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Auditory Evoked Potentials in Rett Syndrome

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Abstract

This study was designed to assess auditory function in subjects with Rett syndrome, a rare neurologic disorder that is characterized by progressive symptoms of dementia, ataxia, respiratory disorder, and communication disorder. Auditory evoked potentials, including the auditory brainstem response (ABR), middle latency response (MLR), and late vertex response (LVR), were recorded in 36 subjects with Rett syndrome. Results showed a systematic decline in auditory function from the peripheral to the central auditory system, with normal ABR in all subjects, normal MLR in 50 percent of subjects, and normal LVR in 36 percent of subjects. Results suggest that hearing sensitivity and the functional integrity of eighth nerve and auditory brainstem pathways are not affected in subjects with Rett syndrome. However, abnormality of both the MLR and LVR suggest the presence of central auditory disorder.

Key Words: Auditory brainstem response (ABR), auditory evoked potentials, central auditory system, hearing disorders, late vertex response (LVR), middle latency response (MLR), Rett syndrome

Rett syndrome is a rare neurologic disorder that is characterized by progressive symptoms, including dementia, ataxia, loss of purposeful hand movement, seizures, and respiratory disorders (Percy et al, 1985, 1987; Al-Mateen et al, 1986). First described by Andreas Rett in 1966 and, subsequently, by Hagberg et al in 1983, the syndrome occurs exclusively in females. Its etiology remains unknown. The incidence of the syndrome is estimated to be 1/15,000 live births (Olsson, 1987). Perhaps the most important differentiating feature of the disorder is its unusual progression. Development of children with Rett syndrome appears to be normal throughout the first 6 to 18 months of life, followed by a discernible arrest of psychomotor function. A period of regression follows, during which loss of acquired motor, cognitive, social, and communication skills occurs (Naidu et al, 1987).

A loss of acquired speech and language is pathognomonic of Rett syndrome. In general, speech and language skills regress to a level that is predominantly prelinguistic. Expressive communication is largely affectual, and receptive communication occurs only in the presence of multimodality cues (DiDonato et al, 1987). The extent to which auditory system function contributes to speech and language deficits is not yet clearly understood. Although hearing sensitivity has been reported to be normal (Naidu et al, 1986), there is some evidence that central auditory disorder may exist (Lenn et al, 1986; Bader et al, 1989).

Attempts to evaluate the auditory system using electrophysiologic measures have led to conflicting results. Some investigators have reported normal auditory brainstem responses (ABRs) in children with Rett syndrome (Hagberg et al, 1983; Zoghbi et al, 1985; Lenn et al, 1986). Others have reported abnormal ABRs (Pelson and Budden, 1987; Bader et al, 1989), middle latency responses (MLRs), and late vertex responses (LVRs) (Bader et al, 1989). Since severe communication disorder is a principal component of Rett syndrome, the nature and extent of any contribution to the problem by an auditory deficit is of substantial interest.

The purpose of this paper is to describe the results of auditory evoked potential measurement in 36 subjects with Rett syndrome. The ABR, MLR, and LVR were measured as part of a comprehensive audiologic evaluation in subjects undergoing a multidisciplinary assessment by the Rett Study Group at the Baylor College of Medicine.

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METHOD

Subjects

Subjects were 36 females with a diagnosis of Rett syndrome. They ranged in age from 2 years, 7 months to 28 years. Mean age was 9 years, 4 months. The diagnosis of Rett syndrome was based on results of a multidisci-plinary clinical evaluation. Criteria for the diagnosis were established by Hagberg et al (1985) and required: (1) that the subject was female; (2) that the pre- and perinatal periods were unremarkable and that psychomotor development throughout the first 6 to 18 months was normal; (3) that head circumference was normal at birth and that head growth decelerated between 6 months and 4 years of age; (4) that behavioral, social, psychomotor, and communicative skills regressed and that the subject showed signs of dementia; (5) that purposeful hand movements acquired between the ages of 1 and 4 years were lost; (6) that hand wringing stereotypes began between the ages of 1 and 4 years; and (7) that gait apraxia and truncal apraxia/ataxia occurred between the ages of 1 and 4 years.

All subjects were thought to have normal hearing sensitivity based on click ABR thresholds of 20 dB nHL or better and parental reports of normal auditory behavior. Because these subjects were multiply handicapped and tended to be quite active during testing, conventional behavioral audiometric measures could not be completed. Although startle responses and localization responses were observed in some children, the behaviors seldom exceeded age-equivalent levels of approximately 9 months in comparison to normally developing children. Because of the rudimentary nature of these responses, audiometric thresholds could not be estimated across the frequency range. Thus, we presumed normal hearing sensitivity based solely on ABR thresholds to clicks and on parental observations of response to sound.

