PERIPHERAL NERVE CONDUCTION ABNORMALITIES IN CHILDREN EXPOSED TO ALCOHOL IN UTERO

MÁRIA DE LOS ÁNGELES AVARIA, MD, JAMES L. MILLS, MD, MS, KARIN KLEINSTEUBER, MD, SOFIA AROS, MD, MARY R. CONLEY, MA, CHRISTOPHER COX, PhD, MARK KLEBANOFF, MD, MPH, AND FERNANDO CASSORLA, MD

Objective We performed a longitudinal study of nerve conduction velocity to determine the effect of prenatal alcohol exposure on the peripheral nervous system.

Study design We studied 17 children exposed to >2 oz of absolute alcohol/day prenatally and 13 unexposed children, identified prospectively from a cohort of pregnant women screened during prenatal care. Nerve conduction assessment was done on the median, ulnar, peroneal and tibial nerves during the newborn period and between 12 and 14 months of age.

Results At both assessments the alcohol-exposed subjects had significantly slower ulnar motor nerve velocity (P = .007), smaller proximal (P = .018) and distal amplitude (P = .051). They also showed reduced tibial nerve velocity (P = .06) and a decrease in distal amplitude.

Conclusions This study demonstrates that prenatal alcohol exposure is associated with abnormalities in nerve electrical properties, and that the pattern is different from that seen in adults. Electrophysiologic abnormalities in peripheral nerves should be added to the problems found in children of alcohol abusing mothers. (J Pediatr 2004;144:338-43)

Clinical and experimental data have shown that consumption of alcohol during pregnancy can have severe teratologic effects on the human fetus. The more severe manifestations of prenatal alcohol exposure, termed fetal alcohol syndrome (FAS) include dysmorphic facies, pre- and postnatal growth restriction, and behavioral and cognitive dysfunction.1 Alcoholic peripheral neuropathy in adults has been recognized for more than 200 years; nevertheless, little attention has been given to possible effects of alcohol exposure in utero on the developing peripheral nervous system. Prenatal alcohol exposure affects the sensory nervous system. Both visual and auditory evoked potentials were abnormal in infants exposed prenatally to alcohol. The general findings suggest that alcohol exposure delays development of sensory neural systems.2 Despite this evidence of alterations in central sensory neural systems, to our knowledge there have been no studies of the effect of alcohol on the developing peripheral nervous system.

We performed a longitudinal study of alcohol-exposed and unexposed newborns to determine whether prenatal alcohol exposure damages the developing peripheral nervous system.

METHODS

Subjects

The infants included in this study were term neonates evaluated in a prospective study of the effects of prenatal exposure to alcohol on offspring of heavy drinking mothers in Chile—The NICHD–University of Chile Alcohol In Pregnancy Study. The infants were classified into two groups, those exposed to alcohol in utero, and unexposed controls. Alcohol exposure was identified prenatally by screening, generally at the first prenatal visit. Those suspected of heavy drinking had a follow-up home visit to confirm their drinking status. These visits identified 101 women who were drinking at least 2 oz of absolute alcohol per day.
alcohol per day on average (Aros et al, unpublished data). Unexposed subjects were selected prenatally from the same cohort. They were confirmed to be nondrinkers by home visits. The groups were closely matched for maternal age, parity, and gestational age at entry.

The nerve conduction study was added when the general alcohol study was already underway. At the time the nerve conduction study was started, there were 17 alcohol-exposed and 13 control children who were in utero or less than one month of age. These were the only children who fit the protocol requirement for study in the neonatal period (one month of age).

Clinical examination, including a complete neurologic examination, was performed by a child neurologist before the recordings. In addition, all the children underwent a neurologic evaluation at 6 months of age and developmental and neurologic assessment at 12 months of age. Neurologic evaluation included mental status, cranial nerves, motor performance (including strength, tone, reflexes, and coordination). All testing and examinations were performed by examiners blinded to the status (alcohol-exposed or unexposed) of the subjects.

Of the 17 alcohol-exposed subjects, 16 had dysmorphology assessments performed during the first year of life by a pediatric geneticist who was blinded to the status of the participants but knew that this was a study of alcohol effects. She focused on factors associated with fetal alcohol exposure including assessment of growth and minor dysmorphic features, eg, palpebral fissure length, philtrum, vermilion border. On the basis of these preliminary results, there were no subjects with the classical FAS phenotype and there was one who had possible fetal alcohol effects. Examinations at one year may not be diagnostic because dysmorphism can be more readily recognized later in life.

