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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Sensory and Sensorimotor Gating in Children with Subclinical Hypothyroidism

Subklinik Hipotiroidili Çocuklarda Duyusal ve Duyusal Motor Kapılama

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Abstract

Objective: Attention and learning problems have been reported in children diagnosed with subclinic hypothyroidism (SH). Sensory gating is an automatic phenomenon that is related to attentional processes. It is known that an impairment in sensory/sensorimotor gating negatively affects the signal processing mechanism and hence attention and learning processes. The aim of the present study was to evaluate the effect of SH on sensory gating processes via P50 suppression and prepulse inhibition (PPI) in children.

Methods: Fifteen children aged 8-16 years, diagnosed with SH, and 15 healthy children were included in the study. Auditory P50 suppression and PPI paradigms were applied during the recordings. P50 suppression was examined via auditory brain potentials recorded by electroencephalography. PPI was evaluated via electromyography, in which the blink reflex was recorded by oculomotor muscle activity.

Results: No statistical difference was found in P50 suppression and PPI processes between children in the SH and control groups. These findings indicate that the sensory gating processes children with SH are not affected.

Conclusion: The findings of this study show that the sensory gating processes of SH children are not affected. However, considering that brain maturation continues until the age of 20s, it may be more useful to scrutinize these processes with a wider age range and a larger number of participants to reveal more clearly how sensory gating is affected by SH.

Keywords: Subclinical hypothyroidism, sensory gating, sensorimotor gating, P50, prepulse inhibition

Öz

Amaç: Subklinik hipotiroidi (SH) tanısı almış olan çocuklarda dikkat ve öğrenme problemleri bildirilmiştir. Duyusal perdeleme, dikkat süreçleri ile ilişkili otomatik bir olgudur. Duyusal perdelemenin bozulması, sinyallerin işlenme mekanizmasını ve dolayısıyla dikkat ve öğrenme süreçlerini olumsuz etkilediği bilinmektedir. Bu çalışmanın amacı, SH'nin çocukların duyusal perdeleme süreçleri üzerindeki etkisini P50 baskılama ve prepulse inhibisyonu (PPI) ile değerlendirmektir.

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Öz

Yöntem: SH tanısı alan 8-16 yaş aralığında 15 çocuk hasta ve 15 sağlıklı çocuk çalışmaya alındı. Kayıtlar sırasında işitsel P50 baskılama ve PPI paradigmaları uygulandı. P50 baskılama süreçleri, elektroensefalografi ile kaydedilen işitsel beyin potansiyelleri ile incelendi. PPI ise, göz kırpma refleksinin okülomotor kas aktivitesi ile kaydedildiği elektrookülografi ile değerlendirildi.

Bulgular: SH ve kontrol grubunda bulunan çocukların P50 baskılama ve PPI süreçleri arasında istatistiksel farklılık bulunmamıştır. Bu bulgular, SH çocukların duyusal perdeleme süreçlerinin etkilenmemiş olduğunu göstermektedir.

Sonuç: Bu çalışmanın bulguları, SH çocukların duyusal perdeleme süreçlerinin etkilenmemiş olduğunu göstermektedir. Fakat, beynin olgunlaşma sürecinin 20'li yaşlara kadar devam ettiğini göz önüne alarak, bu süreçlerin çocuklarda SH'den nasıl etkilendiğini anlayabilmek için daha geniş yaş aralığında ve daha büyük sayıda katılımcı ile incelenmesi gereklidir.

Anahtar Kelimeler: Subklinik hipotroidi, duyusal kapılama, sensorimotor kapılama, P50, ön uyaran aracılı inhibisyon

Introduction

Primary hypothyroidism is characterized by low free triiodothyronine (T3) and thyroxine (T4) levels and increased thyroid-stimulating hormone (TSH) levels and subclinical hypothyroidism (SH) is a metabolic disease characterized by slightly elevated TSH levels and normal T3 and T4 levels[1,2]. Thyroid hormones are crucial in brain maturation and normal brain functions throughout life and have important effects on processes such as neurogenesis, neuronal migration, myelination, and synaptogenesis in the central nervous system[3,4]. Many studies point out that thyroid dysfunctions cause cognitive impairment and mood changes[5-9]. How the cognitive functions are affected in SH and whether hormone replacement therapy is necessary for these patients are still controversial[9-11]. Studies based on neurocognitive function tests have shown that SH children have attention problems[2,12]. Transient perinatal disruption of thyroid functions revealed shortened attention span, hyperactivity, restlessness, and tendency to panic easily[13].

