Early Language Development in Children Exposed to or Infected With Human Immunodeficiency Virus

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ABSTRACT. *Objectives.* **To compare language development in infants and young children with human immunodeficiency virus (HIV) infection to language development in children who had been exposed to HIV but were uninfected, and (among subjects with HIV infection) to compare language development with cognitive and neurologic status.**

Design. **Prospective evaluation of language development in infected and in exposed but uninfected infants and young children.**

Setting. **Pediatric Infectious Disease Clinic, State University of New York–Health Science Center at Syracuse.**

Subjects. **Nine infants and young children infected with HIV and 69 seropositive but uninfected infants and children, age 6 weeks to 45 months.**

Results. **Mean Early Language Milestone Scale, 2nd edition (ELM-2) Global Language scores were significantly lower for subjects with HIV infection, compared with uninfected subjects (89.3 vs 96.2, Mann–Whitney *U* test). The proportion of subjects scoring >2 SD below the mean on the ELM-2 on at least one occasion also was significantly greater for subjects with HIV infection, compared with uninfected subjects (4 of 9 infected subjects, but only 5 of 69 uninfected subjects; Fisher's exact test). Seven of the 9 subjects with HIV infection manifested deterioration of language function. Four manifested unremitting deterioration; only 1 of these 4 demonstrated unequivocal abnormality on neurologic examination. Three subjects with HIV infection and language deterioration showed improvement in language almost immediately after the initiation of antiretroviral drug treatment. Magnetic resonance imaging or computed tomography of the brain were performed in 6 of 7 infected subjects with language deterioration, and findings were normal in all 6. ELM-2 Global Language scaled scores showed good agreement with the Bayley Mental Developmental Index or the McCarthy Global Cognitive Index ($r = 0.70$). Language deterioration, or improvement in language after initiation of drug therapy, coincided with or preceded changes in global cognitive function, at times by intervals of up to 12 months.**

Conclusions. **Language deterioration occurs commonly in infants and young children with HIV infection, is seen frequently in the absence of abnormalities on neurologic examination or central nervous system imaging, and may precede evidence of deterioration in global cognitive ability. Periodic assessment of language development should be added to the developmental monitoring of infants and young children with HIV infection as a means of monitoring disease progression and the efficacy of drug treatment.** *Pediatrics* **1998;102(1). URL: http://www.pediatrics.org/cgi/content/full/102/1/e8;** ***language, speech, HIV, children, development.***

ABBREVIATIONS. HIV, human immunodeficiency virus; CNS, central nervous system; ELM-2, Early Language Milestone Scale, 2nd edition; MDI, Mental Developmental Index; GCI, Global Cognitive Index.

Disorders of speech and language are common in school children with human immunodeficiency virus (HIV) infection.[1–5] Less information is available about language development in very young children infected with HIV. We studied the development of speech and language in a sample of infants and young children born to women with HIV infection, with the following two goals: 1) to compare language development in infants and young children with HIV infection with language development in children who had been exposed to HIV but were uninfected, and 2) (among patients with HIV infection) to compare language development with cognitive and neurologic status.

METHODS

Setting

This study was performed at the Pediatric Infectious Disease Clinic of the State University of New York–Health Science Center at Syracuse. This clinic is the only facility for care of children with HIV infection in Central New York, a 16-county region with a base population of 1.8 million, a yearly birth rate of ~24 000, and a newborn HIV seroprevalence rate of 0.1%.[6] The clinic cares for all identified children with HIV infection in Central New York, regardless of ability to pay or eligibility for enrollment into a research protocol.

Subjects

Potential subjects consisted of 104 consecutive infants and children 6 weeks to 36 months of age when first examined who were evaluated between July 1, 1992, and March 31, 1997 (Table 1). All subjects were receiving Medicaid; almost all parents were unemployed. Informed consent was obtained for central nervous system (CNS) imaging studies and for neurologic and psychological evaluations undertaken as part of approved drug treatment trials. All other data were acquired through the course of routine clinical care. Each child's infection status was classified as infected, uninfected, or indeterminate. Infection status was determined by standard laboratory methods.[7] Nine children were infected, 69 were uninfected, and 26 infants younger than 6 months of age had

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TABLE 1. Study Subjects (n = 78)

Sex (n/%)	
Male	36 (46)
Female	42 (54)
Race (n/%)	
Black	41 (53)
White	23 (29)
Hispanic	12 (15)
Other	2 (3)
Age (mo)	
Mean	15.3
Range	1.5–45
Length of follow-up (mo)	
Mean	15.1
Range	0–38

indeterminate infection status as of March 31, 1997. The 78 children whose infection status was known form the basis for this report.