To test our hypothesis that alcohol in utero may cause neuropathy, we chose to examine nerves in the upper and lower limbs. Polyneuropathy implies diffuse involvement of nerves—motor, sensory, and/or autonomic—which can relate to velocity (myelin damage) or amplitude (axonal damage), or both.

We examined the median, ulnar, peroneal, and tibial nerves because these are more accessible, especially in newborns, making it easier to obtain reproducible results.

Peripheral Nerve Conduction Abnormalities in Children Exposed to Alcohol in Utero

### Table. Nerve conduction studies results: Difference between adjusted means for alcohol-exposed subjects versus controls

<table>
<thead>
<tr>
<th></th>
<th>Newborn Alcohol-control exposed</th>
<th>Follow-up Alcohol-control exposed</th>
<th>Differences between adjusted means for alcohol-exposed vs controls (all observations)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median nerve—R</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal amplitude (mV)</td>
<td>1.61</td>
<td>1.93</td>
<td>4.44</td>
<td>4.97</td>
</tr>
<tr>
<td>Proximal amplitude (mV)</td>
<td>1.71</td>
<td>1.83</td>
<td>5.17</td>
<td>5.69</td>
</tr>
<tr>
<td>F–wave (msec)</td>
<td>18.12</td>
<td>18.07</td>
<td>17.16</td>
<td>16.14</td>
</tr>
<tr>
<td>Sensory conduction velocity (m/s)</td>
<td>30.14</td>
<td>27.06</td>
<td>46.51</td>
<td>47.66</td>
</tr>
<tr>
<td>Motor conduction velocity (m/s)</td>
<td>27.54</td>
<td>29.14</td>
<td>48.15</td>
<td>49.80</td>
</tr>
<tr>
<td><strong>Ulnar nerve—L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal amplitude (mV)</td>
<td>2.13</td>
<td>3.31</td>
<td>4.70</td>
<td>5.55</td>
</tr>
<tr>
<td>Proximal amplitude (mV)</td>
<td>1.66</td>
<td>2.68</td>
<td>4.40</td>
<td>5.56</td>
</tr>
<tr>
<td>F–wave (msec)</td>
<td>18.85</td>
<td>19.08</td>
<td>18.59</td>
<td>17.00</td>
</tr>
<tr>
<td>Sensory conduction velocity (m/s)</td>
<td>34.35</td>
<td>27.06</td>
<td>50.29</td>
<td>49.94</td>
</tr>
<tr>
<td>Motor conduction velocity (m/s)</td>
<td>31.46</td>
<td>36.78</td>
<td>55.52</td>
<td>65.16</td>
</tr>
<tr>
<td><strong>Tibial nerve—L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal amplitude (mV)</td>
<td>2.39</td>
<td>3.82</td>
<td>7.70</td>
<td>7.86</td>
</tr>
<tr>
<td>Proximal amplitude (mV)</td>
<td>1.78</td>
<td>3.08</td>
<td>7.91</td>
<td>6.64</td>
</tr>
<tr>
<td>F–wave (msec)</td>
<td>27.09</td>
<td>26.71</td>
<td>23.92</td>
<td>24.18</td>
</tr>
<tr>
<td>Motor conduction velocity (m/s)</td>
<td>22.96</td>
<td>26.43</td>
<td>43.93</td>
<td>47.98</td>
</tr>
</tbody>
</table>

*For this nerve, the test for interaction was significant. The test for interaction was a comparison of the different age regressions in the two groups. The regression coefficients indicated that the response was increasing more rapidly in the case group than in controls. Because the controls started higher than the cases, the two regression lines actually crossed (at 200 days of age), and the cases then had higher values than the controls.
Motor Nerve Conduction Studies

Measurements of conduction velocity were made by stimulating the motor nerve with rectangular supramaximal stimuli at two different points and recording an evoked muscle action potential. The ulnar nerve was stimulated at the elbow and the wrist; the muscle action potential was recorded from the abductor digiti quinti. The tibial nerve was stimulated in the popliteal fossa and at the medial malleolus; the muscle action potential was recorded from the flexor hallucis brevis. The median nerve was stimulated at the cubital fossa and the wrist, with recording from the abductor pollicis brevis. The peroneal nerve was stimulated at the ankle and the fibular head, with recording from the extensor digitorum brevis.

