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Effects of sedation on auditory brainstem response in Rett syndrome

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Abstract

Prolongation of the I-V interpeak latency intervals have been reported in Rett Syndrome and other neurodevelopmental disorders. It has been suggested that the use of sedation may account for differences in the interpeak latency intervals when comparisons are made across diagnostic groups if sedated control groups are not used for the basis of comparison. This study examined the effects of sedation on Auditory Brainstem Response interpeak latency intervals (i.e., I-III, III-V and I-V) in two groups of individuals: 1) a group with Rett Syndrome who were positive for mutations in the MeCP2 gene, and 2) a group negative for mutations in the MeCP2 gene but who were severe to profoundly delayed with other causes of mental retardation. A third group of sedated and un-sedated female participants taken from our normative ABR data base was also included in order to further assess the effects of sedation. An analysis of variance indicated, 1) longer I-V interpeak latency intervals in the sedated participants with Rett Syndrome; 2) longer III-V interpeak latency intervals in the mutation positive participants as compared to non-Rett Syndrome mutation negative participants and 3) t-tests revealed no significant effects of sedation on the I-III, III-V or I-V interpeak latency intervals among the normative group participants. Our findings suggest a possible biological basis for the discrepancy in the literature on auditory brain stem responses in Rett Syndrome, and warrant cautious interpretation of auditory brain stem responses findings in sedated subjects with Rett Syndrome as well as in those with mental retardation and seizures.

Introduction

The auditory brainstem response (ABR) has been widely utilized in confirmation of the auditory status of infants and children for whom reliable results cannot be obtained utilizing developmentally appropriate behavioral test procedures [1]. The ABR has also been utilized for many years in assessment of the neurologic status of the auditory nerve and brainstem auditory pathways of patients with suspected neurologic disease [2-4]. Sedation is often

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utilized in assessment of individuals with developmental disabilities to minimize myogenic activity and induce a quiet state so that interpretable results might be obtained. The utility of the ABR is that it is generally believed to estimate auditory sensitivity and is not affected by sleep state or the use of moderate sedation [5-7]. Abnormalities consisting of prolongation of waves and increased interpeak latency intervals have been reported in a number of mental retardation syndromes [7] patients with head trauma [8], and hydrocephalus [9]. However, there have been some documented effects of sedation on the interpeak latency intervals of the ABR in children with mental retardation [10], in other neurologic disorders such as central alveolar hypoventilation [11,12] as well as in patients with respiratory insufficiency following encephalitis [13]. Due to the documented effects of sedation on estimates of interpeak latency intervals in some clinical populations, it has been suggested that abnormal interpeak latency intervals reported in patient populations such as fragile × syndrome may be related to the use of sedation as opposed to inherent features of the disorder [10]. Miezejeski et al. [10] demonstrated that irrespective of diagnosis, patients with mental retardation who were sedated for testing had longer III-V interpeak latency intervals than non-sedated patients with mental retardation.

Rett Syndrome is a neurological disorder caused by mutations in the methyl-CpG-binding protein 2(MeCP2) gene located at Xq28 that predominantly affects females [14]. The disorder is characterized by a progressive loss of cognitive and motor skills, communication disorder, and deceleration of head growth [15]. Rett syndrome is characterized by a period of apparently normal prenatal, perinatal and psychomotor development for the first 6 to 18 months, followed by a period of loss of previously developed language skills and purposeful hand use [16]. Seizures, intermittent hyperventilation, ataxia and stereotypical hand movements develop over time. There are conflicting reports as to the presence of abnormalities in the interpeak latency intervals of the ABR in Rett Syndrome. The majority of studies have reported no abnormalities in the ABR interpeak latency intervals in Rett Syndrome [17-20]. It has also been reported that the interpeak latency intervals do not change over time in Rett Syndrome [21], suggesting that Rett Syndrome is not characterized by progressive degenerative changes at the level of the brainstem. However, several studies have reported prolongation in the I-V or the III-V interpeak latency intervals in Rett Syndrome [22-24]. A number of studies have not reported whether the subjects have received sedation [17,18,20,22,25]. Those reports in which patients were sedated tended to note the presence of ABR abnormalities [23,24] whereas an absence of ABR abnormalities were reported when sedation had not been utilized [19].