There is scarce data on event related potential (ERP) responses of hypothyroid patients[14-17]. Studies reveal that auditory ERP P3 latency prolongation in both clinical and subclinical hypothyroid cases, which indicates that cognitive function is adversely affected in hypothyroidism and in SH[15,16]. It has been shown that children with SH had lower P3 amplitudes in comparison to the control group children, which indicates that cognitive functions such as attention and working memory are affected in SH[14].

Sensory gating is the neurological filtering of unnecessary ones among all environmental stimuli and prevents an overload of high cortical regions of the brain with irrelevant information[18-20]. Failure in filtering of the stimuli may disrupt the signal processing mechanism, leading to impairment of attention and learning processes[19,20]. There are two measurement methods designed to evaluate sensory gating processes: prepulse inhibition (PPI) of the startle reflex and suppression ratio of P50 potential. PPI is the startle reflex that occurs in response to a sudden and strong stimulus is usually evaluated by electromyography (EMG) recording of the orbicularis oculi muscle of the blink. The magnitude of the blink response weakens when a weaker stimulus (prepulse) is applied before the severe stimulus that causes startle. Similar to PPI, P50 also reflects the inhibitory effect of the first stimulus on the second identical stimulus on electroencephalography (EEG) data. PPI and P50 suppression have been shown to be disrupted in various psychiatric disorders with cognitive and attention impairments such as schizophrenia, bipolar disorder, multiple complex developmental disorders, attention deficit, and hyperactivity disorder[19-23]. Wada et al.[24] reported that they did not observe the effect of hypothyroidism on PPI, but the startle reflexes of hypothyroid rats were high. Navarro et al.[25] showed an increase in PPI in proportion to the duration of hypothyroidism exposure in rats and stated that neuronal activity was decreased. As far as we know, there is no study examining the effect of SH on sensory and sensorimotor gating in human subjects. Children with SH have smaller P1-N1 and N1-P2 peak-to-peak amplitudes compared to controls[14]. Because the N1 and P2 evoked by auditory stimuli are related to filter mechanisms in triggering and allocation of attention, we presumed that the sensory gating processes may also be affected in children with SH[26,27]. To study the sensory gating processes, we evaluated P50 and PPI responses in children with SH.

Materials and Methods

Participants

Fifteen children who were admitted to our pediatric endocrinology clinic and diagnosed with SH were included

in the study. The TSH level of these patients ranged between 5.23-16.37 mIU/L (mean: 8.70±3.63 mIU/L). SH was defined on the basis of elevated serum TSH levels (TSH, 4.94-20 mIU/L) and serum fT4 levels within the normal range[28]. These levels were confirmed with a second measurement 4-6 weeks later. The control group consisted of 15 healthy children. Children with any systemic disease, neurological, psychiatric disorder, or hearing impairment, and those with metabolic condition having an effect on cognition, or those taking medications/iodine-containing drugs and medication that affect the cognitive processes were excluded in both the SH and the control groups. Additionally, the first-degree relatives were questioned for any cognitive impairment and /or psychotic disorders. None of the participants had a history of cognitive or psychiatric disorders, in first-degree relatives. The children in the study showed normal academic performance at school. The research was conducted with the permission of the Izmir Katip Celebi University Clinical Research Ethics Committee (21.11.2013, approval number: 173). The parents of the children signed the written informed consent and received a copy of it.

Auditory Stimuli

All auditory stimuli were presented binaurally through stereo insert earphones (Koss Ruk30). The stimuli were calibrated by using a digital sound-level meter. Each subject was seated upright in a chair in an isolated room.

PPI Paradigm and Recordings

The prepulse and startle stimuli were bursts of white noise (duration 25 ms and 30 ms, intensity 87 dB and 107 dB, respectively), with an interstimulus interval of 120 ms. The PPI session consisted of a block of 24 randomized trials: 12 startle eliciting stimuli preceded by a prepulse stimulus and 12 without. The intertrial intervals were randomized between 12-23 s[19]. Muscle contraction of the lower orbicularis muscles was measured from the right eye for the startle reflex. The EMG bipolar "raw" signal (gotten by subtracting the signal of the electrode below the pupil from the one placed on the outer edge of the eye) was recorded with Ag/AgCl electrodes using a Brain Vision Recorder (Brainproducts, Munich, Germany). EMG was digitized at 2500 Hz sampling rate with 10-1000 Hz band pass filter.