Immittance measures indicated that 24 of the 36 subjects had type A tympanograms. The remaining 12 subjects showed evidence of middle ear disorder as indicated by a type B or type C tympanogram in at least one ear. In no case did the middle ear disorder result in a conductive hearing loss of sufficient magnitude to preclude assessment of the integrity of auditory evoked potentials.

Procedure

All evoked potentials were recorded using conventional signal averaging techniques. Gold disk electrodes were affixed to the vertex (noninverting), each earlobe (inverting), and the forehead (ground). EEG activity was preamplified at a voltage gain of 200,000:1 and bandpass filtered. The amplified EEG was signal averaged using the Nicolet CA-1000 averager. Auditory stimuli were delivered via etymotic ER-3A insert earphones. A summary of stimulus and recording parameters for the auditory evoked potentials is presented in Table 1.

All evoked potentials were evaluated with the patient in an unsedated condition. In an effort to maximize the recordability of state-dependent potentials, the LVR was evaluated first, followed by the MLR and the ABR. Because the LVR is most dependent on attentive state, measurement of the LVR was carried out at the beginning of the evaluation while the child was awake. Because the acquisition of a MLR may be related to subject state, yet not to the degree of the LVR, the MLR evaluation followed the LVR. At the completion of LVR and MLR testing, the subject typically would either fall asleep, or at least be calm and resting enough to measure the ABR under favorable recording conditions.

Interpretation of the ABR was based on the I–V interpeak interval and the I–V interaural difference. The ABR was considered to be normal if the interval or the interaural difference did not exceed two standard deviations of the mean, based on locally established normative values. For a MLR to be considered normal, it must have had an identifiable, repeatable, vertex-positive Pa wave, with a visible positive rise and negative fall that occurred between 21 and 38 msec following stimulus onset. Interpretation was based on presence of a response and ear symmetry of amplitude, latency, and morphology. For a LVR to be considered normal, it must have had an identifiable, repeatable, vertex-negative N_1 peak that occurred between 59 and 139 msec following stimulus onset. It must also have had a vertex-positive P_2

Table 1 Evoked Potential Signal and Recording Parameters for Recording ABR, MLR, and LVR

	Auditory Evoked Potential		
	ABR	*MLR*	*LVR*
Stimulus Parameters			
Signal type	click	500 Hz tone burst	500 Hz tone burst
Duration (msec)	0.1	10	100
Rate (per sec)	21.1	2.2	0.5
Intensity (dB nHL)	70	70	50
Recording Parameters			
Epoch (msec)	10	100	500
Number averaged	2048	1024	64
Filter passbands (Hz)			
High pass	150	10	1
Low pass	1500	250	30

peak that occurred between 125 and 208 msec. Latency ranges for both MLR and LVR were based on locally determined normative values (Stach and Hudson, 1990). As with the MLR, interpretation of the LVR was based on presence of a response and ear symmetry of amplitude, latency, and morphology.

All evoked potentials were not successfully recorded on all subjects due to poor recording conditions resulting from excessive patient movement, bruxism, or crying. Sedation was not used in an effort to avert influences on the later evoked potentials. As a result, conditions were judged to be acceptable enough to expect successful recording of ABRs in 32 of 36 subjects (89%), of MLRs in 28 subjects (78%), and of LVRs in 25 subjects (69%). When conditions were not judged to be acceptable enough to obtain reliable recordings, data were not included in the analysis. For example, in the case of MLR, recording conditions were judged to be acceptable in 28 of 36 subjects. In these 28, interpretation of the presence or absence of a response was considered valid. In the other 8, data were not considered to be reliable because of poor recording conditions, and no interpretation of the normalcy of the MLR was made.

RESULTS

Absolute and interpeak latencies of the ABR are summarized in Table 2. For comparison, data from two previous studies (Pelson and Budden, 1987; Bader et al, 1989) are also included. For both the right and the left ears, mean absolute and interpeak latencies were within normal limits and compared favorably with previous studies. On an individual basis, results were compared to expected normative maxima for both I–V interpeak interval (4.4 msec) and interaural I–V differences (0.4 msec). In no single case did a latency exceed these normal boundaries. Thus, in all subjects from whom an ABR could be successfully recorded, absolute and interpeak latencies were within normal limits.

Of the 28 subjects (56 ears) from whom an MLR could be successfully recorded, an identifiable response was present in 15 right ears and 14 left ears. Thus, the MLR was present in 52 percent of the testable ears and was present bilaterally in 50 percent of the testable subjects. The mean Pa was 38 msec for the right ears and 36 msec for the left ears.

