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Research paper

Visual evoked potentials after hematopoietic allogeneic stem cell transplantation in childhood

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ABSTRACT

Objective: To study visual pathway pathology detected by visual evoked potentials (VEPs) in patients treated with hematopoietic stem cell transplantation (HSCT) in childhood and to determine the impact of adverse ocular findings, somatic diseases, and conditioning regimens on the VEP results.
Methods: Ophthalmological assessments including pattern VEPs were performed in 47 of 79 patients at a median age of 15 years (range 3–21 years) in median 6 years (1–17 years) after HSCT. Somatic data were extracted from medical records.
Results: Eight patients of 47 (17%) demonstrated pathological VEPs with prolonged latencies bilaterally (n = 3) or unilaterally (n = 5) at their latest VEP test at an age of 12–18 years. A subnormal visual acuity was present in 8/11 eyes with pathological VEPs: one eye had cataract, six eyes had cataract surgery where of two had developed secondary cataracts. One eye had residual retinopathy of prematurity. Pathological VEPs were associated with decreased visual acuity ($p = 0.00019$) but not linked to gender, malignant diagnosis or conditioning.
Conclusion: VEP recordings showed an association with decreased visual acuity but no relationship with irradiation or chemotherapy in the present study.
Significance: VEP recordings might be of clinical value for children with an unexplained subnormal visual acuity undergoing HSCT.

1. Introduction

Transplantation of allogenic hematopoietic stem cells (HSCT) is a recognized treatment for children with severe diseases like leukaemia, other haematological malignancies or non-malignant haematological diseases, immuno-deficiencies, and or inborn errors of metabolism. HSCT offers children who do not respond to conventional treatment a chance. In HSCT the child receives a human leukocyte antigen (HLA) matched, or sometimes mismatched, graft from a sibling, other family member or an unrelated individual. The five-year probability of survival in children diagnosed with malignant and non-malignant disease is now between 60–90% (Remberger et al., 2011; Locatelli et al., 2015; Rousso et al., 2015).

Before the transplant a conditioning regimen is given, to eradicate the disease or to reduce it to a minimal state and to suppress the patient's immune system to allow the engraftment. In general, a standard conditioning regimen for malignant and non-malignant diseases historically has included total body irradiation (TBI), systemic chemotherapy or both. After the HSCT, cyclosporine A (CyA) is used to prevent rejection and graft versus host disease

Abbreviations: BCVA, best corrected visual acuity; CI, cranial irradiation; CNS, central nervous system; CT, computerized tomography; CyA, cyclosporine A; f-TBI, fractionated total body irradiation; GVHD, graft versus host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; IOL, intra ocular lens; MRI, magnetic resonance imaging; ROP, retinopathy of prematurity; s-TBI, single fractio total body irradiation; VEP, visual evoked potentials; TBI, total body irradiation.

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(GVHD) during approximately the first year after HSCT. GVHD is usually treated with corticosteroids.

The conditioning regimen and treatment after HSCT may inflict detrimental effects on the central nervous system (CNS). TBI has been described as damaging the developing brain and causing different neurological and cognitive complications (Phipps et al., 2008; Willard et al., 2014) as have busulfan and CyA (Barba et al., 2009; Azik et al., 2014). Cyclosporine A has been linked to increased intracranial pressure, visual disturbances, papilloedema (Tear Fahnehjelm et al., 2016) and encephalopathy (Shah, 1999; NOE et al., 2010) as well as CNS abnormalities visible on magnetic resonance imaging (MRI) or computerized tomography (CT) scans (Trullemans et al., 2001; Bartynski et al., 2004).

Ocular complications reported in children treated with TBI and or chemotherapy are cataract (Locatelli et al., 1993; De Marco et al., 1996; Suh et al., 1999; Holmstrom et al., 2002; Fahnehjelm et al., 2007; Tear Fahnehjelm et al., 2016), and dry eyes (Locatelli et al., 1993; Fahnehjelm et al., 2008; Ayuso et al., 2013; Kinori et al., 2015). Retinal haemorrhages, optic disc oedema, and chorioretinal lesions have also been described in children receiving TBI (Ayuso et al., 2013). Abnormalities described in the posterior visual pathways or visual cortex are more rarely reported (Gurney et al., 2006; Gong et al., 2011).

Visual evoked potentials (VEPs) are a gross electric potential of the visual cortex in response to visual stimulation and depend on the functional integrity of central vision at all levels of visual pathways including the retina, optic nerve, optic radiations, and occipital cortex.