There is some evidence of brainstem involvement in Rett Syndrome [26,27]. The pervasiveness of issues with breath holding and hyperventilation in Rett Syndrome [28-31], raises questions as to the central control and regulation of respiratory function in these patients [32]. It has been suggested that the unstable respiratory control in the awake state in Rett Syndrome is indicative of immature brain stem function [29] or poor control over brainstem respiratory centers during the wake period [33]. Because the generators for the ABR are in close proximity to the centers for regulation of respiration in the brainstem, it would not be surprising for ABR abnormalities to occur in Rett Syndrome as in some patients with disturbed central control of respiration[13]. In addition, mutations in MeCP2 are associated with a wide range of neurological phenotypes and patients with the mutations typically have deficits in autonomic processes that are regulated at brainstem levels [34]. The purpose of this investigation was to examine the presence of ABR auditory brainstem response abnormalities in a relatively large sample of sedated and non-sedated individuals with Rett Syndrome to determine whether sedation impacts the estimates of the interpeak latency intervals. An additional hypothesis of the study was to determine if there are differences in the ABR interpeak latency intervals between patients who are positive for the MeCP2 mutation and patients with some clinical similarities but without the mutation.

Methods

Participants

Eighty-nine female patients with Rett Syndrome ranging in age from 2.75 years to 36.3 years (mean age= 9.98; SD=6.64) participated in the study. Thirty-one of the patients with Rett syndrome were sedated for ABR testing and 58 did not receive sedation. The audiological status of the majority of the sedated patients has been described in detail previously [35]. Most of the patients were part of an ongoing investigation on the Natural history of Rett Syndrome. ABR measurements were undertaken as one component of a comprehensive protocol that included neurophysiology, clinical assessments, genetics and biochemical studies. All patients met the clinical criteria for Rett Syndrome described by the Rett Syndrome Diagnostic Criteria Work Group [36] and were positive for mutations in the MeCP2 gene. Eleven participants who were functioning in the severe-profound range of mental retardation but were tested and found to be without mutations in the MeCP2 gene also participated in this study. The participants without a mutation in MeCP2 gene ranged in age from 2.42-25.58 years (Mean age= 8.73; SD=7.31). Sedated subjects were studied in a protocol which included only the ABR. Un-sedated subjects were studied in a protocol that included the ABR as well as long latency evoked potentials sensitive to sedation effects and were consequently not sedated for any auditory evoked potential measurements. Subjects in both sedated and un-sedated groups met the identical conditions for selection in their respective protocols.

The normative group of 33 participants ranged in age from 1.5 to 28 years (mean age= 9.49; SD= 8.99) were also examined in this study. Twenty of the participants were sedated and 13 were not sedated. This group of participants were females from our normative ABR data base who had been seen by the Kennedy Krieger Audiology Department for audiological assessment. The group included a range of diagnostic conditions including language delay, developmental delay and cerebral palsy.

Written informed consent was obtained for patients in the study through the Johns Hopkins University School of Medicine Institutional Review Board.

MeCP2 mutation analysis

Patient blood samples, lymphoblast cell lines, or fibroblast cell lines were analyzed for mutations in the MeCP2 gene commercially or as part of our research study as described in the literature [37] including sequencing of exon 1 of the MeCP2 gene and by multiple ligation-dependent probe amplification (MLPA) analysis to identify large deletions or duplications[38].

Auditory brainstem response (ABR) testing

ABRs were recorded to rarefaction clicks presented at the rate of 8.4 sec. at 80 dB nHL. Responses to runs of 1024 clicks were averaged following filtering (100 to 3000 Hz), amplification and rejection of artifacts. The interpeak latency intervals (i.e., I-III, III-V, I-V) were computed. ABR test procedures are described in more detail in Pillion et al [21]. When subjects were sedated, chloral hydrate (75-100 mg./kg.) was utilized.

Analyses

Two factor analysis of variance were undertaken to assess the effect of ear and mutation and ear and sedation on the I-III, III-V and I-V interpeak latency intervals. Due to the limited number of mutation negative participants, a three factor analysis of variance could not be undertaken to examine the presence of interactions between ear, mutation status and the effects of sedation. Mutation negative cases were excluded for the two factor analysis of

variance assessing the effect of sedation due to the limited number of subjects. Differences between sedated and un-sedated control group subjects in the I-III, III-V and I-V interpeak latency intervals were analyzed by means of t-tests.

