Cerebellar Hemorrhage on Magnetic Resonance Imaging in Preterm Newborns Associated with Abnormal Neurologic Outcome

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Objective To investigate the relationship between cerebellar hemorrhage in preterm infants seen on magnetic resonance imaging (MRI), but not on ultrasonography, and neurodevelopmental outcome.

Study design Images from a cohort study of MRI in preterm newborns were reviewed for cerebellar hemorrhage. The children were assessed at a mean age of 4.8 years with neurologic examination and developmental testing using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

Results Cerebellar hemorrhage was detected on both ultrasonography and MRI in 3 of the 131 preterm newborns evaluated, whereas smaller hemorrhages were seen only on MRI in 10 newborns (total incidence, 10%). Adjusting for gestational age at birth, intraventricular hemorrhage, and white matter injury, cerebellar hemorrhage detectable solely by MRI was associated with a 5-fold increased odds of abnormal neurologic examination compared with newborns without cerebellar hemorrhage (outcome data in 74%). No association with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition score was found.

Conclusions Cerebellar hemorrhage is not uncommon in preterm newborns. Although associated with neurologic abnormalities, hemorrhage seen only on MRI is associated with much more optimistic outcomes than that visible on ultrasonography. *(J Pediatr 2011;158:245-50)*.

Cerebellar hemorrhage in preterm infants has been increasingly recognized in recent years, due to the more frequent use of magnetic resonance imaging (MRI) and posterolateral fontanel views on cranial ultrasonography.[1-4] Previous reports of cerebellar hemorrhage concerned mainly infants with notable perinatal risk factors, including traumatic delivery and coagulopathy, and reported high rates of mortality and severe neurologic devastation; indeed, hemorrhage was commonly noted on postmortem studies.[5-7]

Although the routine use of posterolateral fontanel views on cranial ultrasound has improved the detection of cerebellar hemorrhage, MRI has increased the identification of smaller cerebellar hemorrhages not detectable by cranial ultrasound. Recent data suggest that cerebellar hemorrhage in preterm infants may be much more common than previously thought, particularly in extremely low birth weight neonates (<750 g). In one cohort of preterm infants with larger ultrasound-diagnosed cerebellar hemorrhage, 66% were found to have neurologic abnormalities at age 2.5 years, as well as increased risk for cognitive, learning, and behavioral dysfunction.[8] In another cohort of preterm infants with serial MRI studies, cerebellar hemorrhage was seen in 7% of infants, with increased risk for mortality and significant developmental delay.[9] The size of hemorrhage was not considered in either of these analyses, however. Thus, the neurodevelopmental effect of small cerebellar hemorrhages is not well understood. The aim of the present study was to assess the long-term neurodevelopmental outcome of preterm infants with cerebellar hemorrhage, focusing on infants with smaller cerebellar hemorrhages detected only on MRI.

Methods

Preterm newborns admitted to the intensive care nursery at the University of California San Francisco (UCSF) were recruited from 1998 to 2003 as part of an ongoing prospective cohort study of brain injury and development using sequential MRI scans. Inborn and outborn neonates born at <34 weeks gestational age were eligible for

CSE	Conventional spin echo
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
TE	Echo time
TR	Repetition time
UCSF	University of California San Francisco
WMI	White matter injury
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition

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the study. Exclusion criteria for study enrollment were: (1) clinical evidence of a congenital malformation or syndrome; (2) congenital TORCH infection; and (3) clinically instability precluding transport to the MRI scanner. Parental consent was obtained for all infants following a protocol approved by the UCSF Committee on Human Research.

All subjects underwent repeated cranial ultrasound and MRI scans. Each newborn underwent two MRI scans, one soon after birth (mean, 32.2 ± 2.1 weeks postmenstrual age) and another near term-equivalent age (mean, 36.9 ± 2.3 weeks postmenstrual age). Cranial ultrasound was performed routinely at 7 days of life and again at 4 weeks of life. In newborns with additional risk factors for intracranial bleeding, such as acute decreases in blood pressure or hematocrit, cranial ultrasound also was performed at 3 days of life. If abnormalities were found, ultrasound was repeated weekly until findings were stabilized.