Methods

All subjects underwent periodic language testing with the Early Language Milestone Scale, 2nd edition (ELM-2) at ~3-month intervals. The ELM-2 is a standardized instrument that assesses auditory expressive, auditory receptive, visual, and global language ability in children from birth to 36 months of age. The ELM-2 also may be used with developmentally delayed children 36 months of age and older whose language abilities lie within the 0- to 36-month range. Many items on the ELM-2 can be determined by caregiver report. The ELM-2 is standardized with a mean score of 100, and 1 SD = 15 points. As with other developmental tests, −2 SD (standard score, <70) is considered clinically significant. Details regarding the derivation and validation of the ELM-2 have been reviewed elsewhere.[6] All subjects also underwent periodic neurologic examination with a standardized battery, the Neurologic Examination for Children.[8] All infected children in antiretroviral drug treatment protocols also underwent periodic psychological testing with the Bayley Scales of Infant Development[9] or the McCarthy Scales of Children's Abilities.[10] The ELM-2 and Neurologic Examination for Children were administered by one of the investigators (J.C.), who was blind to the infection status of each subject and the results of psychological testing.

We compared the distribution of mean ELM-2 Global Language scaled scores between infected and exposed but uninfected subjects. Because we were particularly interested in identifying children with language delay, we also compared the proportion of infected and uninfected subjects who scored <70 (−2 SD) at least once, by means of a 2 × 2 contingency table. To compare language development with overall cognitive development (infected subjects only), we calculated the Pearson product-moment correlation coefficient between the Bayley Mental Developmental Index (MDI) or the McCarthy Global Cognitive Index (GCI), and ELM-2 Global Language scaled score. We also performed a qualitative review of each infected subject's neurodevelopmental course. We excluded from analysis one uninfected subject with known CNS malformation (agenesis of the corpus callosum) and two Bayley scores from one infected subject that were judged to be invalid. Statistical analyses were performed with Prism 2.0 for Windows (GraphPad Software, San Diego, CA).

RESULTS

Mean duration of follow-up was 15.1 months (range, 0 to 38 months). Infected subjects were evaluated an average of 5.9 times each, and uninfected subjects an average of 4.2 times each. This difference was not statistically significant (P = .0573, Mann–Whitney U test) or was marginally significant (P = .0381, unpaired t test), depending on whether one assumes a Gaussian distribution for the number of evaluations within each group.

Mean ELM-2 Global Language scores were lower for subjects with HIV infection compared with subjects who were seropositive but uninfected (89.3 vs 96.2; P = .026, Mann–Whitney U test) (Fig 1). Language deterioration was observed in 7 of 9 subjects with HIV infection. Unremitting deterioration in language was observed in 4 infected subjects, despite antiretroviral drug treatment in 3 cases (Fig 2A). Two of these 4 subjects had normal neurologic findings, 1 had mild impulsivity, and 1 (whose parents refused antiretroviral therapy) manifested irritability and apathy during the last few weeks before her death from opportunistic infection at 10 months of age. Three subjects with HIV infection manifested progressive language deterioration, followed by marked improvement after initiation of antiretroviral therapy (Fig 2B). Neurologic finding was normal in 1, minimally suspicious in 1 (trace hyperreflexia in the lower extremities without spasticity), and frankly abnormal in 1 (spastic quadriparesis). Improvement in language function in these 3 subjects was accompanied by improved medical status and by partial resolution of quadriparesis in the child affected. Magnetic resonance imaging or computed tomography of the brain was performed in 6 of 7 infected subjects who manifested language deterioration and was normal in all 6. The remaining 2 subjects with HIV infection manifested normal language function at all times. Four of 9 subjects with HIV infection, but only 5 of 69 uninfected subjects, scored <70 on the ELM-2 one or more times (Fisher's exact test, P = .0084). No child in the uninfected group manifested progressive deterioration of language. The ELM-2 showed good agreement with the Bayley MDI and McCarthy GCI among subjects who were infected (r = 0.70, P = .0001) (Fig 3).

