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Evaluating growth failure with diffusion tensor imaging in pediatric survivors of high-risk neuroblastoma treated with high dose cis-retinoic acid

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Abstract

Background—The survival of patients with high-risk neuroblastoma has increased with multimodal therapy, but most survivors demonstrate growth failure.

Objective—To assess physeal abnormalities in children with high-risk neuroblastoma in comparison to normal controls by using diffusion tensor imaging (DTI) of the distal femoral physis and adjacent metaphysis.

Materials and methods—We prospectively obtained physeal DTI at 3.0 T in 20 subjects (mean age: 12.4 years, 7 females) with high-risk neuroblastoma treated with high-dose cis-retinoic acid, and 20 age- and gender-matched controls. We compared fractional anisotropy (FA), normalized tract volume (cm³/cm²) and tract concentration (tracts/cm²) between the groups, in relation to height Z-score and response to growth hormone therapy. Tractography images were evaluated qualitatively.

Results—DTI parameters were significantly lower in high-risk neuroblastoma survivors compared to controls ($P < 0.01$), particularly if the patients were exposed to both cis-retinoic acid and total body irradiation ($P < 0.05$). For survivors and controls, DTI values were respectively

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Conflicts of interest None

[mean $\pm$ standard deviation]: tract concentration (tracts/cm²), 23.2 $\pm$ 14.7 and 36.7 $\pm$ 10.5; normalized tract volume (cm³/cm²), 0.44 $\pm$ 0.27 and 0.70 $\pm$ 0.21, and FA, 0.22 $\pm$ 0.05 and 0.26 $\pm$ 0.02. High-risk neuroblastoma survivors responding to growth hormone compared to non-responders had higher FA (0.25 $\pm$ 0.04 and 0.18 $\pm$ 0.03, respectively, $P=0.02$), and tract concentration (tracts/cm²) (31.4 $\pm$ 13.7 and 14.8 $\pm$ 7.9, $P<0.05$). FA, normalized tract volume and tract concentration were linearly related to height Z-score ($R^2>0.31$; $P<0.001$). Qualitatively, tracts were nearly absent in all non-responders to growth hormone and abundant in all responders ($P=0.02$).

Conclusion—DTI shows physal abnormalities that correlate with short stature in high-risk neuroblastoma survivors and demonstrates response to growth hormone treatment.

Keywords

Children; Diffusion tensor imaging; Growth; High-risk neuroblastoma; Magnetic resonance imaging; Physis

Introduction

Neuroblastoma is one of the most common solid tumors of childhood, with an estimated 750 cases per year in the U.S. [1]. Approximately two-thirds of patients with neuroblastoma have “high-risk” disease, characterized by adverse biological and histological features, metastatic disease and/or presentation in children older than 18 months of age [2]. High-risk neuroblastoma is notoriously difficult to treat. With contemporary intensive multimodal treatment regimens including high-dose chemotherapy, stem cell transplantation, radiation therapy and the addition of novel biological agents including retinoids, immunocytokines and immunotherapy [3–6], 3-year event-free survival now exceeds 50% [7]. Unfortunately, survivors of high-risk neuroblastoma experience multiple late effects, particularly related to the intensity of treatment regimens [8–10]. Late endocrine effects are prominent, with notable growth failure, delayed puberty and severe short stature even in the absence of treatment with total body irradiation [11,12]. Cis-retinoic acid, a biological agent used to treat high-risk neuroblastoma, has a strong impact on physal function resulting in reduced physal thickness and disintegrated loss of columnar architecture [13–15].

Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) are used to evaluate physal and metaphysal structure and function [16, 17]. Previous studies in healthy subjects show that DTI depicts a region with tracts parallel to the main axis of the bone that coincides roughly with the physis and metaphysal spongiosa. The volume, number and length of the tracts are greatest during a growth spurt, peak earlier in girls than in boys, and are greater in taller children. Fractional anisotropy (FA) is a constant value with respect to age and gender in healthy subjects with open physes. Despite the association of DWI and DTI parameters with growth in children with presumed intact physes, DTI has not been used to evaluate children at risk for growth disturbances.

This study used DTI in pediatric survivors of high-risk neuroblastoma. We hypothesized that DWI and DTI demonstrate physal changes as a result of treatment for high-risk neuroblastoma, particularly related to cis-retinoic acid. Our aim was to assess whether DTI is useful in the clinical evaluation and therapy of these children with growth failure.

