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Auditory event related potentials as tools to reveal cognitive late effects in childhood cancer patients

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ABSTRACT

Objective: The purpose of this study was to analyze event related potentials mismatch negativity (MMN) and P3a in childhood cancer patients at the time of diagnosis (Study 1) and after treatment (Study 2) to evaluate their clinical usefulness in screening potential treatment-related neurotoxicity.
Methods: The MMN and P3a to phonetic stimuli were examined in 27 childhood cancer patients with age- and sex-matched controls. Neuropsychological tests were also studied.
Results: The MMN peak amplitude was attenuated in the patient group at Study 1. Between the studies, poorer enhancement of the MMN peak amplitude correlated with deterioration in the Verbal intelligence quotient (IQ) in leukaemia patients. In addition, prolongation of the MMN peak latency correlated significantly with deterioration in the Full Scale and Performance IQ in the patient group. Deterioration in the Arithmetic subtest and Performance IQ correlated negatively with the age at diagnosis.
Conclusions: The MMN changes between the studies associated with deterioration in the neuropsychological tests indicating that the method could be clinically useful. The performance of the younger patients was more likely to deteriorate during the treatment.
Significance: Changes in the MMN response during cancer treatment seem to be of clinical importance as indicates of the cognitive outcome of childhood cancer patients.

1. Introduction

As survivor rates of paediatric cancers have significantly increased during the last three decades, more emphasis has been paid on the late effects of the treatment. Even more than 80% of the paediatric cancer survivors report some morbidity (Grant et al., 2006), and the risk of chronic health conditions is substantially higher as compared to siblings (Oeffinger et al., 2006). Cognitive problems are one of the most often reported concerns, being also common in survivors of childhood acute lymphoblastic leukaemia (ALL) (Fu et al., 2006; Grant et al., 2006; Pogany et al., 2006). The prophylactic central nervous system (CNS) treatment (irradiation and/or intravenous and intrathecal methotrexate) introduced in the 1970s originally increased the childhood ALL survivor rate, and the neurological and cognitive late effects of the therapy are well acknowledged (Eiser, 1978; Bleyer, 1981; Meadows et al., 1981; Copeland et al., 1985; Peckham et al., 1988). In the early reports, clinically significant decreases in IQ ($\geqslant$10 points) have been reported in 61% (Meadows et al., 1981), and difficulties in attention or concentration in even 83% of the survivors (Peckham et al., 1988). Further neuropsychological testing has shown that ALL survivors may suffer from deficits in several specific cognitive abilities. Specifically deficits in attention, memory, speed of information processing and areas of executive functioning have been reported (Campbell et al., 2007; Anderson and Kunin-Batson, 2009; Buizer et al., 2009).

Chemotherapy alone may also cause cognitive deficits, at least in younger and female ALL patients (Buizer et al., 2005; Mennes et al., 2005; Montour-Proulx et al., 2005; Reddick et al., 2006; Krappmann et al., 2007; Harila et al., 2009), and especially high-dose methotrexate seems to play an important role (Carey et al.,

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2007). A recent meta-analysis of cognitive sequelae of the chemotherapy-only treatment further confirms these findings (Peterson et al., 2008). This is also supported by the fact that in the motor evoked potential (MEP) studies the prolongation of the calculated latencies within the CNS (between the cortex and spine) correlated significantly with the number of intrathecal methotrexate injections (Harila-Saari et al., 2001). It is also noteworthy that treatment of ALL includes substantial doses of corticosteroids (prednisolone and dexamethasone) which may potentially affect hippocampus and also contribute to the cognitive late effects of the treatment (for review, see Alderson and Novack, 2002).

Even though the cognitive late effects of modern cancer treatment do not seem to be as drastic as those of the past decades, they still are very significant to individual patients. As thorough neuropsychological testing cannot be performed repeatedly on all the patients at risk for cognitive late effects, there is a need for simple functional methods to screen which patients need extensive neuropsychological testing and possible rehabilitation to optimize their learning capabilities. Conventional EEG recordings have not turned out to be useful in predicting late effects of the CNS prophylaxis (Korinthenberg and Igel, 1990; Ueberall et al., 1997) but the auditory event related potentials (ERPs) seem to be more promising. For example, the P300 (P3b) latency is prolonged in childhood ALL patients (Heukrodt et al., 1988; Moore et al., 1992; Sato et al., 1992; Uberall et al., 1996; Lähteenmäki et al., 2001). Another auditory ERP, the mismatch negativity (MMN), first described by Näätänen et al. (1978), is an attention independent response to any discriminable change in the auditory stimulus stream having its largest amplitude over the fronto-central scalp areas (Näätänen and Alho, 1995; Näätänen, 1995). Of importance is that MMN can be obtained even from individuals unable to co-operate. MMN reflects the auditory short-term memory, which is of crucial importance for correct speech processing and understanding (Näätänen and Alho, 1995; Näätänen, 1995). MMN can be registered even from newborns, and it has been studied in clinical child populations (Korpilahti and Lang, 1994; Holopainen et al., 1997, 1998; Cheour et al., 1998).