VEP examinations were used as routine after HSCT in our clinic but the results have previously not been evaluated. The aims of the current study were to determine the frequency of visual pathway disturbances detected by VEPs in patients after HSCT in childhood and to determine the impact of ocular disease, underlying somatic diagnosis, conditioning regimens and or immunosuppressive drugs on the VEPs. A further aim was to evaluate the clinical benefits of regular VEP assessments post HSCT.

2. Materials/subjects

Seventy-nine patients were originally invited to participate in a larger study when they come for regular annual follow-ups after HSCT. Forty-seven of these 79 patients underwent VEPs. Data on demographics, cataract development, dry eye complications, visual fields results, and optic nerve morphology among the patients in the cohort has previously been reported (Fahnehjelm et al., 2007; Fahnehjelm et al., 2008; Tornquist et al., 2011).Patients were at a greater risk of developing cataract if conditioned with single fractio TBI (s-TBI) or fractionated TBI (f-TBI) when compared to busulfan or other chemotherapeutic drugs (Fahnehjelm et al., 2007). Poorer visual fields outcomes were found in patients who had undergone HSCT compared with normal controls (Tornquist et al., 2011) and long term results have been published (Tear Fahnehjelm et al., 2016).

3. Methods

Most of the patients came for annual examinations more than once during the study period and the findings of the latest VEP assessment with its corresponding ocular examination are presented as well as links to conditioning regimen and somatic diagnoses. Only patients who had corresponding VEP results and ocular examination during the same time period were included. The results were compared with VEPs obtained before HSCT.

4. Ocular assessment

Clinical ocular assessments included best corrected visual acuity (BCVA), slit lamp examination and funduscopy. Refraction under cycloplegia was measured by retinoscopy after a single instillation of a mixture of cyclopentolate (0.85%) and phenylephrine (1.5%). Lens opacities were graded 1–3 where grade 1 was defined as minor/minimal opacities, grade 2 as cataract with slight impact on BCVA or normal BCVA with subjective symptoms, and grade 3 as cataract with pronounced impact on BCVA (Fahnehjelm et al., 2007). The ocular fundii were examined first with indirect ophthalmoscopy and then with biomicroscopy in the vast majority of the children.

5. Visual evoked potential (VEP)

Visual evoked potentials were recorded with a Nicolet Viking Select (Nicolet Biomedical Inc. Madison, WI, USA). The patients were seated comfortably in a darkened room and were instructed to fixate the centre of a reversing checkerboard pattern displayed on a monitor placed 1.3 meters in front of the eyes (Fig. 1). Gold-pleated electrodes were attached across the scalp. The active electrode was placed at Oz (occipital midline), the reference electrode at Fz (frontal midline) and a vertex (Cz) electrode acted as ground. The impedance was maintained below 5 kOhm. Each eye was examined separately with the other eye covered with a black patch. Care was taken to keep the patients as relaxed as possible to minimize artefacts and the cooperation of the subjects (fixation of the pattern) was monitored by the technician.

The field size of the checkerboard pattern was $12^\circ \times 16^\circ$, each individual square subtended 30 min of arc, the contrast of the pattern was approximately 87% and the reversal rate 1 Hz. Filter settings were 1 Hz and 100 Hz respectively. The average response to at least 100 reversals was recorded, the number of reversals was increased if the VEP was poorly defined and, in most cases, each eye was examined at least twice to confirm reproducibility.

The latency and amplitude of the P100 potential were determined with help of cursors and the values were compared with the department's reference values which were based on bilateral examinations of 31 healthy individuals aged between 13 and 66 years. A latency of >2.5 SD of the normal mean (>126 ms), or an inter eye latency difference exceeding 6 ms, was regarded as an abnormal response. VEPs were rated as either normal or pathological/abnormal (Fig. 2). All VEPs were analysed by the same neurophysiologist (T.A.), who was unaware of the illness, therapy and other results of outcome measures.

6. Statistics

The Fisher exact two-tailed test was chosen for comparison between VEP results and abnormal BCVA, presence of cataract, presence of an intraocular lens (IOL) or posterior pole abnormalities, malignant diagnosis, somatic diagnosis, gender, prematurity, conditioning regimen, corticosteroid treatment for more than six months and chronic GVHD. The Mann-Whitney test was used to compare the VEP results among patients who had more than seven occasions of trough levels >250 ng/ml of CyA. A p-value of <0.05 was regarded as significant.

