Original Article

Microstructure changes of occipital white matter are responsible for visual problems in the 3–4-year-old very low birth weight children

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Purpose: The main aim of the study was to evaluate which factors affect the long-time visual function in preterm children, whether it is prematurity or retinopathy of prematurity or perhaps disturbances in the visual pathway. **Materials and Methods:** Fifty-eight children with mean birth weight 1016 g (range 520–1500 g) were evaluated at mean age 48 months (range 42–54 months). All children underwent magnetic resonance imaging (MRI) studies, visual evoked potentials (VEPs), and the Developmental Test of Visual Perception (DTVP). The MRI evaluation included diffusion tensor imaging and fractional anisotropy (FA), and colored orientation maps were calculated for each subject. Based on the results of the VEP evaluation, children were divided into two groups: A-abnormal results of VEP (n = 16) and B-normal VEP results (comparison group, n = 42). **Results:** FA values of inferior left and right occipital white matter (OWM) were lower in the group of children with abnormal VEP compared to the comparison group (0.34 ± 0.06 vs. 0.38 ± 0.06; P = 0.047; 0.31 ± 0.04 vs. 0.36 ± 0.06; P = 0.007, respectively). Furthermore, there were correlations between the latency (r = −0.35; P = 0.01) and amplitude (r = 0.31; P = 0.02) and FA in OWM. Children with abnormal VEP had lower DTVP scores as compared with children with normal VEP results (88 ± 18 vs. 95 ± 16 points, P = 0.048). Finally, a multivariate logistic regression revealed that FA of the inferior OWM was the only independent risk factor for the abnormal VEP (P = 0.04). **Conclusion:** Visual perception, VEPs, and white matter microstructural abnormalities in very low birth weight children at the age of 3–4 are significantly correlated.

Key words: Diffusion tensor imaging, retinopathy of prematurity, very low birth weight infants, visual evoked potentials

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Scientific and technological advances in medicine during the last few decades have been associated with enormous changes in obstetric and perinatal care. The increased use of prenatal steroids and surfactant replacement therapy for premature newborns are the two most important factors in reducing neonatal mortality in very low birth weight (VLBW-birth weight <1.5 kg) children.[1,2] Furthermore, a significant decrease of severe premature birth complications such as cerebral hemorrhages, periventricular leukomalacia, and retinopathy of prematurity (ROP) is observed. Many VLBW children although discharged from hospitals in general good condition, with time present multiple developmental difficulties and cognitive disorders, including visual perception problems, which cannot always be explained by focal retinal or brain lesions.[3,4] The introduction of modern diagnostic tests such as diffusion tensor imaging magnetic resonance (DTI-MR) and combining these studies with previously available methods such as visual evoked potential (VEP) examination and psychological evaluation may help to find the cause of late visual dysfunction in VLBW children.

Using DTI-MR, it is possible to assess the white matter (WM) tracts in different regions of the brain by determining the dominant direction of water diffusion in the tissues. Water diffuses more rapidly in the direction aligned with the internal structure, and more slowly, as it moves perpendicularly to the preferred direction.[5] DTI-MR enables higher sensitivity and accuracy of imaging, helping to assess WM microstructural abnormalities of the preterm brain, which are not always apparent on conventional magnetic resonance imaging (MRI).[6] DTI MRI allows for the measurement of fractional anisotropy (FA): value derived from axial and radial diffusivity. Higher FA values signify a high degree of anisotropy and may indicate better axonal organization and normal myelination.[7,8]

VEP is used primarily to measure the functional integrity of the visual pathways from the retina through the optic nerves to the visual cortex of the brain. It refers to electrical potentials, initiated by brief visual stimuli: A black and white checkerboard (pattern VEP [PVEP]) or a flash of light (flash

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VEP) which are recorded from the scalp overlying visual cortex.[9] The test is performed in accordance with the current standard established by International Society for Clinical Electrophysiology of Vision.[10]

The main aim of the study was to evaluate which factors affect the long-time visual function in preterm children, whether it is prematurity *per se* or ROP or perhaps a disturbance of the visual pathway. The results of the following methods have been compared and correlated: DTI-MRI, VEP, and Developmental Test of Visual Perception (DTVP).

Materials and Methods

Materials

A prospective study was conducted between February 1, 2013, and May 31, 2015.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Methods

After signing the informed consent by the parents, detailed ophthalmologic evaluation including VEP, MRI, and psychomotor evaluation was performed in all children.

