



## Discover Generics

Cost-Effective CT & MRI Contrast Agents



FRESENIUS  
KABI

WATCH VIDEO

# AJNR

## Value of MR in definition of the neuropathology of cerebral palsy in vivo.

J J Volpe

*AJNR Am J Neuroradiol* 1992, 13 (1) 79-83

<http://www.ajnr.org/content/13/1/79.citation>

This information is current as  
of June 6, 2025.

## Value of MR in Definition of the Neuropathology of Cerebral Palsy in Vivo

Joseph J. Volpe<sup>1</sup>

Cerebral palsy refers to a clinical syndrome of nonprogressive motor deficits (usually spastic weakness, uncommonly choreoathetosis, rarely ataxia) of central origin with onset from early infancy. In this issue of the *Journal*, Truwit et al describe the MR findings in 40 patients with the clinical diagnosis of cerebral palsy (1). The purposes of their retrospective study were to define the anatomic substrates of cerebral palsy in the living patient and, from the definitions of the topography of the neuropathology and the analysis of clinical data, to suggest etiology and timing of the brain injury. The authors place particular emphasis on their conclusion that cerebral palsy is usually not related to perinatal factors. The work is relevant to the role of hypoxic-ischemic brain injury in the genesis of cerebral palsy, the means of diagnosis of hypoxic-ischemic brain injury in the neonatal period, the spectrum of the neuropathology associated with cerebral palsy and the role of MR in the later definition of this neuropathology, and the timing of etiologic factors. These issues are discussed in sequence.

### Hypoxic-Ischemic Brain Injury and Cerebral Palsy

Hypoxic-ischemic brain injury occurring either in the prenatal, perinatal, or early postnatal periods may result in the motor deficits categorized as cerebral palsy (20). This brain injury is considered best in the context of five basic neuropathologic states, ie, selective neuronal necrosis, status marmoratus of basal ganglia and thalamus, parasagittal cerebral injury, periventricular leukomalacia, and focal and multifocal ischemic brain necrosis. Although these disorders often overlap in a given patient, the nature of the insult and the gestational age of the infant tend to cause one lesion to be dominant.

### Selective Neuronal Necrosis

Selective neuronal necrosis, a common expression of injury secondary to hypoxic-ischemic insult in the term infant, is characterized by neuronal destruction in a typical distribution (see ref. 2 for review). Cerebral cortical neurons, particularly those of the CA1 region of hippocampus (Sommer's sector), are especially vulnerable. (In the premature infant, neuronal injury occurs principally in inferior olivary nuclei, ventral pons, and subiculum of hippocampus, although periventricular white matter injury tends to be the predominant hypoxic-ischemic lesion in such infants.) The pathophysiology of the typical neuronal injury of the term infant, ie, in hippocampus and neocortex, is related predominantly to the regional distribution of excitatory synapses mediated by the excitotoxic amino acid glutamate (see refs. 3–6 for reviews). Hypoxic-ischemic insults lead to a combination of increased release from nerve endings and decreased uptake by presynaptic neurons and by astrocytes and, consequently, to the toxic accumulation of extracellular glutamate. Glutamate-induced injury occurs by rapid and delayed mechanisms. The latter may be the more important, is calcium-mediated, and probably generates ultimately toxic free radicals. Current studies suggest that therapy with either glutamate receptor blockers, calcium channel blockers, or free radical scavengers could be of major benefit. Regional metabolic factors related to energy metabolism, calcium homeostasis, and free radical scavenging capabilities, may play contributory pathogenetic roles in the determination of the topography of selective neuronal injury, but more data are needed on these issues. Regional circulatory factors also may play a contributory pathogenetic role, since the cortical neuronal injury tends to be worse in arterial border zones and end zones in the depths of sulci and

<sup>1</sup> Neurologist-in-Chief and Bronson Crothers Professor of Neurology, Department of Neurology, Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115. Address reprint requests to J. J. Volpe.

