Clinical Applications of the Middle Latency Response

Nina Kraus
Therese McGee

Abstract
The protocol developed in our laboratory for the assessment of hearing, involving the middle latency response (MLR), is described. Applications are illustrated in cases: (1) where the MLR was used to identify residual low frequency hearing and (2) where the MLR provided the only available threshold data because brainstem damage compromised the use of the ABR for hearing assessment.

An understanding of the MLR generating system can provide insight into the mechanisms responsible for the inconsistency of the MLR in children. Animal models and human data indicate that maturation of the generating network may involve an early developing, variable system influenced by the mesencephalic reticular formation, and a later developing, stable system dominated by the thalamo-cortical pathway. If the thalamo-cortical system is not yet mature, one might expect the response to vary depending upon the subject’s level of alertness. The observed MLR may then be dominated by other, sleep-dependent systems involving the reticular formation.

Key Words: Auditory evoked potentials (AEP), middle latency response (MLR), auditory brainstem response (ABR), electrophysiologic diagnosis, hearing tests, hearing disorders

The auditory middle latency response (MLR) time frame extends from 10 to 80 msec after stimulus onset. It follows the auditory brainstem response (ABR) and precedes the late auditory evoked potentials. A major neurogenic MLR component is Pa, a vertex-positive peak at about 30 msec.

Clinical uses of the MLR include the electrophysiologic estimation of hearing threshold and assessment of auditory pathway function. The MLR is valuable in the assessment of low frequency sensitivity, primarily because it is less dependent than the ABR on neural synchrony. Although the ABR can be elicited with frequency-specific stimuli having rise times of 1 to 2 msec, the response is small, and may be undetectable in clinical situations. The MLR obtained with such stimuli is often more robust.

Our protocol for the evaluation of hearing sensitivity involves both the ABR and the MLR. Because many of our patients have neurologic problems, and neural conduction time along the brainstem pathways is of interest, we obtain a click-evoked ABR. We use that response to assess hearing thresholds for the

Table 1 Recording Parameters

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>Positive: Cz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative: ipsi mastoid or earlobe</td>
<td></td>
</tr>
<tr>
<td>Ground: forehead</td>
<td></td>
</tr>
<tr>
<td>Stimuli</td>
<td>Monaural rarefaction clicks</td>
</tr>
<tr>
<td>Monaural tonebursts</td>
<td>Envelope: 2-1-2 ms with linear ramp or 2-0-2 ms with Blackman ramp</td>
</tr>
<tr>
<td>Recording parameters</td>
<td>Time Base 60, 80, or 100 ms</td>
</tr>
<tr>
<td>Low filter</td>
<td>Adults 3-15 Hz</td>
</tr>
<tr>
<td>High filter</td>
<td>Children 10-15 Hz</td>
</tr>
<tr>
<td>Filter slope</td>
<td>2-3 kHz</td>
</tr>
<tr>
<td>Rate</td>
<td>11/sec</td>
</tr>
<tr>
<td>Simultaneous ABR and MLR recording</td>
<td>Must have computer capabilities to record with a dual time base or record using a time window suitable for MLR and expand initial segment to view ABR</td>
</tr>
</tbody>
</table>
higher frequencies as well. Then we obtain both the ABR and the MLR in response to a 500 Hz tone burst to estimate hearing sensitivity for the lower frequencies.

The equipment settings for recording the MLR are summarized in Table 1. The primary differences between this protocol and a typical ABR protocol are the wider filter settings and the longer time base. The ABR and MLR can be recorded simultaneously, thus obtaining the MLR requires no additional testing time.

CLINICAL APPLICATIONS

In case A (Fig. 1), the MLR was used to test low frequency hearing sensitivity. No ABR was obtained to either click or 500 Hz stimuli. The MLR provided the only electrophysiologic indication that this patient had hearing in the lower frequencies.

The MLR often can be recorded when neural synchrony apparently has been compromised. Since the ABR is highly dependent

![Figure 1 Audiogram, auditory brainstem, and middle latency response results for Cases A and B. (See text for details.)](image-url)
on neural synchrony within the brainstem, damage to the auditory pathway may result in elevated ABR thresholds or an absent ABR, even though the peripheral hearing mechanism is functioning. This occurs primarily in patients sustaining diffuse neurologic damage as a consequence of perinatal asphyxia, hyperbilirubinemia, or head trauma (Worthington and Peters 1980; Kraus et al, 1985b). Case B (Fig. 1) involves such a patient. Although no ABR was obtained, the MLR reflected her audiologic threshold of 30 dB HL.