Ophthalmologic evaluation

The electrophysiological examination was carried out using the TOMEY EP-1000 device. The patients had three electrodes attached according to the international system 10/20: an active electrode in occipital area, a reference electrode about 11 cm away from the nasal bridge on the midline, and a grounding electrode on the earlobe. The patients were seated 1 M away from a 17" monitor (19.5°) with the spectacle correction if it was necessary. Mean luminance of the display was 50 cd/m^2. The contrast between the black and white squares was about 90%. The stimulating pattern of the checkerboard was used in the reversal mode, i.e., black sites were changed into the white ones and vice versa. Stimulation in the on-off mode, where the pattern is alternately switched on and off, may also be used. The patients underwent a clinical protocol with two check sizes: 0.4° and 2.5°. The pattern of the black and white checkerboard with alternate change of phases with 1–2 Hz frequency enables to obtain a transient VEP curve. Duration of the study attributable to a single rate of the pattern was 3 min, and the total time was about 6–10 min per eye. VEPs were recorded monocularly for each check size. Fixation was monitored by the observer, and data were collected only when the child was looking at the pattern. As a result of the above procedure, a transient PVEP curve, composed of a negative N1 wave (N 75) and positive wave (P100), is formed. Other waves were not used in the analysis. Amplitudes and latency time of the P100 wave were assessed.

Magnetic resonance imaging study

Children were subjected to MRI studies using a 1.5T GE HDxt system (General Electric Healthcare, Milwaukee, WI, USA) equipped with an 8-channel head coil. The examination was performed without general anesthesia (the single low dose of midazolam – 0.1 mg/kg – was proposed only to decrease the level of anxiety). Morphological brain changes were assessed using standard sequences:

- Propeller T2 fast spin echo sequence in axial plane (slice thickness 4.0 mm, spacing 2.0 mm, TR 6000 ms, TE 97 ms, FOV 24 cm, matrix 320 × 320)
- T2 FRFSE-XL fast spin echo sequences in sagittal plane (slice thickness 4.0 mm, spacing 2.0 mm TR 3660 ms, TE 88 ms, FOV 24 cm, matrix 384 × 224)
- T2 FRFSE-XL fast spin echo sequences in coronal plane (slice thickness 4.0 mm, spacing 2.0 mm TR 4600 ms, TE 88 ms, FOV 24 cm, matrix 384 × 224)
- Propeller T2 FLAIR in axial plane (slice thickness 4.0 mm, spacing 2.0 mm, TR 8000 ms, TE 123 ms, T1 8000 ms, FOV 24 cm, matrix 288 × 288)
- T1 spin echo sequence in axial plane (slice thickness 4.0 mm, spacing 2.0 mm, TR 320 ms, TE 9 ms, FOV 24 cm, matrix 512 × 224)
- Gradient recalled echo T2* gradient echo sequence in axial plane (slice thickness 4.0 mm, spacing 2.0 mm, TR 720 ms, TE 15 ms, flip angle 20, FOV 24 cm, matrix 320 × 192)
- Fast spoiled gradient echo (FSPGR) T1 gradient echo IR prepared sequence in axial, coronal, and sagittal plane (slice thickness 2.0 mm, spacing - 1.0 mm, TR 10 ms, TE 4.4 ms, TI 450 ms, flip angle 12, FOV 20 cm, matrix 320 × 192)
- Diffusion weighted imaging (DWI) echo planar imaging (DWEPI) sequence in axial plane (slice thickness 4.0 mm, spacing 2.0 mm, TR 8000 ms, TE 98 ms, FOV 24 cm, matrix 128 × 128)
- Diffusion tensor imaging (DTI) echo planar imaging (DWEPI) sequence in axial, coronal, and sagittal plane (slice thickness 5.0 mm, spacing 1.0 mm, TR 8000 ms, TE 109,7 ms, FOV 20 cm, matrix 128 × 128). The diffusion gradient for b = 1000 s/mm^2 were oriented in 25 directions. For each subject, FA and colored orientation maps were calculated. DTI analysis was performed using Functool Image Analysis Software (GE healthcare, Chicago, Illinois, USA).

All sequences were performed in axial, sagittal, and coronal plane. The diffusion gradient for b = 1000 s/mm^2 was oriented in 25 directions.