P50 Suppression Paradigm and Recordings

A block consisting of 36 click pairs with an interstimulus interval of 500 ms and an intertrial interval of 10s was presented. The clicks were 1.5 ms bursts of white noise with an intensity of 86 dB[19]. The first stimulus in the click pairs is the conditioning, and the second is the test stimulus. P50 recordings were conducted by means of a BrainAmp 32-channel system (BrainProducts). The participant's electrical brain activity was recorded with 30 Ag/AgCl electrodes mounted in an elastic cap according to the International 10-20 electrode placement system. The EEG channels were referenced by two electrodes attached to the earlobe (A1+A2). The ground electrode was designated as FCz. Electrode impedances were less than 10 kΩ. EEG was digitized at 1000 Hz/sec sampling rate with 0.1-70 Hz band pass filter. A 50 Hz notch filter was also applied.

Data Analysis

Assessment of PPI

EMG data were processed using a BrainVision Analyser (Brainproducts, Munich, Germany) and filtered offline with a high-pass filter of 30 Hz and a low-pass filter of 200 Hz. Epochs between 50 ms prestimulus and 200 ms poststimulus were extracted from the continuous data. The baseline was corrected using the 50 ms prestimulus data. The data were rectified and the maximum peak amplitude within a window of 20-90 ms after stimulus onset was measured. PPI was computed as the percentage reduction of the startle amplitude for prepulse-pulse trials, compared to the pulse alone trials [PPI=100x (1- pp/p)], where pp indicates the amplitude of prepulse trials and p indicates the amplitude of pulse alone trials.

Assessment of P50

EEG data were analyzed a BrainVision Analyser (Brainproducts, Munich, Germany) and filtered offline with a band-pass filter between 1.6 Hz and 70 Hz. Epochs between 100 ms prestimulus and 400 ms poststimulus were extracted from the continuous data. The baseline was corrected using the 100 ms prestimulus data. Epochs contaminated by eye or other artifacts were manually rejected off-line. Segments were averaged, and separate average event -related potential waveforms were obtained for the conditioning and test stimuli. The P50 waves were identified and scored from the Cz electrode. The greatest positivity, appearing within the range of 40-90 ms after the conditioning stimulus, was evaluated as P50. The amplitude was assessed as the difference between this positivity and the preceding trough, and the latency was assessed as the time from the onset of the conditioning stimulus to the maximum amplitude of this

positive peak. The P50 peak obtained by the test stimulus was also evaluated accordingly.

P50 suppression was computed as the percentage reduction of the response amplitude for conditioning stimuli, compared to the test stimuli [P50 suppression=100x (1- T/C)], where T indicates the amplitude of the Test stimulus and C indicates the amplitude of the conditioning stimulus.

Statistical Analysis

The SPSS 15.00 (Leadtools, USA) program was used for the statistical analysis of data. The Normality of the data distribution was tested using the Kolmogorov-Smirnov test. Paired and independent samples t-tests were applied to data with a normal distribution. Findings with a p value less than 0.05 were accepted to be statistically significant.

Results

The age of the subjects was comparable among SH (12.7±2.7; 9 female) and control group (13.0±2.5; 10 female). The TSH was significantly higher in SH children (7.42±3.63 mIU/L) compared to controls (1.49±0.42 mIU/L) [t(25) =-5.838, p=0.001]. FT4 levels of SH (16.05±1.92 pmol/L) and control group (15.65±1.93 pmol/L) were in normal range and there was no statistical difference between groups.

Prepulse Inhibition Paradigm

The amplitude (μV) and latency (ms) values of EMG responses of pulse alone and prepulse-pulse trials obtained from SH and control group children were measured (Table 1). Data of four patients and four control subjects were rejected because of no distinct startle reaction was elicited. Higher EMG responses were observed in the pulse alone trials compared to prepulse trials in both groups (Figure 1). There was a significant difference in the amplitudes of pulse alone trials (M=10.69, SD=5.92) and prepulse trials (M=5.71, SD= 2.93); t(10)=4.00, p=0.003 in the control subjects. Similarly, in the SH group, a significant difference was found between the amplitudes of pulse alone trials (M=10.06, SD=6.85) and prepulse trials (M=2.97, SD=1.48); t(11)=3.95, p=0.002. No significant difference was found between the latencies of pulse alone and prepulse trials in neither the control group nor the SH group. Neither a significant difference in amplitudes of pulse alone trials nor prepulse trials between the control and SH groups was found, indicating that both groups demonstrated similar amplitudes to pulse alone as well as to prepulse-pulse trials. Furthermore, no significant difference in PPI was found between the groups.