Results

Auditory brainstem Response findings are shown in Table 1. A two-factor analysis of variance was undertaken with ear and sedation as factors and revealed that sedated mutation positive participants had longer I-V interpeak latency intervals $F= 6.04$, $p<0.02$) then un-sedated mutation positive participants. There were no significant differences for the III-V ($F= 0.14$, $p>0.1$) or for the I-III ($F= 3.31$, $p>0.07$) interpeak latency intervals. No significant effects were found for ear for any of the interpeak latency intervals nor for any of the interactions. A two-factor analysis of variance was undertaken with ear and mutation status as factors. It was found that the III-V interpeak latency interval was significantly shorter ($F= 14.45$, $p< 0.0003$) for the mutation negative participants as compared to the mutation positive participants. There were no significant differences for the I-V ($F= 2.40$, $p> 0.1$) or for the I-III ($F= 2.42$, $p>0.1$) interpeak latency intervals between the mutation negative and the mutation positive participants. No significant effects were found for ear for any of the interpeak latency intervals or for any of the interactions. For the control group, there were no significant differences between sedated and un-sedated participants in the I-III, III-V, and I-V interpeak latency intervals.

Discussion

The present investigation sought to determine whether sedation exerts an effect on the interpeak latency intervals in patients with Rett syndrome. We noted that mutation positive patients who were sedated for ABR testing had significantly longer I-V interpeak latency intervals when compared to un-sedated mutation positive Rett Syndrome participants. Overall, all patients who were sedated for ABR testing did not differ significantly from the un-sedated participants in the I-III or III-V interpeak latency intervals. The above findings provide some explanation for the discrepant reports in the literature pertaining to the presence of ABR abnormalities in patients with Rett syndrome. Previous reports of ABR abnormalities in sedated patients with Rett syndrome [23,24] have not been replicated in the one study in which sedation clearly was not utilized [19]. Our previous work has shown that the ABR does not change over time in patients with Rett syndrome [21]. The absence of ABR abnormalities in the un-sedated patients with Rett Syndrome [19] and the lack of progression in the interpeak latency intervals over time reported previously [21] supports a view that Rett Syndrome is not characterized by progressive degeneration in the central auditory pathways in the auditory nerve and brainstem. The ABR III-V interpeak latencies were significantly prolonged in MeCP2+ patients as compared to MeCP2- patients, suggesting the presence of dysfunction in the central auditory pathways at brainstem levels in Rett Syndrome. This finding may be significant as MeCP2 mutations have been found to be associated with brainstem dysfunction such as dysphagia, and autonomic processes mediated at brainstem levels such as respiratory irregularities and sleep wake rhythm abnormalities [39]. A relationship between abnormal ABR findings and some of the clinical symptomatology manifested in patients with Rett syndrome needs close correlation. Many of the early ABR studies in Rett Syndrome did not include mutational analysis in selection criterion; some of those studies may have included a few mutation negative patients. This would be expected to reduce the possibility of obtaining abnormal ABR findings in those studies given the results in the present investigation.

Further studies involving groups selected with matching clinical characteristics and severity, sleep induced electrical abnormalities in EEG, and anticonvulsant use may allow elucidation

of the basis for the effects of sedation on the ABR in Rett Syndrome and other patient groups with mental retardation.

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Table 1

Auditory brainstem response interpeak latency intervals (Mean in msec., SD, 90% confidence intervals, and Range) for sedated and un-sedated participants who were positive or negative for mutation in the MeCP2 gene.

	Sedated		Un-Sedated	
	Positive	**Negative**	**Positive**	**Negative**
I-III	2.18	2.16	2.12	2.22
	(0.20)	(0.05)	(0.15)	(0.17)
	1.95-2.40	2.1-2.2	1.92-2.30	1.97-2.45
	1.80-2.75	2.10-2.20	1.80-2.53	1.92-2.46
III-V	1.96	1.98	1.95	1.77
	(0.18)	(0.08)	(0.16)	(0.15)
	1.80-2.15	1.85-2.05	1.77-2.20	1.56-1.96
	1.65-2.25	1.85-2.05	1.65-2.44	1.56-2.08
I-V	4.15	4.12	4.06	3.99
	(0.24)	(0.13)	(0.20)	(0.14)
	3.85-4.40	3.80-4.32	3.80-4.32	3.95-4.25
	3.75-4.75	3.95-4.25	3.52-4.65	3.76-4.20

Table 2

Auditory brainstem response interpeak latency intervals (Mean in msec., SD, 90% confidence intervals, and Range) for sedated and un-sedated normative group participants

	Sedated	Un-sedated
I-III	2.11	2.06
	(0.12)	(0.10)
	1.94-2.26	1.95-2.23
	1.90-2.35	1.95-2.25
III-V	1.95	1.93
	(0.12)	(0.12)
	1.78-2.11	1.74-2.08
	1.65-2.20	1.70-2.10
I-V	4.04	4.00
	(0.14)	(0.14)
	3.85-4.24	3.73-4.18
	3.85-4.35	3.65-4.20