Analysis of the microstructure of white matter

The integrity of WM connections was scrutinized using gradient DTI sequence. To objectively evaluate microstructural changes of WM, six regions of interest were selected: left and right superior occipital white matter (OWM) [Fig. 1], left and right inferior OWM, and (as control regions) left and right posterior limbs of the internal capsule (PLIC) [Fig. 2]. Apparent diffusion coefficient, FA, and attenuation coefficient values were calculated for each region.

The MRI evaluators were not informed about the results of visual examinations.

Psychomotor development

The neurodevelopmental examination was conducted with the use of the Leiter scale and DTVP.

Leiter scale is a nonverbal psychometric evaluation containing 52 subtests. The scale is designed for children from 3 to 15 years of age. It is a measure of nonverbal intelligence. It was the only standardized test for children aged 4 years available at the time of the study.

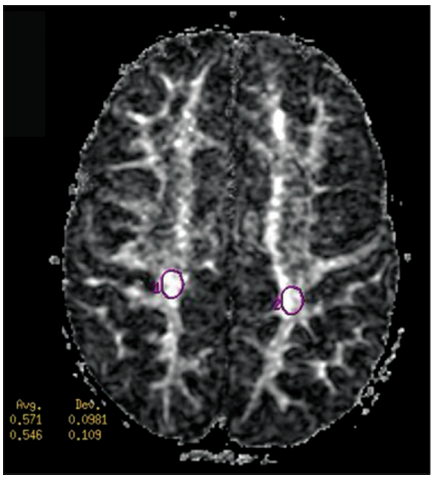

Figure 1: Axial plane images obtained at the level just above the superior margins of the lateral ventricles. The fractional anisotropy gray map was used to determine the regions of interest located in the superior occipital white matter (1 - right side, 2 - left side)

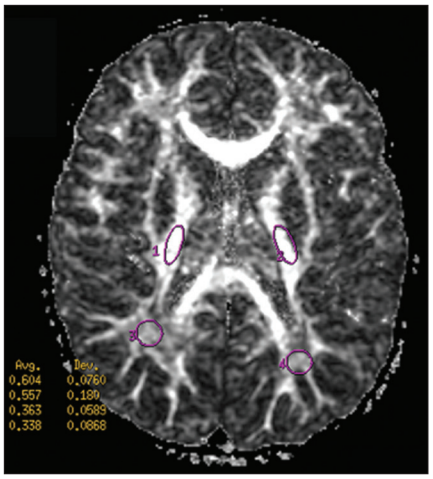

Figure 2: Axial plane images obtained at the level of the basal ganglia and posterior limb of internal capsule. The fractional anisotropy gray map was used to determine the regions of interest located in the middle third of the posterior limbs of internal capsule (1 - right side, 2 - left side) and occipital white matter (3 - right side, 4 - left side)

DTVP-visual perceptive abilities were examined using the most recent polish revised version of the classic Marianne Frostig DTVP. All children were examined using five subtests. In the eye-motor coordination test, they were asked to draw straight or curved lines according to given boundaries. The figure-ground test aimed at isolation of simple, defined figures hidden in an increasingly complex backgrounds. In the constancy of shape, test children were asked to find as many partially covered figures as possible. During the position in space test, children were shown a stimulus figure and asked to choose a corresponding or different one from a series of figures. Finally, in the spatial relationships test, children were shown increasingly complicated line arrangements and asked to copy them. DTVP has been validated and proved to be internally consistent, when compared to other established tools assessing visual perception, such as Beery-Buktenica Developmental Test of visual-motor integration (VMI) and Test of Visual Perceptual Skills-3.[11]

Outcome variables

Primary outcome variable was defined as an abnormal VEP result.

Normal values for latency time in our laboratory ranges from 85 to 115 ms, whereas the amplitude should be over 10 μV. Based on the latency results (three of the four measurements must be correct), the patients were divided into three groups: the group with normal result of the PVEP examination, the group with the abnormal result, and the group of patients who were not examined or the examination did not fulfill quality criteria.

Secondary outcomes included absolute values of latency (P100) and amplitude.

Statistical analysis

The Student's *t*-test, Mann–Whitney U-test, or Fisher's exact test were utilized to compare variables between the groups [Table 1]. Factors associated with abnormal VEP results in univariate analyses were entered as covariates for logistic regression analysis. Logistic regression was performed to estimate odds ratios for abnormal VEP among former VLBW infants. The Pearson's test was used for estimation of the correlations between psychomotor tests results, VEP-derived values, and MRI parameters. The data were analyzed using SPSS Software (version 22, 2013 by IBM Corporation, Armonk, NY, USA).