Recording conditions for LVR measurement were considered to be acceptable in 25 subjects. An identifiable LVR was present in 10 right ears and 8 left ears. For the right ears, the mean N_1 was 128 msec and the mean P_2 was 193 msec. For the left ears, the mean N_1 was 121 msec and the mean P_2 was 200 msec. Considering the left and right ears in combination, LVR was normal in 36 percent and absent or abnormal in 64 percent of the 50 ears.

The percentages of normal and abnormal responses for each of the evoked potentials are presented in Figure 1. These are from the data that were deemed interpretable. Results show that the ABR was normal in 100 percent of the ears, the MLR was normal in 52 percent of the ears, and the LVR was normal in 36 percent of the ears of subjects with Rett syndrome.

We chose to assess the evoked potentials independently, so that, for example, if only an ABR could be recorded successfully in an individual subject, then only the ABR data were considered in the analysis. Thus, the distribution of abnormal responses was from different subsets of subjects across evoked potential types. In an effort to evaluate evoked potentials in the same subjects, a subgroup was formed that included 11 subjects from whom all three mea-sures were considered to be interpretable. Results showed that the ABR was normal in 100 percent of the ears, the MLR was normal in 27 percent of the ears, and the LVR was normal in 9 percent of the ears of these 11 subjects, confirming the systematic decline in auditory evoked potentials at successively higher levels in the auditory nervous system.

Table 2 ABR Latencies in Subjects with Rett Syndrome

	*ABR Latency**			
	Absolute			*Interpeak*
Study	*I*	*III*	*V*	*I–V*
Present study				
Right ear (n = 32)	1.6±0.1	3.7±0.2	5.7±0.2	4.1±0.2
Left ear (n = 32)	1.6±0.1	3.8±0.2	5.8±0.2	4.1±0.1
Bader et al (1989) (n= 7)	1.9±0.5	3.8±0.6	6.0±0.3	4.1±0.4
Pelson & Budden (1987) (n = 11)	1.6±0.1	3.8±0.1	5.7±0.1	4.1±0.2

* Mean ± standard deviation in msec.

ILLUSTRATIVE CASE

To illustrate these findings in an individual case, data are presented from a 7-year-old girl with Rett syndrome who was evaluated as a part of this study. She had a normal pre- and perinatal history and, by parental report, was thriving until the age of approximately 18 months, at which time she stopped talking. Her general psychomotor function then began to regress. At the time of her evaluation, she demonstrated behaviors typical of Rett syndrome, including delayed social, linguistic, and motoric skills. Her developmental skills were at age-equivalency levels ranging from 4 to 10 months across modalities. Immittance audiometry and ABR threshold testing revealed normal middle ear function and normal hearing sensitivity bilaterally. Despite normal sensitivity, her behavioral response to sound was estimated to be at the 13- to 16-month age-equivalency level.

Auditory evoked potentials are shown in Figure 2(A). The ABR is normal, with appropriate absolute and interpeak latencies. The MLR and LVR, however, are absent. In contrast, results from an 8-year-old male with autism are shown in Figure 2(B). A child with autism was chosen for comparison to demonstrate that evoked potentials could be recorded in a child of approximately the same age with a different type of neurologic impairment. Although in the past Rett syndrome has been mistaken for autism, the disorders can be differentiated (Olsson and Rett, 1987), as is obvious in their auditory evoked potentials. Evoked potential testing in this autistic subject revealed normal ABR, MLR, and LVR.

DISCUSSION

These results suggest a systematic decline in auditory function from the peripheral to the central auditory system in girls with Rett syndrome. Peripheral hearing sensitivity was normal in all cases in which evoked potential testing could be carried out, as characterized by click-evoked ABR threshold levels of 20 dB nHL or better. In addition, eighth nerve and lower auditory brainstem pathway function was normal, as characterized by normal absolute, interpeak, and interaural latencies of the ABR. Higher level function was not normal, however, as characterized by abnormal MLR results in 48 percent of the ears and abnormal LVR results in 64 percent of the ears tested.

The ABR latencies compare favorably with previously published results in subjects with Rett syndrome. In both previous papers, however, ABR data from subjects with Rett syndrome were found to be statistically different from normative values. For example, Pelson and Budden (1987) found a difference in absolute latency of Wave V and in the III–V interval between Rett subjects and a normal control group. Bader et al (1989) also found a difference between Rett subjects and normal subjects in absolute latency of wave V. Interestingly, in neither study was there a significant difference in the I–V interpeak latency, the most powerful metric of brainstem function. One explanation for the prolonged latency of wave V in the absence of a prolongation of the I–V interval is the presence of conductive hearing loss in the samples. In the present study, tympanometry suggested abnormal middle ear function in 33 percent of the subjects. A high prevalence of conductive hearing loss from middle ear disorder could easily account for differences between experimental subjects and control subjects. With regard to the III–V interpeak differences described by Pelson and Budden (1987), such differences are difficult to reconcile in the presence of normal I–V and I–III interpeak differences. Perhaps careful measurement on a larger sample would clarify this disparity.