The study was approved by the Regional Ethics Committee in Stockholm and performed according to the Helsinki Declaration. Written informed consent was signed by all participants and or parents before enrolment in the study.

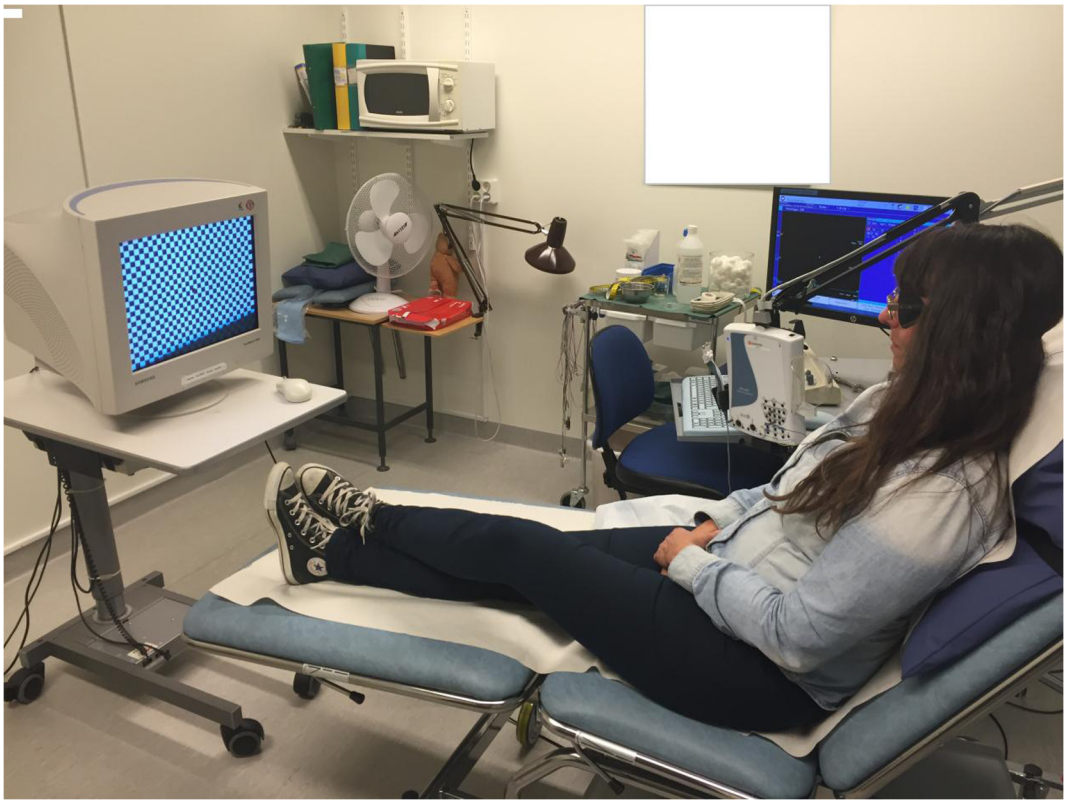

Fig. 1. The patient was seated in a darkened room and instructed to fixate the centre of a reversing checkerboard pattern displayed on a monitor placed 1.3 meters in front of the eyes. Gold-pleated electrodes were attached across the scalp. The active electrode was placed at Oz (occipital midline), the reference electrode at Fz (frontal midline) and a vertex (Cz) electrode acted as ground. Each eye was examined separately with the other eye covered with a black patch. Care was taken to keep the patients as relaxed as possible to minimize artefacts and the cooperation of the subjects (fixation of the pattern) was monitored by the technician.