Results

Eighty-two children born prematurely among 101 survivors discharged home from our unit between October 1, 2008, and October 31, 2010, had responded to our invitation. The psychomotor tests were performed in all children; however, the VEP was evaluated only in 71 infants. The VEP examination was contraindicated in seven children due to the history of epilepsy. Four children did not cooperate and were also excluded from the study. Among 71 VEP-examined children, parents of 59 children agreed to participate in the MRI study. The result of one MRI study had low quality so finally, the analyzed population included 58 children. The patients were evaluated at the mean age of 48 months (range 42–54). The mean birth weight of included children amounted to 1016 g (standard deviation 250 g).

Based on the results of the VEP evaluation, children were divided into two groups: Group A – abnormal results of VEP (n = 16) and Group B – normal VEP results (n = 42). The comparison of selected demographic variables is shown in Table 1. The groups were similar with respect to age and gender. Children with abnormal VEP were nonsignificantly more immature, however, their body mass at birth was significantly lower than in the comparison group. Univariate analysis showed that the history of ROP was a significant risk factor for abnormal VEP at the age of 4 years in VLBW children.

Table 2 presents the result of diffusion-weighted imaging measurements in the areas of OWM and PLIC. The FA values of inferior right OWM were significantly higher in the comparison group compared to the group of children with abnormal VEP. No other DTI parameters correlated with the VEP status. Similar results were obtained using ROP as a covariate in statistical analysis.

There were significant correlations between the latency and amplitude measured during VEP procedure and FA values in inferior OWM voxels [Table 3 and Fig. 3] shows correlations between latency, amplitude, and FA values in inferior OWM voxels.

The analysis of the results of the psychomotor evaluation showed that the children with abnormal VEP had significantly lower DTVP scores as compared with the children with normal VEP results (81 ± 18 vs. 95 ± 16 points; $P = 0.008$). The results of the Leiter test were similar in both groups (96 ± 18 vs. 99 ± 18 points; $P = 0.57$). In addition, the DTVP scores correlated not only with the latency and amplitude after high-contrast chessboard stimulation but also with the FA measurements of inferior OWM [Table 4].

Table 1: Comparison of selected demographic and clinical variables between children with abnormal visual evoked potential and the control group*

	Abnormal VEP (*n*=16)	Control group (*n*=42)	*P*
Birth weight (mean±SD)	864±255	1073±224	0.003†
Gestational age (mean±SD)	26.8±1.9	28.2±2.1	0.02†
Male (%)	9 (56)	21 (50)	0.77‡
Vaginal delivery (%)	4 (25)	17 (41)	0.37‡
Small for gestational age (%)	4 (25)	4 (10)	0.2‡
5 min Apgar score median; (25^{th}-75^{th} percentile)	5 (3-7)	6 (5-7)	0.2§
Age at evaluation (months) median (25^{th}-75^{th} percentile)	48 (46-50)	48 (46-49)	0.9§
ROP requiring laser-therapy (%)	12 (75)	11 (26)	0.001‡
IVH Grade III (%)	3 (19)	4 (10)	0.38‡
IVH Grade IV	0	0	1.0‡
PVL (%)	2 (12.5)	3 (7)	0.61‡

*Expressed as a, *n* (%) of patients unless otherwise indicated, †*P* value for Student's *t*-test, ‡Fisher's exact test, §Mann-Whitney U-test. ROP: Retinopathy of prematurity, IVH: Intraventricular hemorrhage, PVL: Periventricular leukomalacia, SD: Standard deviation, VEP: Visual evoked potential

Table 2: Comparison of selected fractional anisotropy values measured on the axial magnetic resonance imaging scans between children with abnormal visual evoked potential and the control group*

	Abnormal VEP (*n*=16)	Control group (*n*=42)	Student's *t*-test (*P*)
FA values of the left OWM at the level just above the superior margins of the lateral ventricles	0.39 (0.07)	0.39 (0.05)	0.8
FA values of the right OWM at the level just above the superior margins of the lateral ventricles	0.39 (0.07)	0.38 (0.06)	0.7
FA values of the left OWM at the level of the basal ganglia and PLIC	0.34 (0.06)	0.38 (0.06)	0.047
FA values of the right OWM at the level of the basal ganglia and PLIC	0.31 (0.04)	0.36 (0.06)	0.007
FA values of the left PLIC at the level of the basal ganglia and PLIC	0.55 (0.06)	0.55 (0.06)	0.7
FA values of the right PLIC at the level of the basal ganglia and PLIC	0.54 (0.05)	0.54 (0.06)	0.9