A custom MRI-compatible incubator with a specialized neonatal head coil was used to provide a quiet, well-monitored environment for the neonate, minimizing patient movement and improving the signal-to-noise ratio.[10] MRI of the brain was performed with a 1.5-T Signa EchoSpeed unit (GE Medical Systems, Milwaukee, Wisconsin), including (1) T1-weighted sagittal spin echo images (4 mm thickness) with a repetition time (TR) of 500 ms, an echo time (TE) of 11 ms, one excitation, and a 192 × 256 acquisition matrix; (2) T2-weighted conventional spin echo (CSE; 4 mm thickness) with a TR of 3000 ms, TEs of 60 and 120 ms, and a 192 × 256 acquisition matrix; and (3) coronal 3-dimensional spoiled gradient recalled T1-weighted images (partition size, 1.5 mm) with a TR of 36 ms, minimal TE, a flip angle of 35 degrees, two excitations, and a field of vision of 18 cm, as described previously.[11]

MRI images were reviewed for the presence of intraventricular hemorrhage (IVH), white matter injury (WMI), and cerebellar hemorrhage by a pediatric neuroradiologist (A.B.) blinded to clinical history and ultrasound findings. IVH was classified using the grading system of Papile et al.[12] WMI was classified using a scoring system previously associated with neurodevelopmental outcome at 12-18 months of age.[11] Cerebellar hemorrhage was identified by the presence of hypointensity on the T2-weighted sequences that "bloomed" on the second echo. T2-weighted CSE sequences are very sensitive to the detection of blood in the unmyelinated neonatal brain.[13] The location, number, and size of cerebellar hemorrhages were recorded.

Cranial ultrasonography was performed as clinically indicated. A Siemens Sequoia ultrasound unit with 8- to 10-mHz sector transducers (Siemens, Mountain View, California) was used for views through both the anterior and posterolateral fontanels. Clinical reports from the electronic health records were reviewed for the presence of intracranial hemorrhage (including IVH and cerebellar hemorrhage), and cerebellar hemorrhage was confirmed by a pediatric ultrasonologist (R.G.) blinded to the clinical history and MRI findings. For purposes of classifying IVH, because of the repeated imaging by multiple modalities, the highest score was recorded as the true IVH score for each subject.

Neurodevelopmental Outcome

After discharge from hospital, children enrolled in this prospective cohort underwent repeated assessments in the UCSF intensive care nursery follow-up clinic. At each visit, the child was assessed by a physician (either a pediatrician specialized in newborn follow-up or a pediatric neurologist) and a developmental psychologist blinded to the child's neonatal course.

A standardized neurologic examination was performed by the physician and recorded. If the assessing physician was not a pediatric neurologist, the report was reviewed by a pediatric neurologist. Abnormalities seen on neurologic examination were scored using a validated neuromotor scale that scores subjects on the basis of tone, deep tendon reflexes, primitive reflexes, power, and cranial nerve involvement.[14,15] For the purposes of analysis, the scores were dichotomized to the presence or absence of abnormalities on the neurologic examination.

Between age 3 and 6 years, follow-up visits also included formal developmental assessments by a psychologist using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). Scores recorded included composite verbal IQ, performance IQ, and full-scale IQ. The WPPSI-III is standardized and validated, with a mean of each composite score of 100 with a standard deviation of 15.

Statistical Analysis

All statistical analyses were performed using Stata version 10 (StataCorp, College Station, Texas). Descriptive statistics were used to examine the distribution of neurologic and developmental outcomes in children with cerebellar hemorrhage on ultrasound or MRI. Logistic regression analysis was used to assess the relationship between cerebellar hemorrhage seen on MRI but not on cranial ultrasound and neurologic outcome. Linear regression analysis was used to assess developmental outcome via WPPSI-III scores. The analysis was performed adjusting for other known risk factors for adverse outcome, including gestational age at birth, and other common preterm brain pathologies, including severity of IVH and WMI.