Materials and methods

Participants

Children and adolescents, ages 6–16 years, diagnosed with high-risk neuroblastoma and treated at our institution were eligible to participate if in complete remission (≥ 2 years). Exclusion criteria included: 1) treatment with bisphosphonates, 2) estimated glomerular filtration rate <60 ml/min/1.73m², 3) full skeletal maturity, 4) active malignancy, 5) pregnancy, 6) history of trauma or fracture of the knee, or knee symptoms at the time of imaging and 7) metallic hardware precluding MRI examination. We prospectively enrolled 20 (44%) of 45 eligible patients. Participant demographics and high-risk neuroblastoma disease characteristics did not differ between eligible patients who declined participation and those who enrolled. Twenty gender- and age- (within 1 year) matched, healthy controls were invited to participate in the study. Matched controls were excluded based on: 1) history of cancer; 2) hepatic, renal, thyroid, neuromuscular or joint disease; 3) skeletal maturity; 4) malabsorption syndromes; 5) medications impacting growth or bone mineral density such as anticonvulsants, bisphosphonates, oral contraceptives, glucocorticoid therapy (equivalent to prednisone 10 mg per day for more than 2 weeks/year), use of oral retinoids for acne; 6) pregnancy, 7) history of trauma or fracture of the knee, or knee symptoms at the time of imaging and 8) metallic hardware precluding MRI examination. The study protocol was approved by the Institutional Review Board at our institution and performed in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Informed parental consent and assent were obtained for all study participants.

Anthropometry and physical maturation

Weight was measured using a digital scale (Scaletronix, White Plains, NY) and height was measured using a stadiometer (Holtain, Crymych, UK). Pubertal stage was determined according to the method of Tanner by a pediatric endocrinologist in the high-risk neuroblastoma participants, and using a validated self-assessment questionnaire in controls [18]. Physical activity was evaluated using a validated questionnaire [19]. Tibial length was measured from the distal margin of the medial malleolus to the proximal border of the medial tibial condyle. Short stature was defined as height Z-score ≤ -1.7. Growth failure was categorized as moderate, severe or profound based on the following parameters: height Z-score < -1.7 to -2 (moderate growth failure), height Z-score < -2 to -2.5 (severe growth failure) and height Z-score < -2.5 (profound growth failure).

Neuroblastoma disease and treatment characteristics

High-risk neuroblastoma participants received treatment as per the Children's Oncology Group High Risk Neuroblastoma Consortium protocols CCG 3891, CHP594, ANBL0532, ANBL0931, ANBL00P1, ANBL0032 and ANBL1021. Medical charts were reviewed for diagnosis of high-risk neuroblastoma and treatment details including surgery, chemotherapy, radiation dose (cGy) and field, number of autologous stem cell transplants, and immunobiological and immunocytokine treatment history. Treatment-related complications including disease relapse, additional treatment and time since completion of therapy were determined. Medical (including endocrine abnormalities) and fracture history, as well as calcium and vitamin D supplements, were reviewed at the study visit.

Survivors with growth hormone deficiency were diagnosed using conventional assessment including growth failure, abnormal growth velocity for age, laboratory testing and formal stimulation testing of the growth axis. Survivors with confirmed growth hormone deficiency were treated with growth hormone using standard treatment daily dosing (0.3 mg/kg/week) and adjusted based on treatment response and laboratory evaluation at follow-up visits.

Isotretinoin (cis-retinoic acid) is a standard treatment for high-risk neuroblastoma and given as total daily dose 160 mg/m²/day x 2 weeks per month for 6 months, beginning approximately 3 months following autologous stem cell transplantation. Patients with relapse or refractory disease may receive additional courses of cis-retinoic acid. The cumulative dose of cis-retinoic acid for each participant was calculated as the sum of total mg dose (mg per m² of body surface area, multiplied by participant's body surface area) for all cycles of therapy.

MRI imaging parameters

Magnetic resonance imaging (MRI) of the right knee was performed at 3 T (Verio; Siemens Medical Systems, Erlangen, Germany) using a 15-channel knee coil (Quality Electrodynamics, Mayfield Village, OH).