Sensory Nerve Conduction Studies

The sensory nerve compound action potential was recorded with ring electrodes placed over the index finger for the median nerve and the fifth finger for the ulnar nerve with stimulation at the wrist. Surface electrodes placed over the ankle were used to record superficial peroneal nerve potentials after stimulation at the lateral aspect of the leg, 4 cm proximal to the recording electrode in the newborn and 8 cm in the 1-year-old.

Statistical Analysis

Repeated measurements of nerve conduction velocity in groups of alcohol-exposed and unexposed control subjects at approximately 10 to 20 days and one year of age were analyzed by analysis of covariance, using a mixed model to account for the within-subject correlation between repeated measurements on the same subject. The independent variables in the model were group (exposed/unexposed) and age of testing. The analysis included a comparison of individual regressions in each group (a test for different slopes). If this test indicated a lack of parallelism (different slopes), then the difference between the two groups is age-dependent, and is interpreted by examining the separate regressions. If this test was negative, then a second model was used, assuming parallel regressions. In this case the difference between the two groups is independent of age, and is reported as the difference between the age-adjusted means.

RESULTS

There were 17 offspring of heavy alcohol-drinking mothers and 13 offspring of nondrinking mothers studied. The alcohol-exposed group contained 10 males and 7 females; the unexposed group contained 6 males and 7 females. The
birth weight range was 2630 g to 4080 g for the alcohol-exposed group and 2690 g to 3830 g for the unexposed group. The alcohol-exposed and control groups did not differ significantly in maternal age (21.8 ± 6.7 and 24.8 ± 9.6 years, respectively), parity (11 [64.7%] and 10 [76.9%] respectively of primiparous women), gestational age at entry (15.4 ± 9.3 and 10.8 ± 3.8 weeks, respectively) or sex (males 10 [58.8%] and females 6 [46.2%]), respectively.

The median (interquartile range) age at first testing was 13.5 days (11-14.5) for the alcohol-exposed group and 15 (9-24) for the unexposed group. At the second test it was 401 (374-429) days for the alcohol-exposed group and 400 (391-413) days for the unexposed group. To determine whether differences between the two groups in nerve conduction remained the same or changed over time, we conducted a longitudinal analysis adjusting for age at testing. There were measurements available on 11 alcohol-exposed and 5 unexposed subjects at both time points; for the remaining subjects, data from the one time point that they were tested was included.

The longitudinal analysis showed that differences between the groups seen at the first examination persisted at the time of the second examination, except in the case of the proximal amplitude of the tibial nerve. The tibial nerve proximal amplitude was initially higher in alcohol-exposed subjects then became higher in unexposed subjects, a finding that we suspect is the result of chance.

The alcohol-exposed subjects had significantly slower velocities in the ulnar motor nerve ($P = .007$), smaller proximal amplitude ($P = .018$), and distal amplitude of the ulnar nerve ($P = .051$). The alcohol-exposed subjects also showed a reduced velocity of the tibial nerve ($P = .06$) and a decrease in distal amplitude of borderline significance. The adjusted mean differences are shown in Table I.

Thus, the alcohol-exposed children showed significant abnormalities in nerve conduction velocity and amplitudes on the assessment of these two nerves. No statistically significant differences were found in median, peroneal nerve, or sensory nerve conduction velocities or amplitudes between alcohol-exposed and unexposed children.

Figure 1 shows the results for each subject at each time period with a least-squares regression line illustrating the overall difference between the two groups by age at examination. The figures indicate, as noted above, that the differences seen in the newborn period remained at the time of the second examination. In addition, alcohol-exposed children
showed statistically significant smaller proximal and distal amplitudes (CMAP) in ulnar nerves in the newborn period as shown in Figures 2 and 3, respectively; this difference persisted at one year of age.

Thus, there was little or no evidence that the alcohol-exposed children had any catch-up or improvement in nerve conduction in ulnar and tibial nerves, relative to the unexposed children in the first year of life or beyond.

The neurologic assessment done before nerve conduction testing showed no abnormalities in mental status, cranial nerves, motor performance, including strength, tone, reflexes, and coordination, in alcohol-exposed or unexposed subjects. Age-appropriate sensory examination items such as response to tactile and fork stimulation were normal in both groups. Because some women reduced their consumption of alcohol or stopped drinking after being advised of the danger, we compared nerve conduction study results in women who drank throughout pregnancy, women who stopped in the third trimester, women who stopped in the second trimester, and women who did not drink at all (control subjects). Those who stopped drinking did not have significantly better outcomes on their nerve conduction studies than those who drank throughout pregnancy.