*Expressed as a mean (SD). SD: Standard deviation, FA: Fractional anisotropy, PLIC: Posterior limb of internal capsule, OWM: Occipital white matter, VEP: Visual evoked potential

Table 3: Correlation between the results of visual evoked potential and selected magnetic resonance imaging variables in the group of 3-4-year-old very low birth weight infants

	Latency (high contrast)	Amplitude (high contrast)	Latency (low contrast)	Amplitude (low contrast)
FA value of the superior WM	−0.08	0.12	0.11	0.07
P	0.57	0.52	0.27	0.75
FA value of the inferior WM	−0.35	0.31	−0.41	0.11
P	0.01	0.02	0.001	0.22
FA value of the PLIC	−0.12	−0.12	−0.08	−0.11
P	0.2	0.19	0.54	0.27

Data are presented as correlation coefficient value (*r*) and *P* value for Pearson test. FA: Fractional anisotropy, WM: White matter, PLIC: Posterior limb of internal capsule

Finally, a multivariate logistic regression revealed that the FA of the inferior OWM was the only independent risk for the abnormal VEP [Table 5].

Discussion

This study assessed the relationship between the results of VEP and brain microstructure in a cohort of VLBW children at the age of 3–4 years. The study links abnormalities of VEP with the structure of OWM. One of the primary goals of our study was to combine electrophysiological evaluation (VEP) and psychological assessment with modern imaging techniques to improve our understanding of pathophysiology of late visual problems in VLBW children.

All children participating in our study have been subjected to a thorough and systematic multidisciplinary follow-up that was initiated on discharge and continued throughout the whole observation period. To further objectify our results, we introduced blinding in MRI assessment. The person describing the study results was not aware of the patient's data, group assignment or VEP, and psychomotor tests results.

Table 4: Correlation between the developmental test of visual perception scores and results of visual evoked potential and selected magnetic resonance imaging variables in the group of 3-4-year-olds very low birth weight infants

	r for Pearson test	*P*
Latency (high contrast)	−0.30	0.004
Amplitude (high contrast)	0.28	0.005
Latency (low contrast)	−0.17	0.08
Amplitude (low contrast)	0.18	0.07
FA value of the superior OWM	0.19	0.06
FA value of the inferior OWM	0.24	0.012
FA value of the PLIC	0.04	0.67

FA: Fractional anisotropy, OWM: Occipital white matter, PLIC: Posterior limb of internal capsule

Table 5: Logistic regression analysis with abnormal visual evoked potential as the outcome variable

Factor	OR (95% CI)	*P*
Birth weight (/100 g)	0.83 (0.59-1.16)	0.43
ROP	1.90 (0.38-9.5)	0.28
FA of the OWM (/0.1)	0.37 (0.14-0.98)	0.04

ROP: Retinopathy of prematurity, FA: Fractional anisotropy, OR: Odds ratio, CI: Confidence interval, OWM: Occipital white matter

The PVEP is an electrophysiological appraisal of the entire visual pathway from photoreceptors to areas 17, 18, and 19 of the occipital cortex. The application of this method in preterm infants was described in 1987.[12] Taylor *et al*. found the existence of disparities in the development of ocular function in intrauterine and extrauterine environment in 75 children born between 22 and 42 weeks of gestation. In 1995, Leaf *et al*. performed VEP examination in children between 3 and 6 months of age in groups of term and preterm infants. The authors concluded that VEP was very useful to monitor the development of visual function in both groups.[13] More recently, the clinical utility of VEP in premature neonates has been confirmed by Feng *et al*.[14,15] It is known that the result of VEP depends on retinal development, optic nerve myelination, lateral geniculate nucleus maturation, and occipital cortex development, but there are still some controversies about the influence of ROP on VEP examination results in preterm children.[16,17]

It the present study, children were divided into two groups: with abnormal results of VEP ($n = 16$, 28%) and with normal VEP results ($n = 42$, 72%) depending on the analysis of amplitude and latency of P100 wave. The prevalence of VEP abnormalities in the study group was high. The explanation of this observation is probably the fact that the study was conducted on a specific group of patients. All children were outborn most often in district hospitals without adequate prenatal care. The prenatal steroid rate was only 35%. Moreover, the incidence of ROP in these children was 40%. From one point of view, it is the major limitation of the study, however, uniqueness of this group allows to carry out scheduled evaluation and to answer the question what is the cause of late visual disturbances in VLBW children. Univariate analysis showed that birth weight and history of ROP were significant risk factors for abnormal VEP at the age of 4 years in VLBW children.