**Index terms:** Cerebral palsy; Commentaries

AJNR 13:79–83, Jan/Feb 1992 0195-6108/92/1301-0079 © American Society of Neuroradiology



in the parasagittal regions of cerebral cortex. The subsequent motor correlate of selective neuronal injury is usually quadriplegia, spastic or hypotonic.

#### *Status Marmoratus of Basal Ganglia and Thalamus*

Status marmoratus of basal ganglia and thalamus, an unusual form of selective injury, involves neuronal injury, gliosis, and hypermyelination in caudate, putamen, globus pallidus, and thalamus (2). The pathophysiology is related principally to two major factors: the transient maturation-dependent dense concentration of glutamate receptors in basal ganglia of perinatal human brain (7) and the vulnerability of neurons undergoing active differentiation in the perinatal period. Circulatory factors may contribute. The subsequent motor correlate is choreoathetosis.

#### *Parasagittal Cerebral Injury*

Parasagittal cerebral injury, the principal ischemic lesion of the term infant, is characterized by cerebral cortical and subcortical injury in a characteristic superomedial distribution, bilateral, with the posterior cerebrum affected more than anterior (2). Pathophysiology is based on the presence of characteristic arterial border zones and end zones in the parasagittal regions. These zones are particularly vulnerable to a fall in cerebral blood flow, which is especially likely to occur in the newborn with systemic hypotension during and after perinatal asphyxia because of an accompanying pressure-passive cerebral circulation (8). The latter lack of autoregulation occurs in the asphyxiated newborn because of several interrelated factors. The subsequent motor correlate is spastic quadriplegia, with the proximal limbs affected more than distal and the upper extremities more than lower extremities.

#### *Periventricular Leukomalacia*

Periventricular leukomalacia, the principal ischemic lesion of the premature infant, is characterized by necrosis of periventricular white matter, dorsal and lateral to the external angle of the lateral ventricle (2). Although more common in the premature infant, periventricular leukomalacia is by no means rare in the term infant subjected to ischemic insult. The pathophysiology is related to the occurrence of periventricular arte-

rial border zones and end zones, a pressure-passive state of the cerebral circulation, the relatively limited vasodilatory capability of the blood vessels in periventricular white matter, relatively active anaerobic glycolysis in periventricular white matter, and the intrinsic vulnerability of actively differentiating periventricular glial cells (9). The increasing recognition of more diffuse injury to periventricular white matter in small premature infants (10, 11), out of the bounds of presumed arterial border zones and end zones, emphasizes the possibility that the intrinsic metabolic properties of periventricular white matter may be as important as the vascular factors. The subsequent motor correlate of periventricular leukomalacia is spastic diplegia, a kind of spastic quadriplegia in which lower extremities are affected much more than upper extremities.

#### *Focal and Multifocal Ischemic Brain Necrosis*

Focal and multifocal ischemic brain necrosis is characterized by injury to all cellular elements (ie, an infarction) *in a vascular distribution* (2). Single or multiple vessels, arteries or veins, may be involved. The distribution of the middle cerebral artery is the single most common vascular territory affected. The pathophysiology is multifactorial. Obstructions of vessels by vascular maldevelopment, vasculopathy, embolus and thrombus have been documented. By mechanisms not yet clear, apparent generalized circulatory insufficiency in the perinatal period also may be followed by focal or multifocal cerebral ischemic lesions. The subsequent motor correlates consist of spastic hemiparesis or spastic quadriplegia.