**DISCUSSION**

We report on electrophysiologic study of the peripheral nervous system in neonates and young children exposed to alcohol in utero. Alcohol-exposed children showed a significant reduction in both nerve-conduction velocity and amplitude in the newborn period that persisted at one year of age. Changes were present in both the ulnar and tibial nerves, and reflect both myelin involvement (reduced velocity) and axonal damage (decreased amplitude).

The absence of statistically significant differences in the peroneal nerve could be ascribed to the very small size of the CMAP amplitudes, as expected at this age, because of the small muscle bulk in the extensor digitorum brevis where the potential is recorded. With respect to the median nerve, the negative results could be ascribed to different patterns of involvement depending on age, as is the case with some toxic neuropathies. Peripheral neuropathies of toxic origin can be classified into three distinctive pathologic classes: (1) neuronopathies, where the target is the neuronal cell body; (2) myelinopathies, with impairment of the Schwann cell function; and (3) axonopathies usually in the form of a distal axonopathy, in some cases with secondary demyelination. It has been recognized that, although the majority of toxic...
neuropathies produce an axonal degeneration, they show a wide variety of individual, electrophysiologic differences. For example, lead intoxication leads to a pure sensory segmental demyelination in adult rats, but an encephalomyelopathy in suckling rats. In guinea pigs it produces a different type of damage: a mixed axonal degeneration and segmental demyelination. The clinical picture also differs according to age, appearing as a pure motor upper extremities involvement (with a predilection for the radial nerve) in adult lead intoxication, compared with the predominantly lower limb neuropathy with associated encephalopathy in childhood lead intoxication.

Both electrophysiologic and histologic studies have confirmed that alcoholic neuropathy in adults is predominantly an axonal neuropathy. Nerve conduction studies show severely reduced sensory nerve amplitudes with normal or mildly reduced conduction velocities. Needle electromyography may reveal signs of denervation and reinnervation in distal muscles of the lower extremities. This examination was not performed in our study because of its invasive nature and associated discomfort for the patient.

Electrophysiologic findings in our study cannot exclude sensory small fibers involvement, because this requires quantitative measurements of pain and temperature thresholds in which full collaboration is needed for its assessment.

The results of our study could reflect a form of damage age-related to the immature developing peripheral nervous system different from that seen in adults. Alcohol neuropathy in adults resolves after discontinuation of ingestion. Our results show that differences persist at one year; therefore, this is not like adult neuropathy. It suggests that alcohol can cause permanent, or at least persistent, damage to developing nerves, not temporary damage as it does to developed nerves.

Alcoholic peripheral neuropathy was described by Lettsom in 1787 and confirmed later by Jackson. Axonal degeneration of both myelinated and unmyelinated fibers has been described by Behse and Buchthal in 1977. However, the precise pathogenesis of alcohol neuropathy remains unclear. Nutritional deficiency (frequently associated with alcohol neuropathy) and the direct toxic effect of alcohol have both been implicated. Behse and Buchthal, in their study of alcoholics compared with nonalcoholic control subjects, concluded that nutritional deficiencies alone did not produce the neuropathy. Monforte et al concluded that alcohol appears to be toxic to autonomic and peripheral nerves in a dose-dependent manner.

The limitations and strengths of this study should be noted. This was a small study. It was, however, sufficiently large enough to find statistically significant changes in the alcohol-exposed subjects. A larger study might have been able to demonstrate additional abnormalities. In fact, we used extremely conservative two-tailed significance tests. It is universally recognized that alcohol can disrupt nerve function, but not improve it. Therefore, a one-tailed significance test might be more appropriate. Using a one-tailed test, the tibial motor conduction test would be significant ($P = .031$) and the tibial distal amplitude would be of borderline significance ($P = .07$). We were only able to study the later entrants into the parent study. None of the controls had any prenatal alcohol exposure, therefore, those we studied were no different from the rest of the main control population.

This study was a geographically-based prospective study with good documentation of alcohol exposure during the pregnancies of interest. It had concurrently studied unexposed subjects matched on the age of testing.

There is overwhelming evidence that heavy alcohol consumption during pregnancy is dangerous to the developing fetal nervous system, yet peripheral nerve function has not been examined. This is the first study to demonstrate that prenatal alcohol exposure is associated with abnormalities in nerve electrical properties, including both axonal and demyelinating effects. Moreover, these effects persist at one year of age. Although there was no clinical evidence of peripheral neuropathy, clinical damage cannot be ruled out because of the age of the children. Pediatricians and pediatric neurologists should add abnormal nerve conduction to the problems that can result from alcohol abuse during pregnancy.