DTI parameters were identical to those of previous studies of physeal DTI [16, 17]. To assess reliability, we obtained two sagittal DTI sequences per participant. Imaging consisted of a fat-suppressed single-shot spin-echo echo-planar sequence in 20 non-collinear directions; b values of 0 and 600 s/mm²; repetition time (TR) ms/echo time (TE) ms 7,100/82; matrix, 128×128; field of view, 256×256 mm; bandwidth, 1,446 Hz/pixel; parallel imaging factor, 2; signal averages, 2, and frequency selective fat-suppression with spectral adiabatic inversion recovery (SPAIR). Voxel dimensions were 2.0×2.0 mm in plane with 3.0-mm section thickness and no gap between sections. The duration of each DTI sequence was 5:20 min.

Conventional MRI images included coronal T1-weighted image (800/10 ms; matrix, 320×320; field of view, 140×140 mm; slice thickness, 3 mm; bandwidth, 269 Hz/pixel), sagittal fat-suppressed T2-weighted image (4,790/68 ms; matrix, 320×256; field of view, 140×140 mm; slice thickness, 3 mm; bandwidth, 130 Hz/pixel), and sagittal gradient-echo double-echo steady-state sequence (3-D DESS) (15.32/4.44 ms; flip angle, 25°; matrix, 320×320; field of view, 150×150 mm; slice thickness, 0.7 mm; bandwidth, 211 Hz/pixel) with coronal and axial reconstructions.

DTI segmentation and analysis

We calculated DTI and performed tractography using standard software (Diffusion Toolkit version 0.6.4, trackvis.org; Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA) [20]. To obtain physeal tracking, we used a deterministic fiber tracking algorithm with a minimum FA threshold of 0.15, and a maximum turning angle of 40° between two adjacent voxels [16, 17]. Tractographic visualization of diffusion direction was done with standard color coding (blue, superior to inferior; green, anterior to posterior, and red, right to left). A research assistant (J.D.) with 5 years of experience in DTI post-processing drew regions of interest (ROIs) in the distal femoral physes overlaying the ROI

on the color FA maps and the echo-planar images with a b value of 0 s/mm², which are part of the DTI acquisition. Every ROI on each of the two DTI sequences was drawn independently and blinded to the ROI of the other DTI sequence. All ROIs were drawn by using multiple sagittal and coronal sections. All ROIs had a single voxel in thickness in the craniocaudal direction and the size of the ROIs was dependent on the knee size. The mean ROI areas (cm²) for high-risk neuroblastoma and reference participants were 15.67 (range: 10.56–21.81) and 17.28 (range: 12.15–22.65), respectively. This technique has adequate interobserver and intraobserver agreement and sufficient signal-to-noise ratios for tractography calculation [16, 17].

ROI data were used to export apparent diffusion coefficient (ADC) and FA values, and fiber tract data were used to export absolute number of tracts, tract length and tract volume.

To account for differences in joint size (affected by a participant's age, gender and overall growth failure), absolute tract number and the tract volume were normalized by the area of the ROI:

$$\text{Tract concentration per cm}^2 = \frac{\text{Absolute tract count}}{\text{ROI area (cm}^2\text{)}}$$

$$\text{Normalized tract volume (cm}^3\text{/cm}^2\text{)} = \frac{\text{Tract Volume (cm}^3\text{)}}{\text{ROI area (cm}^2\text{)}}$$

Agreement of physeal DTI measurements

To calculate agreement of physeal DTI measurements between the two b=600 DTI sequences, we compared the ROI-based ADC and FA values, and the normalized tract volume and tract concentration.

DT images

Two pediatric musculoskeletal radiologists (D.J. and N.A.C., with 9 and 25 years of experience, respectively) blinded to all clinical information, graded the tractography maps independently according to the following scale: nearly absent tracts throughout the entire physis (grade 1), nearly absent tracts in a focal area of the physis (grade 2), short abundant tracts (grade 3) or long abundant tracts (grade 4) (Fig. 1). For statistical analyses, the scale was simplified to: 1=diffuse or focal nearly absent tracts and 2=abundant tracts.

Assessment of physeal injury on conventional MRI

Two pediatric musculoskeletal radiologists (D.J. and N.A.C.) reviewed the MR images independently, blinded to all clinical information.