In addition to bilateral supratemporal cortices, frontal lobes are also involved in the generation of MMN, and studies in patients with e.g. frontal cortical lesions have shown diminished MMN (Alho et al., 1994; Näätänen et al., 2007). White matter changes are known to be associated with childhood cancer treatment, particularly with intravenous methotrexate (Reddick et al., 2005). Demyelination, loss of oligodendroglia, atrophy of the deep white matter, and subsequent loss of white matter volume seem to be the long-term effects, and especially right frontal white matter seems to be affected (Reddick et al., 2007, 2009; Carey et al., 2008). The white matter changes have been found to correlate with neurocognitive performance, especially with deficits in attention and processing speed, but complex MRI methods are required for detailed analysis (Paakko et al., 2000; Reddick et al., 2006, 2009). MMN is often followed by the positive P3a (novelty P3), a fronto-central positivity around 300 ms after the stimulus onset, which is a sign of a brief, involuntary attention switch towards the distractor (the deviant sound) (Näätänen, 1995; Friedman et al., 2001). While MMN reflects the preattentive level processes of the detection of the deviance, P3a is thought to reflect the activation of an attentional switching mechanism, and more evaluative and conscious aspects of the orienting response (for review, see Friedman et al., 2001). Studies in patients with brain lesion suggest that dorsolateral prefrontal cortex has a major role in the generation of P3a, and temporo-parietal regions and posterior hippocampus also contribute to it, especially to the frontal aspect of P3a (Friedman et al., 2001). As an index of processing speed, P3a has been found to correlate with neuropsychological measures, especially with performance intelligence quotient (Walhovd et al., 2005; Light et al., 2007).

As MMN and P3a have both structural and neuropsychological correlates related to the deficits seen in childhood cancer survivors, they might serve as new and sensitive indicators of cognitive late effects in childhood cancer patients, as an earlier study suggests (Lähteenmäki et al., 2001). Thus, they might be useful in screening patients who may need extensive neuropsychological testing after childhood cancer treatment. The purpose of this study was to analyze the MMN and P3a patterns in childhood cancer patients at the time of diagnosis (Study 1) and after treatment (Study 2), and to evaluate the clinical usefulness of this method in assessing potential treatment-related neurotoxicity.

2. Methods

2.1. Patients

All new paediatric cancer patients (age 2.5–16 y) with leukaemia or solid tumour (excluding the CNS tumours), admitted to the Department of Paediatrics in Turku University Hospital between March 2001 and March 2004, were included in this study. All the patients agreed to participate in the study and informed consent was obtained from the patients and their parents (in writing from the parents and the children who were old enough to write). The research plan was accepted by the Commission on Ethics of Southwest Finland hospital district.

A total of 27 patients (13 males) were enrolled in the study (Table 1), and the auditory ERP recordings and neuropsychological tests were carried out as later indicated. Study 1 took place at the time of diagnosis, and Study 2 after finishing the treatment. Time between Study 1 and 2 varied according to the diagnosis and duration of the treatment (Table 1). Age- and sex-matched healthy controls were studied using the same protocol. The first ERP registration could not be performed for five of the patients within one month of the diagnosis, so they were excluded from the statistical analyses of Study 1. Neither ERP registrations nor neuropsychological studies were performed within 24 h from anaesthesia or operations, to ensure that the patients were not under the influence of sedative drugs at the time.

One leukaemia patient dropped out before Study 2 because of moving into another part of the country, and one patient (leukaemia) had a relapse and he died before Study 2. Their control subjects were not studied at the end of the follow-up. Four other control subjects refused to participate at Study 2. Out of the 27 patients and controls, a total of 25 patients (93%) and 21 controls (78%) stayed throughout the follow-up. (Table 1).

2.2. Setting and stimuli of the ERP recordings

The ERP recordings were performed at the Language and the Developing Brain – laboratory at the Turku University Hospital until July 2002, and after that in similar conditions at the Department of Clinical Neurophysiology of Turku University Hospital until may 2006.

Two different phonetic sounds, synthesized Finnish vowels /o/ and /e/ were used as stimuli in a passive oddball paradigm. The probability for the standard sound /o/ was 0.90 and for the deviant sound /e/ 0.10. The inter-stimulus interval (ISI, from the offset to the onset of successive stimuli) was 350 ms, and the stimulus duration 400 ms, with the rise and fall times of 10 ms. The intensity of the stimulus was about 65 dB SPL with the same loudness for each vowel. The stimuli were presented in four blocks of 500 sounds, and there was a silent break of 2.5 min between each block. The stimuli were presented through stereophonic