Results

A cohort of 131 preterm newborns was enrolled, all of which underwent both cranial ultrasound and MRI scans during their hospital stay. Cerebellar hemorrhage was seen on cranial ultrasound in 3 newborns. All 3 of these hemorrhages were confirmed on MRI, and an additional 10 cerebellar hemorrhages that were not detected by ultrasound were seen on MRI. Three newborns died during admission in the nursery, two of whom had ultrasound-detected cerebellar hemorrhage. Of the 128 survivors, 94 underwent periodic neurodevelopmental assessments until age 3-6 years (mean age, 4.8 ± 0.1 years for those without cerebellar hemorrhage and 4.9 ± 0.2 years for those with cerebellar hemorrhage). Thus, outcome data were available for 74% of the original

cohort, including 1 child with ultrasound-detected cerebellar hemorrhage and 8 children with solely MRI-detected cerebellar hemorrhage. No statistically significant differences in gestational age at birth, birth weight, sex, severity of IVH, or severity of WMI were seen between those with and without follow-up data ($P > .30$) (Table I).

Distribution of Cerebellar Hemorrhage

All 3 newborns with cerebellar hemorrhage detected on cranial ultrasound had a large hemorrhage, ranging from 7 × 8 mm to bilateral extensive hemorrhages filling the posterior fossa. Of the 10 newborns with cerebellar hemorrhage seen only on MRI, size ranged from 1 to 3 mm in diameter, and the hemorrhages were presumed to be germinal matrix hemorrhages given their close proximity to the cerebellar cortex. Three of the newborns had a single hemorrhage, one newborn had two hemorrhages in the same cerebellar hemisphere, and the remaining 6 newborns had multiple hemorrhages in both cerebellar hemispheres. The Figure shows examples of the hemorrhages detected on ultrasound and MRI.

Neurologic Outcome

Of the 3 newborns with ultrasound-visible cerebellar hemorrhage, 2 died during initial hospitalization. The sole survivor demonstrated no deficits on follow-up neurologic examination at 4.7 years. All of the 10 newborns with cerebellar hemorrhage seen only on MRI survived their initial neonatal course. Of the 8 newborns who were assessed at age 3-6 years, 4 (50%) had abnormalities on neurologic examination (Table II). Abnormalities included hypertonia and hyperreflexia, with no functional impairments in ambulation; although this was not specifically tested, no specific observations of ataxia or impaired coordination were noted. Of the 85 remaining children without cerebellar hemorrhage, 14 (16%) had abnormalities on follow-up neurologic examination, including truncal hypotonia, lower limb hypertonia, and lower limb hyperreflexia.

Table I. Demographic data for subjects with follow-up to 3-6 years

	No cerebellar hemorrhage (n = 85)	Cerebellar hemorrhage (n = 9)	*P* value
Gestational age at birth, weeks, mean ± SD	28.0 ± 2.4	27.4 ± 2.4	.5
Birth weight, g, mean ± SD	1064 ± 383	974 ± 262	.5
Male sex, n (%)	40 (47%)	6 (67%)	.3
IVH, n (%)			
Mild (grade 1-2)	29 (34%)	3 (33%)	1.0
Severe (grade 3-4)	8 (9%)	1 (11%)	.8
WMI			
Mild	26 (31%)	1 (11%)	.2
Severe	19 (22%)	2 (22%)	1.0

Mild WMI is defined as ≤3 signal abnormalities on T1-weighted MRI imaging of <2 mm diameter; severe WMI, as >3 signal abnormalities or involvement of >5% of the cerebral hemisphere. The *P* value arises from a *t* test comparing two means or from Fisher exact test comparing two proportions.

On logistic regression analysis, the surviving children with cerebellar hemorrhage seen on MRI but not on cranial ultrasound had a 5.1-fold increased odds of having abnormalities on follow-up neurologic examination compared with those without cerebellar hemorrhage (95% CI, 1.1-22.7; $P = .03$). Of the 8 children who returned to follow-up with cerebellar hemorrhage seen only on MRI, one had mild WMI and two had severe WMI, two had mild IVH and one had severe IVH, and 4 had neither WMI nor IVH. After adjusting for gestational age, IVH, and WMI, the odds ratio was 5.0 (95% CI, 1.1-23.1; $P = .04$).