We defined a bony bridge as an interruption of the physeal cartilage greater than 3 mm on sagittal or coronal DESS images. Bony bridges were central if located between 25–75% of the width of the physis in the mid-coronal plane.

A metaphyseal tongue, a cartilaginous extension into the metaphysis [21], was defined as a clear extension of high signal intensity perpendicular to the physeal plane with a width 5mm. Lastly, we recorded the presence of angular deformities and osteochondromas.

Statistical analysis

Stata 14.0 (College Station, TX) and SPSS 20.0 (IBM, Armonk, NY) were used for all analyses. A P -value <0.05 was considered significant, and two-side tests of hypotheses were used throughout. Group differences between high-risk neuroblastoma and controls were tested using the t -test or Wilcoxon rank sum test if indicated. Age- and gender-specific Z -scores for height and BMI were calculated using National Center for Health Statistics data [22]. Linear regressions were used to evaluate associations between Z -scores and DTI parameters. Interclass correlation coefficient model with absolute agreement was used to assess agreement of DTI measurements. Kappa values were used to assess agreement between raters for the qualitative DTI imaging evaluation, with values 0.60–0.74 indicating good and 0.75–1.00 excellent agreement [23].

Results

Participant disease and treatment characteristics

Forty participants (20 survivors of high-risk neuroblastoma and 20 matched, healthy controls; 7 females and 13 males per group) were studied. High-risk neuroblastoma survivors (mean age: 12.45 years, range: 9.46–16.03) and matched-control participants (mean age: 12.18 years, range: 10.36–14.11) were recruited during a 17-month period. The group characteristics are summarized in Table 1. The oldest survivor had a younger control for comparison as we were unable to find an age-matched control with open physes. One high-risk neuroblastoma survivor was excluded from the study due to multiple MR incompatible abdominal hemoclips. None of the subjects included in the study had knee fractures or a history of trauma.

There was no significant difference in demographic characteristics of the high-risk neuroblastoma and the control participants (Table 1). High-risk neuroblastoma was associated with delayed pubertal maturation. Table 1 also shows that height and weight Z -scores were markedly lower in high-risk neuroblastoma survivors, whereas body mass index Z -scores did not differ significantly. The median height Z -score was -1.73 for high-risk neuroblastoma survivors compared to height Z -score 0.34 for healthy controls ($P<0.001$). Median growth velocity was lower in high-risk neuroblastoma survivors (4.25 cm/year.) compared to controls (6.31 cm/yr.) ($P=0.02$).

Table 2 summarizes high-risk neuroblastoma disease and treatment characteristics. Seventeen high-risk neuroblastoma survivors (85%) were diagnosed with an endocrinopathy and all received appropriate hormone replacement therapy. Since this study, two of the female high-risk neuroblastoma survivors (29%) started ovarian hormone replacement for primary ovarian failure. Eleven survivors (55%) received growth hormone for deficiency.

Fifteen high-risk neuroblastoma survivors received six cycles of cis-retinoic acid (Table 2). Three survivors received slightly different schedules (5.5, 7 and 9 cycles), and two received

extended cis-retinoic acid treatment (14 and 17 cycles) due to relapse and refractory disease. Eight high-risk neuroblastoma survivors received total body irradiation (40%) (Table 2).

Conventional MRI evaluation

Three high-risk neuroblastoma survivors (3 males; age range: 11.6–14.1 years) had bony bridges involving less than 25% of the physis (2 central, 1 peripheral). Nine high-risk neuroblastoma participants had femoral metaphyseal tongues greater than 5 mm; 8 of them had undergone radiation therapy. Six high-risk neuroblastoma participants treated with growth hormone (55%) showed metaphyseal tongues, 3 responders and 3 non-responders. Osteochondromas were found in 8/20 (40%) high-risk neuroblastoma participants; 6/8 subjects with osteochondromas were treated with total body radiation.

Incidental findings included a small tibial non-ossifying fibroma and a tiny popliteal cyst among the survivors; among the control subjects, two cortical desmoids of the distal femur, a 3-mm osteochondroma of the distal femur, and two areas of minimal widening (<2 mm) of the distal medial femoral physis consistent with mild physeal stress changes were found.

