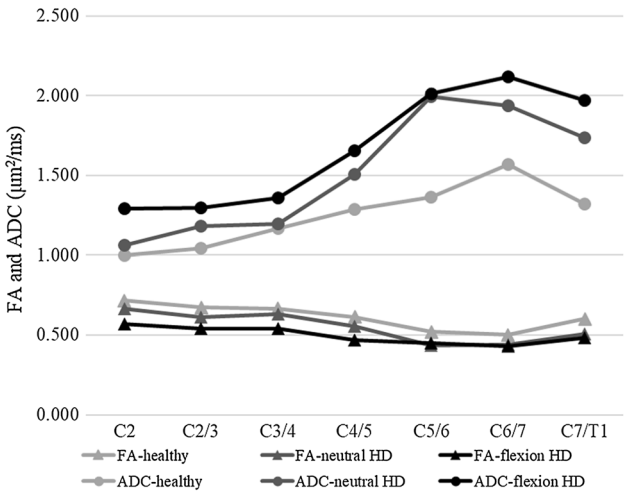

Fig. 2 The trends in variation of DTI parameters. From C2 to C6/7, the FA value decreased gradually and then increased in C7/T1. For the ADC value, the trend became opposite. Among the three groups, parameters of HD patients in the cervical flexion position were the most abnormal in nearly all the levels. ADC unit: $\mu m^2/ms$

Correlation between DTI parameters and DASH scores

The DASH score of the patients was 10.8 ± 5.6, with a range of 3.3–23.3. Spearman's correlation analysis showed that both the FA and ADC values in the dynamic compressed level were correlated with the DASH scores (FA, $R^2 = 0.520$, $P = 0.001$; ADC, $R^2 = 0.421$, $P = 0.005$), as presented in Figs. 3 and 4. The FA values seemed to have a stronger relationship with the DASH scores than the ADC values did.

Discussion

The hypothesis is that compression on the spinal cord during cervical flexion is the most likely pathogenesis of HD [2–4, 25]. Clinically, doctors use cervical flexion MRI as a primary method to locate the compressed levels and to evaluate the severity in patients with HD. The MR images present asymmetrical atrophy of the spinal cord, forward displacement of the posterior dural sac and, therefore, secondary spinal cord compression against the posterior wall of the vertebrae [12, 13, 15]. Nevertheless, an individual's tolerance of and response to cord compression is variable, and the interpretation of conventional MRI findings might

Table 3 Comparison of DTI parameters between the dynamic compressed level of HD patients and the lower levels of controls

	FA	ADC
Neutral HD (average of dynamic compressed levels)	0.399 ± 0.087	2.115 ± 0.438
Healthy(average of C4/5-C7/T1)	0.547 ± 0.093	1.414 ± 0.241
P value	< 0.001	< 0.001

Healthy—healthy young males; neutral—cervical neutral position; ADC unit: $\mu m^2/ms$

Table 2 Comparison of DTI parameters between cervical flexion and neutral position and between patients and controls

P value	C2	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1
Flexion HD versus neutral HD							
FA	0.002	0.053	0.020	0.019	0.611	0.861	0.420
ADC	0.003	0.128	0.044	0.220	0.862	0.288	0.193
Neutral HD versus healthy							
FA	0.299	0.163	0.424	0.287	0.565	0.253	0.020
ADC	0.506	0.163	0.758	0.215	0.002	0.042	0.020

Healthy—healthy young males; flexion—cervical flexion position; neutral—cervical neutral position; $P < 0.05$ was considered statistically significant

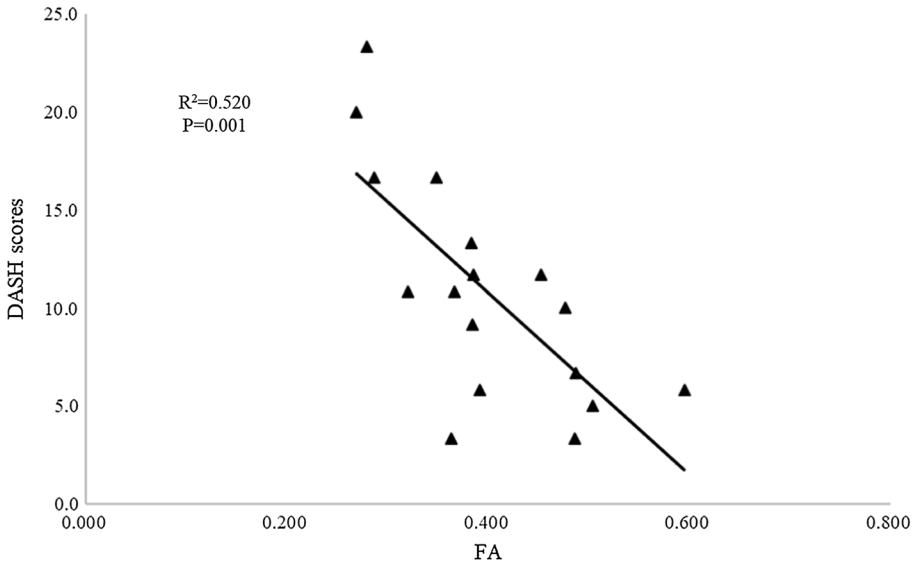

Fig. 3 Correlation between FA and DASH scores. The FA value of the dynamic compressed level is significantly correlated with DASH scores ($R^2 = 0.520$, $P = 0.001$)