DISCUSSION

Neurodevelopmental assessment of infants and toddlers with HIV infection generally has been limited to measures that stress sensorimotor skills, such as the Bayley, coupled with traditional neurologic examination.[11–16] Condini et al,[17] reporting on 18- to 30-month-old infected but not ill subjects, noted reduced verbal output in the second year of life. Wachtel et al,[18] reporting on a cohort of children evaluated at 6, 12, and 18 months, noted a statistically significant difference in language development between infected and uninfected subjects at 12 months, but not at 6 or 18 months.

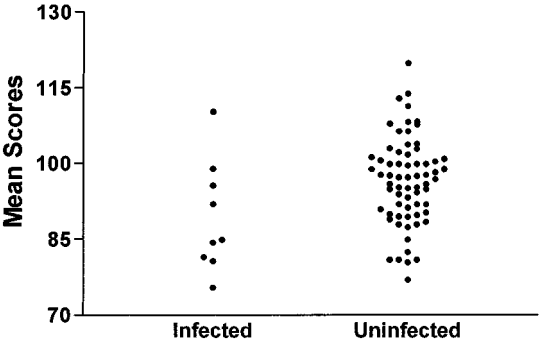

Fig 1. Distribution of mean ELM-2 Global Language scaled scores for infected and uninfected subjects.

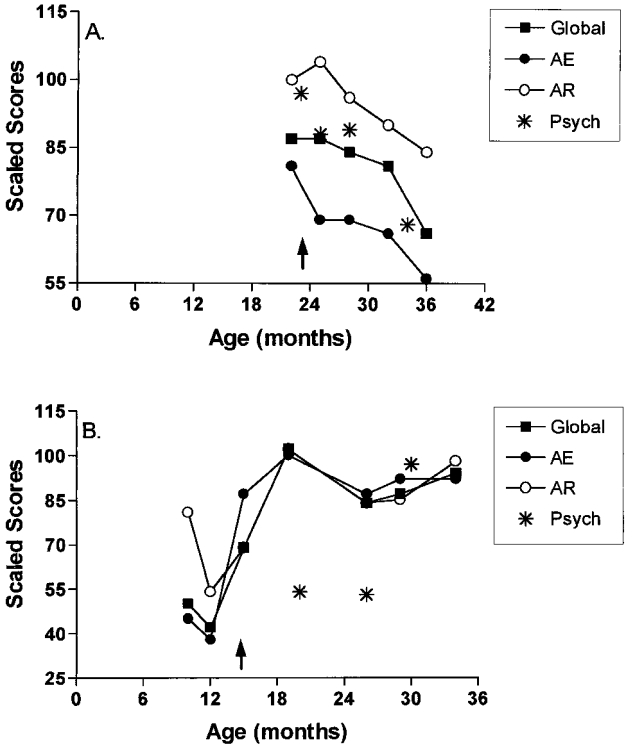

Fig 2. Two subjects with HIV infection. Subject A manifests progressive deterioration of language ability. Expressive language delay preceded decline in global cognitive function by ~8 months. Subject B manifests deterioration of language function, followed by rapid improvement almost immediately after institution of antiretroviral therapy. Return of language ability preceded improvement in measures of global cognitive function by nearly 12 months. Vertical arrows indicate initiation of antiretroviral drug therapy. Global indicates ELM-2 Global Language scaled score; AE, Auditory Expressive scaled score; AR, Auditory Receptive scaled score; Psych, psychological test scaled score (Bayley Scales of Infant Development).

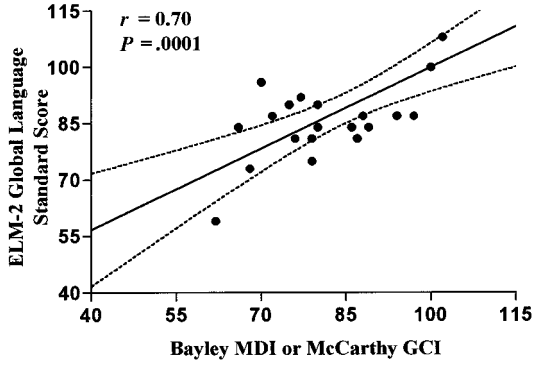

Fig 3. Comparison of ELM-2 Global Language scaled scores with the Bayley MDI or the McCarthy GCI.