Diffusion-weighted imaging measurements (Table 3)

FA was related with height Z-score ($R^2=0.323$; $P<0.001$) (Fig. 2). FA was significantly higher in controls (mean $\pm$ standard deviation [SD] $[0.26 \pm 0.02]$) than in survivors (0.22 ± 0.05) ($P<0.01$), and greater in survivors who responded to growth hormone (0.25 ± 0.04) than non-responders (0.18 ± 0.03) ($P=0.02$). ADC was smaller in controls (mean $\pm$ SD $[0.00146 \pm 0.00009]$) than in survivors (0.00154 ± 0.0001) ($P=0.04$). ADC was no different in responders to growth hormone than in non-responders ($P=0.36$).

Diffusion tensor imaging measurements (Table 3)

Normalized tract volume was related to height Z-score ($R^2=0.318$; $P<0.001$). Normalized tract volume was greater in controls (mean $\pm$ SD $[0.70 \text{ cm}^3/\text{cm}^2 \pm 0.21]$) than in high-risk neuroblastoma survivors ($0.44 \text{ cm}^3/\text{cm}^2 \pm 0.27$) ($P<0.01$), and greater trend in growth hormone responders ($0.58 \text{ cm}^3/\text{cm}^2 \pm 0.26$) than non-responders ($0.30 \text{ cm}^3/\text{cm}^2 \pm 0.14$) ($P=0.08$).

Tract concentration was related with height Z-score ($R^2=0.358$; $P<0.001$) (Fig. 3). Tract concentration was greater in controls ($36.7 \text{ tracts}/\text{cm}^2 \pm 10.5$) than high-risk neuroblastoma survivors ($23.2 \text{ tracts}/\text{cm}^2 \pm 14.7$) ($P<0.01$); and greater in growth hormone responders ($31.4 \text{ tracts}/\text{cm}^2 \pm 13.7$) than non-responders ($14.8 \text{ tracts}/\text{cm}^2 \pm 7.9$) ($P=0.05$).

Agreement of physeal DTI quantitative measurements

Agreement between quantitative measurements performed on the two DTI series done on each participant was good to excellent. Agreement between the two $b=600$ DTI sequences for the ROI-based measurements was: ADC 0.90 (95% confidence interval [CI] 0.82–0.95) and FA 0.86 (95% CI 0.76–0.93). Agreement for the tract-based measurements was tract concentration 0.91 (95% CI 0.84–0.95) and normalized tract volume 0.92 (95% CI 0.85–0.95).

Qualitative evaluation of diffusion tensor images

Nearly absent, disorganized tracts were present in seven high-risk neuroblastoma survivors (diffuse in six and focal in one), but none of the controls ($P=0.008$). All controls had abundant tracts, 8 short evenly distributed and 12 long evenly distributed. Six high-risk neuroblastoma survivors with excellent growth hormone response demonstrated abundant tracts, whereas all 5 non-responders demonstrated nearly absent tracts ($P=0.02$) (Fig. 4). Agreement for the 4-point scale was 0.67 (good) and agreement for the 2-point scale was 0.84 (excellent).

Discussion

Our study demonstrates that FA, tract concentration, tract length and tract volume are greater in healthy pediatric controls than in survivors of high-risk neuroblastoma treated with cis-retinoic acid and radiation. These parameters are also greater in survivors on growth hormone treatment with excellent clinical response compared to those with minimal treatment response. Nearly absent tracts were seen only in high-risk neuroblastoma survivors; all survivors responding to growth hormone had abundant tracts.

The FA is high when a tissue is organized and decreases with structural disorganization. In the brain, decreased FA is seen in conditions with architectural disruption such as dementia and traumatic injury [24, 25]. We believe that in high-risk neuroblastoma survivors, decreased FA reflects disorganization of the columnar architecture of the physis and metaphysis likely related to the effect of treatment with cis-retinoic acid and radiation. FA does not vary in normal physes [16]; however, our data demonstrate FA decreases with physal insults. ADC is increased in survivors compared to controls, probably due to changes in the cartilage from the increased death of chondrocytes and degradation of the cartilage matrix.