P50 Suppression Paradigm

The amplitude (μV) and latency (ms) values of P50 responses for conditioning and test stimuli obtained from SH and control group children were measured (Table 1). There was a remarkable difference in the P50 responses to test and conditioning stimuli in both groups (Figure 2). The amplitude of the testing stimuli was reduced compared to the amplitude of conditioning stimuli. There was a significant difference in the amplitudes of test stimuli (M=2.23, SD=1.24) and conditioning stimuli (M=3.92, SD= 1.61); t(13)=5.73, p=0.001 in the control subjects. Similarly, in the SH group, a significant difference was found between the amplitudes of the test (M=2.62, SD=1.94) and conditioning stimuli (M=3.78, SD=2.17); t(13)=5.11, p=0.001. Independent sample test revealed that the amplitudes elicited by conditioning stimuli and test stimuli did not differ significantly between the SH and control groups. Accordingly, no significant difference in P50 suppression was found between the groups.

Discussion

The current study was designed to investigate sensory and sensorimotor gating in children with SH and healthy controls. Since attentional deficiencies in children with SH have been detected, the question was whether it is preattentive filter mechanisms (sensory gating) that cause the impairment in attention[2,9,12,14]? However, neither a significant difference for PPI nor for P50 suppression was found between the groups. It was shown that there

Table 1. PPI and P50 suppression values of children with SH and control groups

Group	PPI					P50				
	%	PA		PP		%	C		T	
		Amp (μV)	Lat (ms)	Amp (μV)	Lat (ms)		Amp (μV)	Lat (ms)	Amp (μV)	Lat (ms)
SH	54.42±25.33	10.06±6.85	83.37±7.79	2.97±1.48	93.00±6.95	31.41±21.36	3.78±2.17	65.14±11.63	2.62±1.94	66.00±11.18
Control	41.53±14.82	10.69±5.92	93.43±12.42	5.71±2.93	98.14±13.72	42.95±20.92	3.92±1.61	57.21±10.16	2.23±1.24	54.86±10.18

PA: Pulse alone trials, PP: Prepulse-pulse trials, C: Response to the conditioning stimulus, T: Response to testing stimulus, Amp: Amplitude, Lat: Latency, SH: Subclinic hypothyroidism, PPI: Prepulse inhibition

were outstanding differences in terms of auditory evoked responses during attentive (N1, P2, P3) phases of information processing between the children in the SH and control groups[14]. It is stated that the lower P3 amplitudes in comparison to the control group children indicate that cognitive functions such as attention and working memory are affected in children with SH. Besides, the smaller P1-N1 and N1-P2 peak-to-peak amplitudes found in children with SH were considered to imply impairments in attention triggering and orienting[14]. Since, these attentive phases of information processing are affected by SH in children, we intended to study the preattentive processing by using P50 suppression and PPI. These two processes are controlled by different neural mechanisms. Although both paradigms measure the filtering of incoming information, they are based on different physiological events: P50 suppression is measured by EEG, while PPI is measured by EMG. PPI of the startle reflex is controlled by the brain structures at, and below the mesencephalon[29,30]. It has been stated by many research that the superior temporal gyrus, hippocampus, dorsolateral prefrontal cortex, and thalamus contributed to the generation of P50 and suppression of P50[31,32]. To study the probable impairments in these neural mechanisms, we assessed both paradigms. To our knowledge, there is no study investigating the effect of thyroid functions on P50. Our findings indicate that SH children showed normal P50 suppression. There was a remarkable difference in P50 responses to test and conditioning stimuli in both groups, but no difference in P50 suppression was found between the groups. While speculative, it could be inferred that the brain areas at the pre-attentive processing level may not be affected in SH children. While N1-P2 responses were weakened[14], the P50 responses were found to be unaffected in SH children in this study. These findings suggest that these brain potentials are revealed by different underlying mechanisms. Thyroid hormone modulation can alter crucial brain neurotransmitter systems[33-37]. It has been shown that hypothyroid states lead to decreased dopamine function, which plays a key role in PPI[38,39]. The findings of several studies have indicated that neonatal hypothyroid rats showed a significant decrease in PPI[38,24,25]. Furthermore, Uziel et al.[40] showed structural abnormalities in the cochlea and organ of corti in hypothyroid rats. Therefore, it is concluded that, mild chronic hypothyroidism may cause irreversible loss in the auditory system[40,41]. The findings of this study indicated that children in the SH and control groups demonstrated similar amplitudes to pulse alone as well as to prepulse-pulse trials. Statisticaly, no significant difference in PPI was found between the groups. The present study indicates that SH has no effect on sensory gating processes in children. Nevertheless, deficiency in gating processes may be a developmental abnormality that increases in years and is minor in childhood[42]. Structural MRI studies and analysis of brain electrical activity indicate that the human brain does not reach its mature state until the late teens or mid-20s[43,44]. Moreover, brain maturation is likely to be influenced by genetic, hormonal, and environmental factors[45-47]. Therefore, studies with larger