In our study, language deterioration was observed in 7 of 9 infants and young children with HIV infection. Of these 7, 1 had spastic quadriparesis and 1 died of opportunistic infection. The remaining 5 were medically stable with normal or near-normal neurologic examinations. The improvement in language function observed in 3 subjects shortly after initiation of antiretroviral therapy replicates similar observations by previous researchers.[4,19] Five of 69 uninfected subjects scored <70 on the ELM-2 on at least one occasion. However, none of these children manifested the pattern of progressive deterioration in language seen in the infected group.

Speech and language acquisition are sensitive to a variety of neurodevelopmental insults, including global cognitive delay, central disorders of language function or auditory perception, central or bulbar disorders of motor function (oromotor apraxia, dysarthria), and hearing loss. Thus, language acquisition in young children is a good barometer of CNS integrity in general. In the present study, language deterioration or return of language function after starting antiretroviral drug treatment coincided with or preceded similar changes on sensorimotor tests of cognitive function (the Bayley Scales of Infant Development). Changes in language function preceded similar changes in cognitive function by 8 months in one instance and by 12 months in another. Language deterioration or recovery also preceded, or occurred in the absence of, changes on formal neurologic examination or CNS imaging studies. These data suggest that abnormal findings in speech and language assessment can serve as an early warning mechanism to identify children with clinically significant deterioration in neurodevelopmental status in a timely manner. Likewise, language function may be useful as an early indicator of the beneficial effects of antiretroviral drug therapy.

We enrolled only 9 infants and young children with HIV infection. However, this represents 100% of the known cases of HIV infection in this age group in the 16 counties of Central New York during the study period. Furthermore, we were able to achieve excellent follow-up of all subjects reported here, in part attributable to the relatively small total population of infected and seropositive children in the region and because our clinic is the only facility providing subspecialty medical care for children with HIV infection in Central New York. Although the number of subjects is small, the present study also includes more data points per subject, followed for a longer time span, than previous studies of language development in infants and young children infected with HIV. Thus, what our data lack in terms of sample size is offset partly by the completeness of the dataset. Subjects with HIV infection were tested slightly more frequently than subjects who were uninfected. We consider it unlikely, however, that the pattern of progressive language deterioration observed exclusively in the infected subjects, or the dramatic improvement in language function after the initiation of antiretroviral drug therapy, are artifacts of the small excess in the mean number of tests per infected subject. Additional limitations to this report include the lack of data regarding audiologic status, teratogenic exposure, or the impact on child development of psychosocial stressors such as disruption of caregiving because of maternal illness. Although we have no specific data regarding teratogenic or psychosocial stressors, all subjects in this study were born to women who were themselves infected with HIV and experiencing related medical complications. All children in this report lived in households dependent on public assistance. Therefore, we doubt that

environmental confounds underlie the differences in language development observed between the 9 subjects with HIV infection and the 69 subjects who were exposed to HIV but uninfected. Some of these methodologic concerns will be addressed in a large-scale prospective study currently being developed.

SUMMARY

We tracked the language development of 9 infants and young children who were infected with HIV and 69 children who had been exposed to HIV but were uninfected (mean age: 15.3 months, range: 6 weeks to 45 months; mean length of follow-up: 15.1 months, range: 0 to 38 months). Language deterioration was observed in 7 of 9 subjects with HIV infection but in none of the uninfected subjects. Three subjects with HIV infection and language deterioration showed marked improvement in language ability immediately after the initiation of antiretroviral drug therapy. Language deterioration coincided with or preceded loss of global cognitive ability. Likewise, recovery of language function after the introduction of antiretroviral drug treatment sometimes preceded improvement on measures of global cognitive function, in one instance by nearly 12 months. We conclude that language deterioration and recovery of language ability after antiretroviral drug treatment are clinically useful indices of neurodevelopmental integrity in infants and young children with HIV infection. We suggest that routine assessment of language ability be added to the developmental monitoring of infants and young children with HIV infection.

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