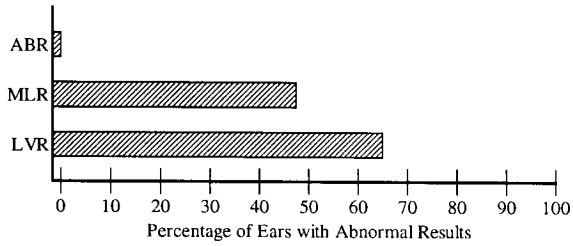

Figure 1 Distribution of abnormal results in subjects with Rett syndrome on the auditory brainstem response (ABR), middle latency response (MLR), and late vertex response (LVR).

Bader et al (1989) reported the presence of peak Pa in all seven of the subjects tested, but delayed latencies in four. They also reported the presence of LVR peaks in all seven subjects, with delayed latencies in two. These results are in substantial contrast to the present study and raise a question about the effect of patient age on the development of these later potentials. Subjects in the Bader et al study ranged in age from 10 to 22 years, while in the present study, they ranged in age from 2 to 28 years, with a mean age of 9 years. MLRs and LVRs have been successfully recorded in younger children with normal neurologic function, given control over subject physiologic state and stimulus rate. In the present study, all subjects were tested while awake, and stimulus rates were slow (2.2/sec) for measurement of the MLR. Thus, we would have expected to record responses in children in this age group. The absence of responses might be explained by the neurodevelopmental arrest that character-

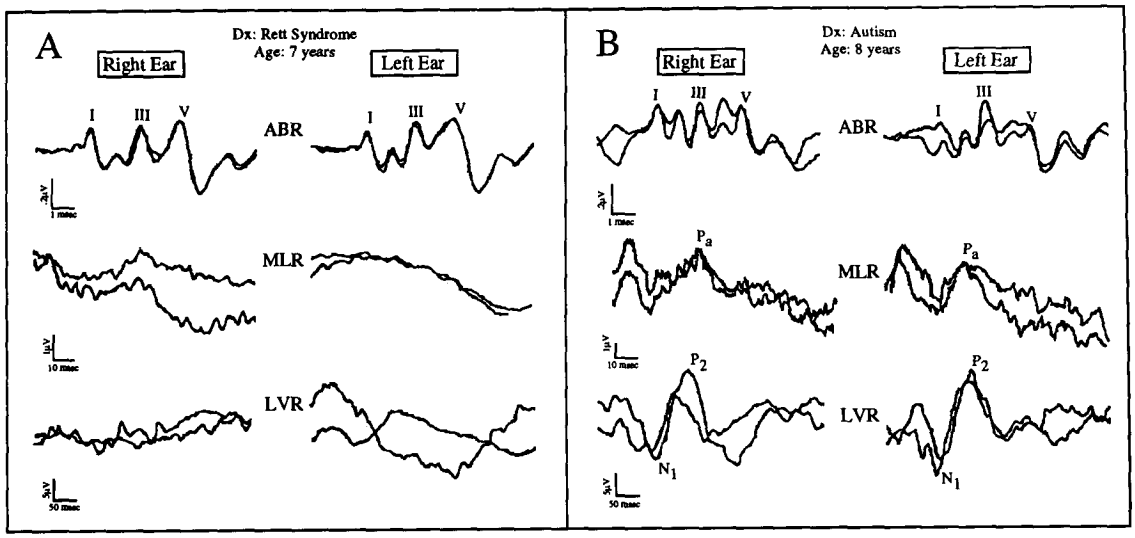

Figure 2 Auditory evoked potentials in *A*, a 7-year-old subject with Rett syndrome and *B*, an 8-year-old subject with autism.

izes this syndrome. We are not certain what to expect in the recording of MLRs and LVRs in children as young as 12 to 18 months, when such developmental arrest occurs. If it is assumed that the MLR and LVR are not recordable in this age group, then the absence of responses in older children might simply reflect a cessation or slowing of maturation related to the onset of the disorder. A longitudinal study of these evoked potentials in such children would be helpful in sorting out whether abnormalities in MLRs and LVRs reflect disordered or delayed central auditory nervous systems.

These results illustrate the abnormality of auditory evoked potentials in some children with Rett syndrome. The nature of the abnormality is in contrast to the normal auditory evoked potentials that are found in other neurologic disorders, such as autism. Regardless of whether or not these abnormal evoked potentials reflect deviation or developmental delay, the auditory dysfunction that they reflect must be considered as a possible contributor to the overall communication disorder exhibited by children with Rett syndrome. At pre-sent, the relation of the developmental arrest in speech and language function to auditory disorder measured later in life is not known.

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