Clinical use of the MLR is limited by the following:

1. As a hearing test for children, use of the MLR is currently limited by the variability of the response.
2. As a neurologic test of central brainstem function, use of the MLR is limited by an incomplete understanding of the MLR generating system.

An understanding of the mechanisms underlying the inconsistency of MLRs in children and the identification of the generating system can, in our opinion, considerably enhance clinical use of the response.

THE MLR DURING DEVELOPMENT

Our efforts to assess low frequency thresholds are directed at very young, difficult-to-test patients. However, the MLR is much more labile in children than in adults. The probability of obtaining an MLR in a very young child is about 20 percent. The response follows a systematic developmental course, being obtained in 90 percent of 12-year-olds (Kraus et al, 1985a). The fact that the MLR is sometimes present in young children indicates that at least part of the MLR generating system develops early in life, but it is later developing generators that impart stability to the response.

We know that MLRs can at times be measured in children. If we can determine what underlies the response lability, then it should be possible to manipulate the test protocol to maximize the acquisition of responses. A significant key to understanding the response lability is the identification of the MLR generator system.

MULTIPLE GENERATOR CONCEPT—ANIMAL RESEARCH

Experimental animal models have been useful in identifying the mechanisms and multiple neural structures that constitute the MLR generating system (Kraus et al, 1988). In contrast to the human MLR waveform, guinea pigs and gerbils have a complex MLR topography (Fig. 2). In these animals, recording electrodes over the temporal lobe contralateral to the stimulus ear yield an MLR waveform with three waves, A, B, and C. With the electrodes at the midline, a response with two waves, M− and M+, is obtained. The ABC complex is a large robust response, while the M−/M+ waveform is smaller in amplitude and more labile.

Interestingly, in gerbils, all waves show a developmental pattern with a systematic increase in the detectability of response with age. Individual waves show different developmental time courses, with the M−/M+ response developing much earlier than the ABC complex. Lesions in the primary auditory cortex may eliminate the ABC complex, yet have no effect on the M−/M+ waveform. Other data corroborate hypotheses that the ABC complex is generated by the thalamo-cortical pathway, while the M−/M+ response is dominated by subcortical generators, perhaps including areas of the reticular formation. In essence, proposed generator sites for the MLR include all auditory specific structures central to the inferior colliculus and some nonauditory specific structures such as the reticular formation and polymodal thalamus. Historically, scientists have taken the approach that a given MLR wave is generated by a particular anatomic structure. It seems more likely that the MLR is the product of a complex system involving the interactions from many brain structures.
MULTIPLE GENERATORS IN HUMANS

In humans, there is evidence that wave Pa is affected by temporal lobe lesions. A one-sided lesion will reduce Pa amplitude on the affected side (Kraus et al., 1982; Scherg and Von Cramon, 1986; Kileny et al., 1987). With bilateral temporal lobe lesions, the MLR can be very disorganized (Ozdamar et al., 1982). However, there have been reports that a small Pa can be recorded at the vertex in some patients with bilateral temporal lobe lesions (Parving et al., 1980). This argues for the contribution of other generating influences.

If, similar to the animal MLR, the human MLR has cortical and subcortical generators with different developmental time courses, then the MLR will reflect the contributions of different generators depending on the child's age. We hypothesize that the later developing thalamocortical generators of the auditory system give stability to the response, while the early developing subcortical generators are more labile, and fluctuate with awareness state. As the cortical generators mature, the response becomes stable even during sleep.

Despite the superficially chaotic nature of the MLRs obtained in children, what we are learning about the MLR is orderly and systematic. Through an understanding of the underlying physiologic processes strategies can be devised to make the MLR more clinically effective.

CONCLUSIONS

Although the MLR can provide valuable information, its clinical use has been limited in children due to low detectability. Clinical and animal data indicate that multiple generators contribute to the MLR and that these generators vary in their developmental time courses. It is becoming increasingly apparent that a systematic developmental process underlies the detectability of MLRs in children. We expect that a better understanding of the developmental process will further the clinical utility of MLR.

Acknowledgment. We thank Trent Nicol for his contributions in the preparation of this manuscript.

Supported by NIH DC00264 and the Foundation for Hearing and Speech.

REFERENCES