It has been suggested that minor visual disorders in children born preterm may have a cerebral origin even with normal conventional MRI findings.[18,19] Immaturity of WM microstructure in preterm neonates has been previously

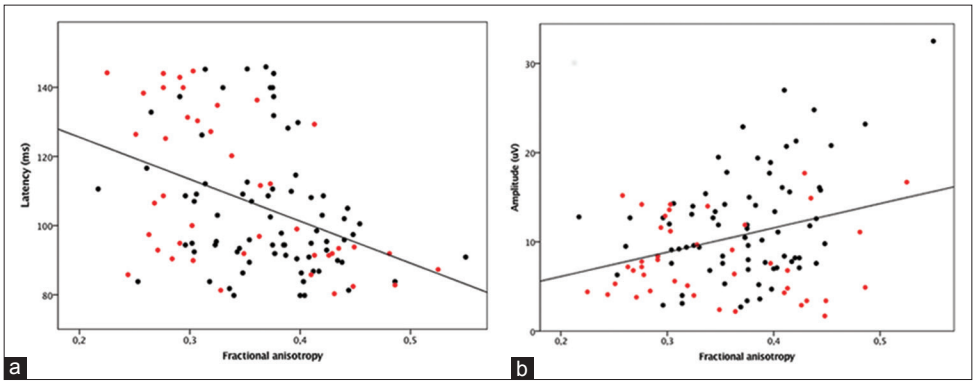

Figure 3: Correlation between fractional anisotropy measurements of the occipital white matter at the level of basal ganglia and posterior limb of internal capsule and the P100 latency (a) and amplitude (b) after high-contrast chessboard stimulation. Red dots indicate children with the history of retinopathy of prematurity, black dots – children without retinopathy during early infancy

described using DTI.[20] DTI is a highly sensitive technique for investigating the integrity of WM microstructure and can be very useful in assessing the optic tract integrity by FA measurements.[20-22] Correlation between VEP and FA has been already confirmed in patients with neuromyelitis optica and sclerosis multiplex.[23,24] Our results show that FA values of inferior left and right OWM were significantly higher in the comparison group compared to the group of children with abnormal VEP. This has been not recorded in superior OWM. Furthermore, there was a correlation between the latency and amplitude and FA in OWM. The abnormality of FA in inferior OWM may result from its immaturity or perhaps from greater susceptibility of this area to damage and hypoxia.

VLBW children perform significantly worse on a simple neurodevelopmental examination compared to term-born individuals.[25] Visual-motor impairment can have far-reaching consequences including perceptual, cognitive, and mental health disorders in preterm born children and adults.[26-29] To assess visual perceptive abilities, we used the DTVP-3, most recent revised version of the classic Marianne Frostig DTVP which offers a useful measure of visual perception and visual-motor skills integration in children. The analysis of the outcomes showed that children with abnormal VEP had significantly lower DTVP scores as compared to children with normal VEP results. Furthermore, we found that low scores in psychomotor evaluation were notably related to FA values of the right and left OWM in VLBW children. The correlation between scores of the developmental test of VMI and FA values was also confirmed by Skranes *et al*.[21] VMI, motor coordination, and visual–perceptual impairments in preterm VLBW individuals may have a common etiology associated with microstructural changes of the WM.

Our study has some limitations. The lack of control group of healthy term individuals hinders our ability to precisely estimate the impact of the microstructural abnormalities. Finally, the sample size of the study cohort and the analysis protocol optimized primarily for clinical use preclude drawing large-scale population-wide conclusions. The scope of data accessible for analysis was also limited due to restrictions imposed by the software package that was used.

Conclusion

We found a significant correlation between VEPs, perception, and microstructure of the OWM in VLBW children at the age of 3–4.

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Conflicts of interest

There are no conflicts of interest.

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