#### *Diagnosis of Hypoxic-Ischemic Brain Injury in the Neonatal Period*

The diagnosis of the five lesions described above in the living infant has been based primarily on brain imaging, ie, cranial ultrasonography (US), computed tomography (CT), and recently, magnetic resonance (MR), and on neurophysiologic techniques. Selective neuronal necrosis currently is assessed most commonly by neurophysiologic techniques, especially electroencephalography (EEG), but also brain stem auditory evoked responses and visual evoked responses. Such EEG patterns as burst-suppression or persistent and pronounced voltage suppression are indicative of serious cortical neuronal injury (2). However, less severe degrees of neuronal injury are



not defined clearly by neurophysiologic techniques. Moreover, in our experience, brain imaging modalities have not been highly useful in the neonatal period in identification of cortical neuronal injury, except in its most severe form. However, experience with MR in this setting still is relatively limited. (The later cortical atrophy, which correlates with neuronal loss and gliosis, of course is detected readily by CT and MR.)

Injury to basal ganglia and thalamus is detected best by MR. Thus, Keeney et al (12) showed that MR detected hypoxic-ischemic basal ganglia injury in five infants, whereas US identified abnormality in four of the five infants and CT in only one of the three studied by this modality.

Parasagittal cerebral injury has been identified most readily by radionuclide brain scanning (2, 13) or positron emission tomography (2, 14), only uncommonly by CT (15), and never, in our experience, with US. However, the recent demonstration of neonatal parasagittal cerebral injury by MR (12, 16) suggests that this lesion now may be detectable with this modality and, of course, with superior localization to radionuclide scanning.

Periventricular leukomalacia is identified most readily in the newborn by cranial US (see ref. 9 for review). Bilateral periventricular echogenic areas, especially in the peritrigonal regions, in the first week, correlate with necrosis accompanied by vascular congestion and/or hemorrhage; echolucent foci, after 1 to 3 weeks in the same distribution, correlate with formation of periventricular cysts; ventricular enlargement, often with disappearance of cysts after 3 months or more, correlates with diminished myelin deposition and collapse of cysts with gliosis. MR also is particularly useful in the identification of periventricular white matter injury in the neonatal period (12), and in subsequent months and years, the appearance of increased signal on T2-weighted images in the periventricular white matter is a particularly prominent indicator of old periventricular leukomalacia (17).

Focal and multifocal ischemic brain necrosis generally is effectively identified by CT (except in the first day or two after the insult), although the recent data of Keeney et al suggest that MR may prove to be superior (12). Acute focal cerebral ischemic lesions also are identifiable as echogenic lesions by US, although smaller and more peripherally placed infarcts, eg, in posterior parietal regions, may be missed by US.

### Spectrum of Neuropathology Associated with Cerebral Palsy as Defined by Later MR

The study of Truwit et al (1) provides important information regarding the spectrum of neuropathology associated with cerebral palsy in patients between 1 month and 41 years of age and the value of MR in defining that spectrum. Their first observation of particular interest is that MR detected an abnormality of brain in 93% of their patients with cerebral palsy (1). This is a remarkable yield for any modality in such a heterogeneous group of patients.

The neuropathology defined in the *premature* infants consisted of a diminution in periventricular white matter in every patient (1). Moreover, the findings were consistently suggestive of periventricular leukomalacia. Thus, the topography of the white matter involvement usually was peritrigonal and/or accompanied by prolongation of T2 relaxation. Interestingly, three patients also had small brain stems, perhaps in part because of the pontine and olivary neuronal necrosis referred to earlier. In nine of the 11 infants, the perinatal course was characterized by clinical circumstances suggestive of fetal or neonatal hypoxic-ischemic insults, usually neonatal. No developmental abnormalities of brain were noted in the premature infants. Thus, these data suggest that cerebral palsy in the premature infant is related to periventricular myelinoclastic disease, occurring most often in the postnatal period, and is rarely related to underlying developmental brain abnormality.