Developmental Outcome

On the WPPSI-III, the children without cerebellar hemorrhage had a mean performance IQ of 99 ± 2, a verbal IQ of 98 ± 2, and a full-scale IQ of 99 ± 2, whereas the children with MRI-only cerebellar hemorrhage had a mean performance IQ of 100 ± 5, a verbal IQ of 95 ± 7, and a full-scale IQ of 98 ± 6. Using linear regression analysis, adjusting for gestational age, IVH, and WMI, the surviving children with cerebellar hemorrhage seen on MRI but not on cranial ultrasound did not have significantly different performance IQ (+2; 95% CI, -11 to 14; $P = .80$), verbal IQ (-1; 95% CI, -14 to 12; $P = .90$), or full-scale IQ (0; 95% CI, -13 to 14; $P = .90$) scores compared with those without cerebellar hemorrhage.

Discussion

Although large cerebellar hemorrhage carries a high risk of mortality and severe neurodevelopmental deficits,[8] the effects of smaller cerebellar hemorrhages seen on MRI but not on cranial ultrasound have not been reported previously. The results of the present prospective cohort study suggest that smaller cerebellar hemorrhages seen only on MRI are associated with an increased risk for abnormalities on neurologic examination, but that the presence of these hemorrhages is not associated with abnormalities on developmental testing at age 3-6 years.

This study of neuroimaging in preterm newborns found a 2% incidence of ultrasound-detected cerebellar hemorrhage and an 8% incidence of solely MRI-detected cerebellar hemorrhage. These rates are comparable with those reported by other groups.[1,16] In agreement with previous studies,[8,9] large cerebellar hemorrhages seen on ultrasound were associated with a high risk for adverse outcome, with 67% mortality during the initial hospitalization. However, the few cases of such hemorrhages in the survivors in this cohort precluded us from assessing neurodevelopmental outcomes.

This study highlights the power of MRI to detect cerebellar hemorrhages of 1-3 mm in diameter—hemorrhages previously not detected on cranial ultrasound. Given the increasing use of MRI for diagnosing brain injury in preterm newborns and the resulting increasing identification of these smaller hemorrhages, understanding the neurodevelopmental consequences of such findings is important to help guide parental