The DTI metrics revealed fewer, shorter tracts and an overall smaller volume of tracts in high-risk neuroblastoma survivors. We hypothesize that tract concentration, length and volume reflect the number and length of parallel columns of cartilage and new bone resulting in organized diffusion. A reduction in chondrocyte columns or disorganization will result in a lack of a palisade arrangement and subsequent diminished tracts. The physal changes that result from cis-retinoic acid and radiation decrease the number and length of functional columns [14, 26, 27]. DTI metrics, therefore, reflect abnormalities in the physis that mirror the expected histological changes. Tract length is a less sensitive metric affected by noise and certain technical factors. The visual inspection of the tractography maps confirms these abnormalities: Nearly absent tracts were only found in survivors, whereas all controls and survivors who responded to growth hormone had abundant tracts.

Although exposure to cis-retinoic acid results clinically in considerably greater growth failure than total body irradiation, the two factors play a role. Teasing the relative influence of both is beyond the scope of the study, although it is clear that many patients in the cohort had growth failure despite a lack of prior exposure to radiation. Our objective was to evaluate growth failure with DTI and show that patients with growth failure had parameters that were significantly lower than controls.

DTI is not just an instrument to depict physeal and metaphyseal abnormalities; it can also serve as a clinical tool to aid management. Many children diagnosed with growth hormone deficiency are treated with growth hormone. The clinical prediction of response and the assessment of therapeutic effect are inefficient and often require a year or more time to assess treatment response after initiation of growth hormone therapy. Thus, DTI may help select patients with a relatively intact physis with better potential for adequate responses to growth hormone therapy. Importantly, DTI may identify early treatment responders and non-responders before measurable anthropometric changes in stature over a year, which is the current clinical parameter used to assess treatment response. Our study suggests that growth hormone non responders demonstrate differences in DTI compared to responders (Fig. 4), but more data are needed to evaluate the value of DTI in showing growth hormone response.

The limitations of this study include the small number of patients (pilot study) and lack of histological confirmation to assess treatment-related damage to the physis and metaphysis. Additional limitations include variation in high-risk neuroblastoma therapies for participants including the administration of whole-body radiation to 40% of subjects, and variability in the interval since cancer therapy completion. Nonetheless, the variability was markedly lower than prior high-risk neuroblastoma studies and all high-risk neuroblastoma participants were treated with a minimum six courses of cis-retinoic acid. Given challenges in remission and survival, our group represents a large cohort for high-risk neuroblastoma survivors recruited before physeal closure.

This study has several strengths. First, it represents the first use of DTI of the physis and metaphysis to assess growth disturbance. Second, it is the first study to enroll young survivors of high-risk neuroblastoma after completion of treatment with subsequent assessment of the physis. Third, the inclusion of a matched, healthy control group facilitated adjustment for DTI outcomes and thus accounted for normal growth and developmental changes expected in the physis.

Conclusion

DTI shows physeal abnormalities that correlate with short stature in high-risk neuroblastoma survivors. A larger study is necessary to evaluate the utility of DTI as a tool to monitor responses to growth hormone therapy.

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Fig. 1.

Grading scale for evaluating physeal tractography pattern on coronal diffusion tensor images. **a** A 14-year-old girl, a high-risk neuroblastoma survivor without growth hormone treatment with nearly absent tracts throughout the entire physis (grade 1). **b** A 14-year-old boy, a high-risk neuroblastoma survivor non-responder to growth hormone treatment with nearly absent tracts in a focal area of the physis (grade 2). **c** A 10-year-old boy, a high-risk neuroblastoma survivor responder to growth hormone treatment with short abundant tracts (grade 3). **d** A 12-year-old girl (control subject) with long abundant tracts (grade 4). For all analyses, the scale was simplified to: diffuse or focal nearly absent tracts (grades 1 and 2) and abundant tracts (grades 3 and 4). Standard color coding for diffusion direction was used (blue, superior to inferior; green, anterior to posterior, and red, right to left)

Fig. 2.

A scatterplot with linear regression shows the relationship between fractional anisotropy (FA) value and height Z-score. Survivors (cases) tend to have lower FA values and height Z-score

Fig. 3. A scatterplot with linear regression graph shows the relationship between tract concentration and height Z-score. Survivors (cases) tend to have lower tract concentration and height Z-score.

Fig. 4.