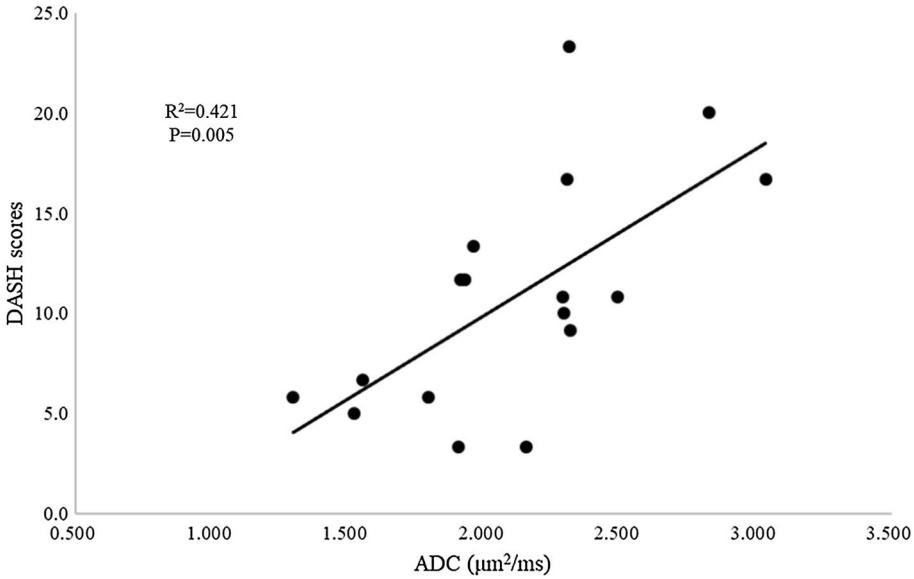

Fig. 4 Correlation between ADC and DASH scores. The ADC value of the dynamic compressed level is significantly correlated with DASH scores ($R^2 = 0.421$, $P = 0.005$)

be unclear due to a poor association between the detectable degree of cord compression and symptom manifestation. Therefore, the morphological compression and features on conventional MRI may be inaccurate.

DTI enabled noninvasive investigation of the neural architecture and function by utilizing the diffusion of water molecules to act as a probe for assessing tissue microstructure, allowing for a combination of morphological and functional examinations [19–22]. Intensive research has indicated that DTI represents a promising solution to overcome the limitations imposed by the conventional MRI performed alone. Notably, DTI parameters are detectable before the appearance of T2-weighted hyperintensity on MRI for CSM, with FA values correlated with baseline myelopathy scores, including the JOA scores and Nurick scales [20–22, 26]. Additionally, kinetic DTI has proved to be a valuable method to detect the functional change of the spinal cord in different neck positions [27].

Our study verified the feasibility of the application of a kinetic DTI scan in HD patients. The variation trends in the healthy young males reflect the normal tendency of DTI parameters in different spinal cord levels. Our results clearly show that in HD patients, FA and ADC values during cervical flexion are worse than those in the cervical neutral position. This phenomenon strongly supports the dynamic compression hypothesis of HD. However, most of these differences were insignificant. We think the time of cervical flexion was too short to cause obvious pathological changes in the spinal cord and that our sample needed to be larger. Thirty minutes for flexion might simply induce mild

swelling of neurons and axons. The actual pathogenesis is based on repetitive cervical flexion over the long term in daily life.

Since DTI parameters reflect the current status of the spinal cord, we directly compared these parameters in HD and healthy patients in a cervical neutral position as in CSM. Interestingly, the upper levels showed no difference, but the lower levels reflected significant differences, especially for the ADC values. Clinically, a majority of HD patients have a larger cervical flexion range of motion (ROM) and morphological compression in the lower levels, a phenomenon our team has reported before [15]. The results in the current study also revealed the chronically injured spinal cord in the lower levels from the perspective of neural architecture and function. We defined the dynamic compressed level's parameters based on the most and the second most abnormal FA and ADC values, as described in "Materials and methods". The compressed level's parameters obviously differed from those of the controls, which proved that they were important indices and could be used in clinic.

No known scoring scale of functional disorder for HD has been widely used so far. Although some patients with a long course of their disease could progress into abnormalities of tendon reflexes and pyramidal signs like CSM, this disease usually affects motor function in the upper extremities [4, 14]. Thus, the DASH scoring scale, which focuses on the function of the upper limbs [16, 24], can be applied to assess HD to a certain extent. Zheng et al. conducted a prospective clinical study to evaluate the outcome of surgery for HD using DASH scores, and slight improvement from preoperation to postoperation was confirmed [16]. In our study, we similarly used the DASH scoring scale to assess the functional disorder for HD and correlated those scores with the DTI parameters. FA and ADC values showed good linear correlation with DASH scores, particularly the FA values. This kind of relationship was also found in DTI research on CSM using JOA scores [22]. Our results revealed that FA and ADC values have great potential utility in evaluating the functional status of HD patients as well.

There were some limitations in the present study. First, the number of healthy young males included in the study was small, and a larger number of volunteers should be included in the future. Second, the ROI used in the mid-sagittal plane was drawn manually, which might introduce bias. The ROI covered the whole spinal cord and did not distinguish white matter from gray matter. Further investigation using ROIs in the axial plane might be able to differentiate various part of the spinal cord. Third, several spinal cord pathologies could lead to changes in DTI parameters such as spinal cord edema, myelin destruction, nerve fiber interruption, Wallerian degeneration, and demyelination. Therefore, it was not clear whether our method of determining FA and ADC values could reveal the actual spinal cord status.

Conclusions

This study was the first to evaluate the neural status of the cervical spinal cord in healthy patients and those with Hirayama disease using diffusion tensor imaging. DTI parameters could support the hypothesis of dynamic cervical flexion compression and may noninvasively reveal the morphological and functional status of nerves in HD. DTI is a valuable examination technique for precise evaluation in HD.

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Compliance with ethical standards

Conflict of interest None of the authors have any potential conflict of interest.

Human and animal right We declare that all human and animal studies have been approved by university and hospital and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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