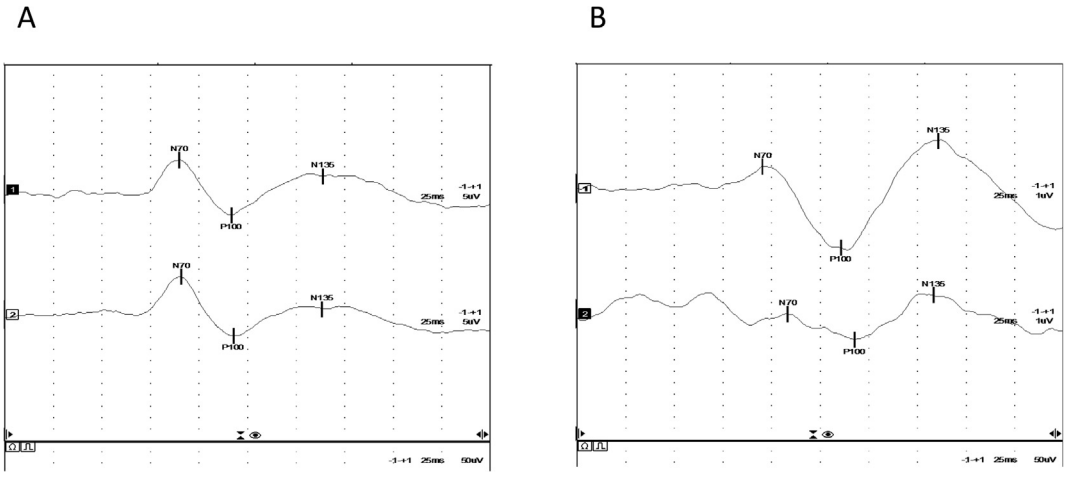

Fig. 2. Visual evoked potential (VEP) recordings from a patient with normal VEPs (A) and a patient with abnormal responses with prolonged latencies (right eye) and also a poorly defined response (left eye) (B). Upper traces are right eyes and lower traces left eyes.

7. Results

In all 47 (20 boys and 27 girls) with a median age of 15.1 years (range 3.3–20.8 years) who had been examined with pattern reversal VEP examination post HSCT and had a corresponding ophthalmological examination from the same month were evaluated. The median time from HSCT to the latest VEP was 6 years (range 1–17 years).

Out of the 47 patients, pathological VEP results were found in eight (17%) individuals (4 boys and 4 girls), with an age between 12 and 18 years. Three patients had bilateral pathological findings and five unilateral. All unilateral cases were left eyes. Three of the subjects with pathological VEP had slightly prolonged latencies in the first examination but they were then between 3 and 8 years old, which makes the interpretation difficult.

A summary of the results, the patient's age, gender, visual functions, ocular status, and VEPs pre and post SCT of the eight children who presented pathological VEPs post HSCT is provided in Table 1.

A subnormal BCVA ranging between 0.3 and 0.65 (0.5–2.0 log MAR) decimal was present in 8/11 eyes with pathological VEPs.

Table 1
Characteristics and visual and ocular features of the eight patients with pathological visual evoked potentials (VEPs) after haematopoietic stem cell transplantation (HSCT).

PN	Gender	Age (yrs) HSCT	Diagnosis	Conditioning therapy	GVHD	Cortico-steroids > 6 months	Occasions CyA > 250 ng/ml	Age VEP (yrs)	VEP latency RE/LE ms	VEP post HSCT RE/LE	Visual Acuity RE/LE decimal	Grade cataract/IOL RE/LE	Fundus RE/LE
1	F	8.4	CML	s-TBI/CY	A/C	Yes	9	17	122/128	N/P	0.8/0.3	IOL/IOL	N/N
2	F	9.8	AA	f-TBI/CY	A/C	Yes	6	16	116/142	N/P	0.65/0.65	0/I	N/P*
3	M	3.0	CML	f-TBI/CY	A/C	Yes	11	12	117/126	N/P	1.3/0.65	IOL/IOL + Sec cat.	N/N
4	M	6.8	ALL	f-TBI/CY	A/C	Yes	12	14	129/127	P/P	0.5/0.65	II/II	N/N
5	M	3.7	AA	Busulfan/CY		No	5	18	130/132	P/P	1.0/1.0	I/I	N/N
6	M	10.7	ALL	f-TBI/CY	A/C	Yes	0	15	105/112	N/P	1.0/0.8	I/I	P**/P**
7	F	6.0	ALL	s-TBI/CY	A	No	9	15	127/126	P/P	0.8/0.65	IOL/IOL	N/N
8	F	10.1	Amega	s-TBI/CY	A/C	Yes	14	17	124/129	N/P	0.8/0.65	IOL/IOL	N/N

A: acute AA: Aplastic Anaemia, ALL: Acute Lymphoblastic Leukaemia, Amega: Amegakaryocytic thrombocytopenia, C: chronic, CML: Chronic Myeloid Leukaemia, CY: cyclophosphamide, CyA: Cyclosporin A, GVHD; Graft versus host disease, f-TBI: fractionated total body irradiation, s-TBI: single dose total body irradiation, Y:Yes, No: number, N:Normal P:Pathological, PN: patient RE: right eye, LE: left eye, μV: micro Volt, ms milli second IOL: intraocular lens, Sec cat: Secondary cataract, 0.0 =; I =; II = grades of cataract. Pink colour: pathological already pre-HSCT and also post HSCT. Yellow colour: pathological post-HSCT * Pathological fundus with retinal dragging and cryo effects due to treatment for retinopathy of prematurity (ROP).
** Pathological fundi due to retinal mottling.