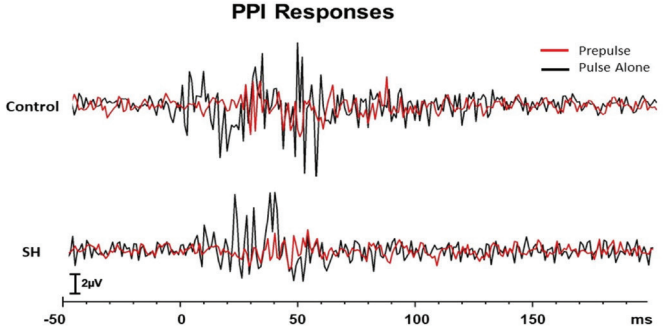

Figure 1. Grandaverage PPI responses of children with SH and control groups are presented. Shown on the horizontal axis is the 50 ms prestimulus and 200 ms post stimulus interval. Pulse alone is depicted in black and prepulse-pulse is depicted in red

SH: Subclinic hypothyroidism, PPI: Prepulse inhibition

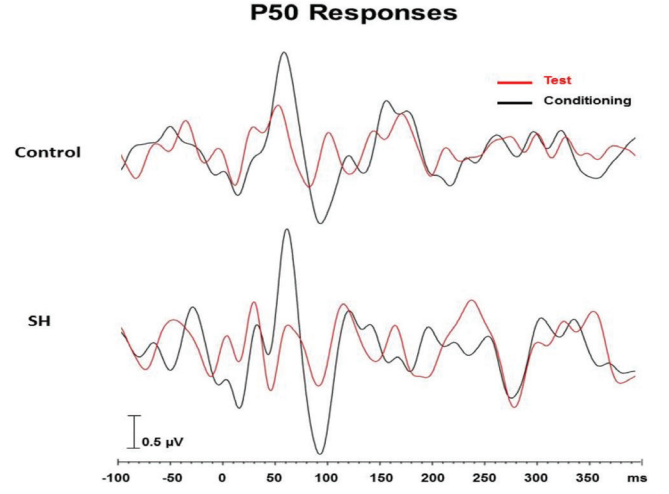

Figure 2. Grandaverage P50 responses of children with SH and control groups are presented. Shown on the horizontal axis is the 100 ms prestimulus and 400 ms post stimulus interval. Conditioning stimuli and test stimuli are depicted in black and red respectively

SH: Subclinic hypothyroidism

age variability and possibly longitudinal studies should be planned to investigate whether these impairments develop later in the disease.

Study Limitations

Although the number of participants and trials are consistent with the literature[29,19,48], the relatively small number of participants is a possible limitation of the current study. Also, it would be valuable to determine how the cognitive processes are affected by the level of TSH by setting the TSH level between 5-10 µIU/L and above 10 µIU/L groups.

Conclusion

Consequently, children with SH showed no deficits in filtering of auditory information in this study. However, between groups studies comprising a larger age range as well and longitudinal studies are needed to assess the effect of SH on sensory gating mechanisms.

Ethics

Ethics Committee Approval: The research was conducted with the permission of the İzmir Katip Çelebi University Clinical Research Ethics Committee (21.11.2013, approval number: 173).

Informed Consent: The parents of the children signed the written informed consent and received a copy of it.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.O.D., G.Ç., P.G., B.N.D., Concept: S.K.A., N.O.D., U.E., N.E.E., T.O.B., M.C.K., G.Ç., B.N.D., Design: S.K.A., N.O.D., U.E., N.E.E., T.O.B., G.Ç., B.N.D., Data Collection or Processing: S.K.A., U.E., N.E.E., T.O.B., M.C.K., G.Ç., P.G., B.N.D., Analysis or Interpretation: S.K.A., N.E.E., M.C.K., G.Ç., P.G., B.N.D., Literature Search: S.K.A., N.O.D., Writing: S.K.A., N.O.D., U.E., N.E.E., T.O.B., M.C.K., G.Ç., P.G., B.N.D.

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