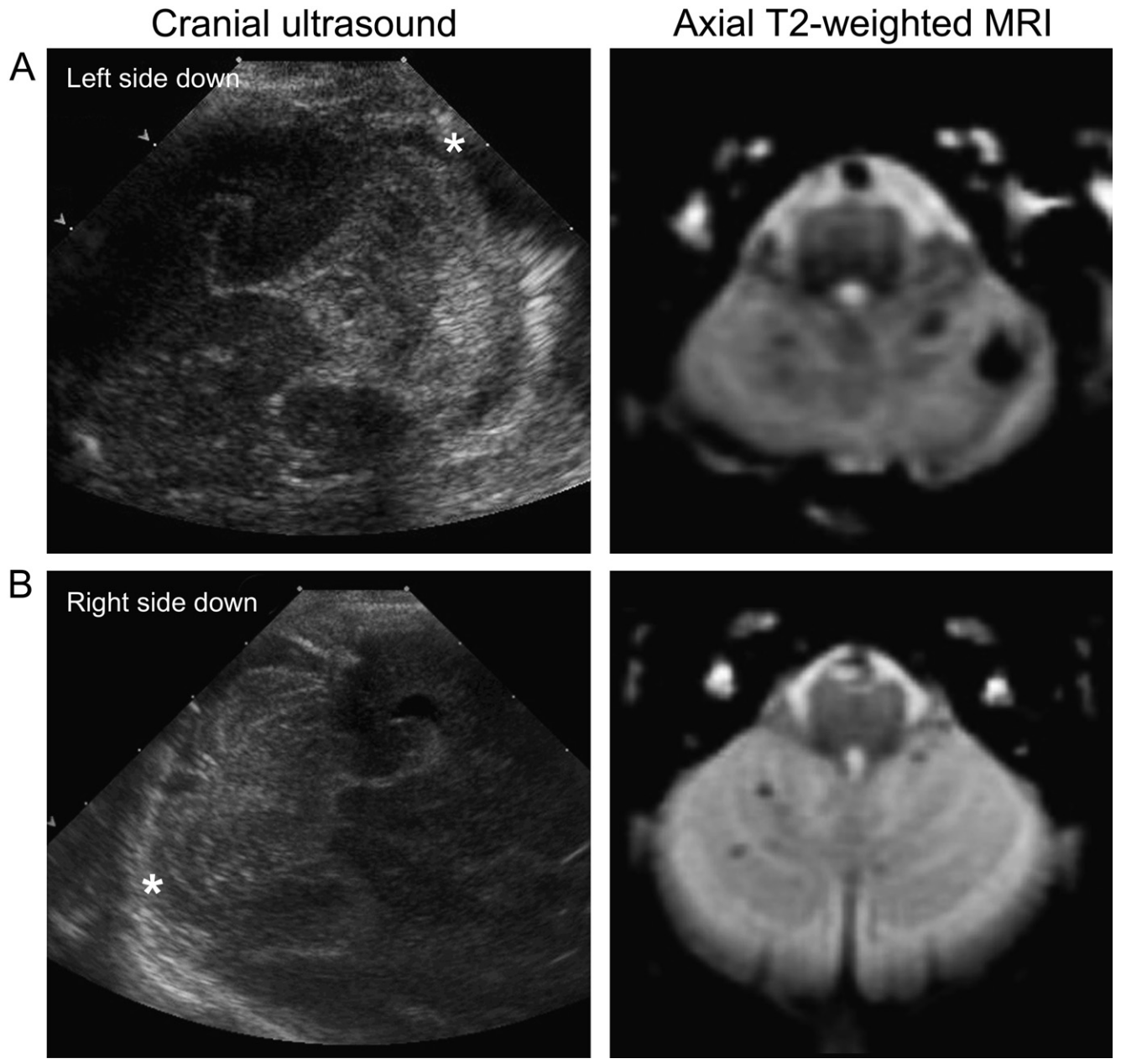

Figure. Appearance of cerebellar hemorrhage on MRI and cranial ultrasound in a newborn with **A,** ultrasound-visible cerebellar hemorrhage and **B,** a newborn with cerebellar hemorrhage detected only by MRI. **A,** The patient in died during the perinatal period, whereas **B,** the patient in had normal neurodevelopmental outcomes at 4.5 years. The right cerebellar hemisphere is indicated by an asterisk.

counseling and patient therapy. Of note, the MRI sequences used in this study had a scan thickness of 4 mm and thus might have missed some of these small hemorrhages. The actual incidence of these hemorrhages may be higher than reported here.

In this study, the children with solely MRI-detected cerebellar hemorrhages had a 5-fold greater rate of abnormalities on neurologic examination compared with the children without cerebellar hemorrhage. Because different physicians (pediatricians and neurologists) performed the follow-up neurologic examinations, nondifferential misclassification of this outcome measure might have occurred. As a result, this study might actually have underestimated the magnitude of the association between MRI-only cerebellar hemorrhage and abnormal neurologic examination findings. Abnormalities tended to include hypertonia and hyperreflexia, normally associated with spastic diplegic cerebral palsy. These associations were not dampened after adjusting for the severity of IVH and WMI. Of note, however, these deficits were less severe than those reported previously in children with larger

Table II. Severity of brain injury and neurologic deficits in the 8 children with solely MRI-detected cerebellar hemorrhage with outcome data available

Subject	IVH grade	WMI grade	Location of cerebellar hemorrhage	Distribution of hypertonia and hyperreflexia
1	2	0	Right single	None
2	2	0	Bilateral multiple	None
3	1	0	Left multiple	Bilateral lower limbs
4	3	2	Left single	Right upper and lower limbs
5	2	0	Bilateral multiple	Bilateral lower limbs
6	0	2	Bilateral multiple	Bilateral lower limbs
7	2	0	Bilateral multiple	None
8	1	1	Bilateral multiple	None

IVH is scored using the grading system of Papile et al.[12] For WMI, 0 represents no injury, 1 represents ≤3 T1 signal abnormalities of <2 mm, 2 represents >3 T1 signal abnormalities of <2 mm, and 3 represents >5% hemisphere involvement.

ultrasound-detected cerebellar hemorrhages, and they did not prevent ambulation.

Our finding of similar neurologic deficits in cerebellar hemorrhage as those classically described in IVH and WMI raises new questions as to the possible neural pathways involved in these deficits. One possibility is that cerebellar injury directly results in changes in tone and reflexes; another is that limitations in cerebellar function magnify the deficits associated with IVH and WMI, resulting in increased recognition of these findings by the evaluating clinician.