One eye in one patient had a significant cataract whereas six eyes had had cataract surgery and had implanted IOL of which six two turned out to have secondary cataracts. One eye from a child born preterm had residual retinopathy of prematurity (ROP) changes while two eyes in another patient showed retinal mottling.

Visual evoked potentials were significantly pathological in patients with abnormal BCVA in the left eye ($p = 0.0019$) and in the presence of IOL in the left eye showed a tendency ($p = 0.051$). Pathological VEPs were not associated with malignancy, gender, prematurity, pathological ocular fundi, treatment with TBI, or treatments with corticosteroids more than six months, high doses of CyA, cataract grade II or III, but did have a tendency to pathological more often in patients that had developed cGVHD ($p = 0.057$). MRI was performed in one single patient and showed normal results.

8. Discussion

In the current study of 47 children treated with HSCT, VEP recordings were found to be abnormal in 11 of 94 eyes (12%) of eight patients (17%) at a median of 6 years post HSCT. Pathological VEP was associated with poor visual acuity but was not linked to TBI, CyA or malignant disease.

In a study by Kaleita et al. VEP abnormalities were shown to be present before HSCT in 7 of 14 patients with lymphoblastic leukaemia (ALL) or acute myeloblastic leukaemia (AML) (Kaleita et al., 1984). Three patients showed retarded conduction after HSCT without ocular manifestations but instead had pathological visual perception. Four patients had optic nerve pathology. The follow-up with VEP after HSCT was short and only available for two patients but showed reduced conductivity.

Outcomes from VEP examinations without correlation to HSCT but to other treatments have previously been reported in children with ALL treated with cranial irradiation (CI) and neurotoxic drugs (Russo et al., 1985; O'Hare et al., 1987; Uberall et al., 1996). The results vary from normal (O'Hare et al., 1987) to pathological presentation of increased latencies (Russo et al., 1985; Uberall et al., 1996). Children exposed to CI tended to have more abnormalities than non-irradiated patients in one study (Russo et al., 1985) but VEP abnormalities were equally common in another study in which only one group had irradiation. However, in the latter study, the VEP recordings showed a close relationship with radiation-induced CNS white-matter disturbances (Uberall et al., 1996). As MRI was only performed in a single patient with pathological VEP in the current study, no comparison is possible.

Out of the eleven eyes in eight children with pathological VEPs in the current study six children had BCVA $\leq$ 0.65 decimal (0.2 log-MAR) of whom one had dense cataract and four patients had IOLs due to previous cataract surgery with a secondary cataract in one patient. However, cataract or IOLs have previously not been reported to affect the standard pattern VEP results (Fuest et al., 2014) and therefore these results need further evaluation.

One patient in the present study had fundus pathology due to sequelae of ROP. Prematurity has also previously been reported to affect the VEP results (Kuba et al., 2008). No patient had abnormal optic discs while two patients with abnormal VEP were noticed to have a clinically thin retina. The pathological outcome in the other patient with abnormal VEPs was not due to any visual or ocular causes.

CyA has been reported to cause retinal and cortical blindness (Edwards et al., 1995; Shah, 1999; Trullemans et al., 2001; Bartynski et al., 2004) but was not associated with pathological VEP in the current study. The fact that the VEPs were more commonly pathological in the left eye could be due to tiredness and poor cooperation in the second eye.

A limitation of the current study were that most of the patients included in this study had VEPs prior to HSCT using a different device with different standard values and the pre HSCT data was not in detail comparable in detail with the post HSCT results. Three of the subjects with abnormal VEP post HSCT had slightly prolonged latencies initially, but they were only 3–8 years old and these recordings could not be regarded as abnormal.

To conclude, VEP recordings showed an association with decreased visual acuity but no relationship with irradiation or high doses of CyA in the present study. Thus, VEP seems to have minor clinical significance as a tool for follow-up of visual pathway pathology in children who have been treated with HSCT. This is important knowledge as outline VEP recordings after HSCT can be avoided in these children who are undergoing many other regular assessments after HSCT. However, VEP might be of clinical value for those with an unexplained subnormal visual acuity. Further studies on the role of cataract and intra ocular lenses on VEP results are warranted.

Conflict of interest

No financial disclosure.

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