A comparison of coronal DESS and DTI in a 12-year-old male high-risk neuroblastoma survivor who responded to growth hormone (**a** and **c**) and a 13.5-year-old male high-risk neuroblastoma survivor who didn't respond to growth hormone (**b** and **d**). Although the physes are open in both survivors on the DESS images, the tracts are abundant in the responder and nearly absent in the non-responder

Table 1

Characteristics in high-risk neuroblastoma and matched-control participants

	HR-neuroblastoma <i>n</i> =20)	Matched controls ^a (n20)	<i>P</i> -value
Age, years	12.4±1.6	12.2±1.1	--
Gender, male	13 (65%)	13 (65%)	--
Race, black	4 (20%)	4 (20%)	--
Pubertal status			
Tanner Stage 1	10 (50%)	6 (30%)	0.33
Tanner Stages 2–3	9 (45%)	8 (40%)	>0.99
Tanner Stages 4–5	1 (5%)	6 (30%)	0.09
Weight (kg)	35.8±9.9	46.5±12.6 *44.0 (32.3 to 86.4)	<0.01
Weight Z-score	−1.30±1.43	0.34±0.96	<0.001
Sitting height (cm)	117.0±6.1	123.7±5.4	<0.001
Height (cm)	139.7±12.0	153.5±10.1	<0.001
Height Z-score	−1.73±1.38	0.34±1.12	<0.001
BMI (kg/m ²)	18.0±2.4	19.5±3.6 *18.8 (16.3 to 30.8)	0.13
BMI Z-score	−0.25±0.93	0.30±0.90	0.09
Physical activity level ^b	2.6±0.7	2.4±0.6	0.47

Values are *n* (%) or mean±standard deviation.

* Data were skewed so values are also reported as median (range)

^aControls were gender-, race- and age-matched (± 1 year) to high-risk neuroblastoma participants^bPhysical activity level was quantified using the Physical Activity Questionnaire for Older Children (PAQ-C) or Adolescents (PAQ-A), where applicable [19]*BMI* body mass index, *NS* not significant

Table 2

Disease and treatment characteristics in high-risk neuroblastoma participants

Characteristics	
Age at study enrollment, years	12.2 (9.5 to 15.8)
Age at diagnosis, years	2.8 (0.3 to 9.1)
Total body irradiation	8 (40%)
Cis-retinoic acid	20 (100%)
Cumulative dose (mg)	8,540 (5,040 to 27,580)
Endocrine abnormalities, <i>n</i> (%)	
Hypothyroidism on treatment	10 (50%)
Growth hormone deficient	15 (75%)
Growth hormone therapy	11 (55%)
On growth hormone therapy at visit	11 (55%)
Response to growth hormone therapy	6 (55%)

Values are *n* (%) or median (range)

Table 3

Quantitative diffusion tensor imaging parameters in high-risk neuroblastoma and control participants *

	HR-neuroblastoma (n=20)	Matched controls ^a (n=20)	P-value
ROI ADC	0.00154±0.0001	0.00146±0.00009	0.04
ROI FA	0.22±0.05	0.26±0.02	<0.01
Normalized tract volume (cm ³ /cm ²)	0.44±0.27	0.70±0.21	<0.01
Tract concentration (tracts/cm ²)	23.2±14.7	36.7±10.5	<0.01
Mean tract length (mm)	6.12±1.77	7.15±1.50	0.03

* mean ± 1 standard deviation

^a Controls were gender-, race-, and age-matched (± 1 year) to high-risk neuroblastoma participants

ADC apparent diffusion coefficient, FA fractional anisotropy, HR high risk, ROI region of interest

Table 4

Quantitative diffusion tensor imaging parameters in high-risk neuroblastoma participants who were responders and non-responders to growth hormone therapy^{*}

	Responders to growth hormone (n=6)	Non-responders to growth hormone (n=5)	P-value
ROI ADC	0.00155±0.000068	0.00160±0.000117	0.36
ROI FA	0.25±0.04	0.18±0.03	0.02
Normalized tract volume (cm ³ /cm ²)	0.58±0.26	0.30±0.14	0.08
Tract concentration (tracts/cm ²)	31.4±3.7	14.8±7.9	0.05
Mean tract length (mm)	6.45±2.73	6.57±1.59	0.86

^{*} mean ± 1 standard deviation

ADC apparent diffusion coefficient, *FA* fractional anisotropy, *ROI* region of interest