In contrast with previous studies showing cognitive and language impairment associated with cerebellar hemorrhage, the present study found no association between solely MRI-detected cerebellar hemorrhage and deficits in performance or verbal domains on the WPPSI-III test. This suggests a dramatic difference between the effects of these smaller MRI-only hemorrhages on cognitive outcome compared with previous reports on larger ultrasound-visible hemorrhages. The wide age range of our subjects at developmental testing may be a limitation of this study, although we found no difference in the age at assessment between those with and without cerebellar hemorrhage, and found only a small variability in scores. In addition, more subtle neurocognitive deficits that can result from these cerebellar hemorrhages might become evident at a later age than what we evaluated.

Although we were able to study the effect of overall cerebellar injury on outcome, the number of cases of cerebellar hemorrhage was insufficient to allow us to compare the effects of bilateral versus unilateral cerebellar hemorrhage or left hemisphere versus right hemisphere hemorrhage, or to examine the association between particular regions of injury and specific neurologic findings. Larger studies of preterm newborns with localized cerebellar hemorrhage on MRI would help elucidate whether the location of cerebellar hemorrhage can inform the specific deficits that might ensue.

Our finding of an increased risk of neurologic deficit after cerebellar hemorrhage not visible on ultrasound adds to the growing body of evidence demonstrating additional benefits of using MRI along with routine cranial ultrasound to screen for brain injury in preterm newborns.[17-19] Considering that preterm newborns with cerebellar hemorrhage not visible on cranial ultrasound have a 5-fold increased odds of abnormal neurologic examination by school age, this would provide additional information to help identify those children requiring closer follow-up after hospital discharge and earlier interventions.

With an increasing awareness of the risk of cerebellar hemorrhage in preterm newborns and the associated risk for mortality and severe developmental delay comes the need to better understand the range of cerebellar hemorrhage that can occur and the associated possible outcomes. Compared with large cerebellar hemorrhages previously identified by cranial ultrasound, small (1-3 mm) hemorrhages detected on MRI in the preterm cerebellum are associated with an increased risk of abnormalities on neurologic examination, but not with cognitive impairment. Our findings can help guide physicians in counseling parents regarding potential outcomes in their newborn children, and underscore the utility of MRI in assessing preterm cerebellar injury. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Initial Tuberculous Infection Due to Drug-Resistant Organisms: With Review of the World Literature on Initial Infection Due to Isoniazid-Resistant Tubercle Bacilli

Zitrin CM, Lincoln EM. J Pediatr 1961;58:219-25.

In this series published in 1961, Zitrin and Lincoln present the first review of tuberculosis (TB) caused by bacillus resistant to either isoniazid or streptomycin in American children. Their finding of severe pulmonary and disseminated disease challenged the popular concept that isoniazid-resistant organisms were attenuated and unlikely to cause illness. Although it is now clear that drug-resistant TB can be lethal, the relative fitness of resistant organisms remains incompletely understood.

Infection with drug-resistant *Mycobacterium tuberculosis* has become both more complicated and common since the publication of this report. Worldwide, there are approximately half a million cases of multidrug-resistant (MDR) TB reported annually, and in the past decade, extensively drug-resistant (XDR) TB, which expresses resistance to both first- and second-line drugs, has been documented in >50 countries. Zitrin and Lincoln's primary recommendation that specimens be obtained from children for culture and drug susceptibility testing (DST) remains sound. However, this is unattainable in most of the developing world, where the overwhelming majority of TB is found. Even relatively simple public health interventions that limit the spread of TB in general, and MDR TB in particular, such as directly observed therapy and contact tracing, have not been widely implemented in endemic settings. Consequently, it is unlikely that the spread of MDR TB will be slowed any time in the foreseeable future.

There are reasons to be optimistic, however. Several existing medications, such as the fluoroqiunolones and linezolid, have been used successfully to treat MDR TB, and additional compounds are in development. New techniques for rapid DST are now in use. However, a lack of funding and public health infrastructure in TB endemic settings has limited the beneficial impact of these advances. Moreover, few of these therapeutic innovations have been adequately studied in children.

The fundamental challenge to the diagnosis and management of pediatric MDR TB has not changed in the past 50 years: obtaining specimens for microbiological confirmation of infection and DST. Focusing research and public health resources on this objective is essential for developing optimal treatment strategies for children with TB in a world where drug resistance has become routine.

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