The spectrum of neuropathology defined in the *term* infants with cerebral palsy differed clearly from that in the premature infants. Thus, 31% of the 29 term infants exhibited evidence for neuronal migrational disturbance (1). The largest proportion (59%) had an apparently heterogeneous collection of abnormalities that included particularly diminished cerebral myelin, with cortical thinning and/or cerebral infarction and/or hydranencephaly and/or multicystic encephalomalacia and/or basal ganglia and thalamic lesions. Only 10% had no definable abnormality. The relatively high proportion of disturbances of neuronal migration included particularly focal cerebral cortical disturbances with an "abnormally thick" cortical mantle, characterized by Truwit et al (1) as "polymicrogyria" (eight of nine cases), and a single case of schizencephaly. Of the 59% with the heterogeneous collection of abnormalities, apparent cerebral cortical atrophy (thinning of cerebral cortex) was present in three cases and abnormal



signal intensities in basal ganglia and thalamus in six cases. We consider these two groups the probable correlates of selective cerebral cortical neuronal injury and basal ganglia/thalamus injury as described earlier. The abnormalities in white matter are more difficult to characterize. Thus, 19 term infants exhibited diminution of myelin, but in only eight cases were long T2 signals observed, and in only nine cases was the diminution of myelin peritrigonal (1). These findings suggest that only approximately 50% of the infants with myelin abnormality had periventricular leukomalacia. The remaining approximately 50% of cases with diminished myelin did not have features highly suggestive of periventricular leukomalacia and appeared to require other explanations for the myelin diminution. Such explanations would include a developmental defect of myelin formation, perhaps analogous to that recorded in neuropathologic studies by Richardson and coworkers (18), or a secondary disturbance of myelin deposition because of impaired axonal formation. The impaired axonal formation could be present either as a consequence of neuronal migrational disturbance (six of the 19 infants with diminution of myelin had evidence for neuronal migrational defect as defined above), an intrinsic derangement of neuronal outgrowth, ie, a so-called organizational event of brain development (2), or prior neuronal injury with subsequently stunted axonal development.

### Timing of Lesions Responsible for Cerebral Palsy in Term Infants

The *timing* of the abnormalities in the *term* infants with cerebral palsy relates to the nature of the pathologies. Thus, the neuronal migrational disturbances must originate during the peak time period for migrational events in the human cerebral cortex, ie, 3 to 5 months of gestation. The nature of the focal cerebral cortical disturbance described by Truwit et al (1) as polymicrogyria was characterized by a thick cortical mantle, a finding which is compatible with pachygyria as well as with polymicrogyria. If the latter, the disturbance would be expected to originate in approximately the fifth month of gestation; if the former, the disturbance would be expected to originate in the fourth month of gestation (2). The timing of the apparent selective neuronal injury involving cerebral cortex or basal ganglia and thalamus is unclear. In several patients, perinatal hypoxic-ischemic insults appear to have been

responsible, although the retrospective nature of the study precludes more refined definition of timing. The timing of the disturbance of cerebral myelin that appears to be related to periventricular leukomalacia is unclear, ie, an ischemic insult either in the third trimester of pregnancy or in the perinatal period could produce the abnormality. A developmental disturbance of neuronal development with secondary impairment of myelination could have its onset from the latter months of gestation to approximately the first year of postnatal life. Similarly, a developmental disturbance of cerebral myelination per se presumably would have its onset around the time of birth.

Truwit et al considered that 5 of the 29 term infants (17%) had MR and perinatal historical data suggestive of "perinatal" hypoxic-ischemic injury (1). Two additional infants (7%) had data suggestive of both prenatal and perinatal injury. Despite the problems of attempting to draw conclusions about timing from a retrospective study, this value (ie, 17%–24%) is similar to that obtained in several large-scale epidemiologic studies of patients with cerebral palsy. Thus, studies in recent years from Sweden, Finland, the United States, Australia, and Ireland suggest a perinatal origin of cerebral palsy in approximately 12%–24% of cases who were term infants (19–26). Although Truwit et al (1) emphasized that "only 24% exhibited perinatal brain injury, it should be recognized that, because of the relatively high prevalence of cerebral palsy, this 24% represents *a large absolute number of infants*. Moreover, although current methods of fetal monitoring have not led to a marked decrease in the number of infants with cerebral palsy secondary to perinatal events, it remains entirely reasonable to suspect that perinatal causes of cerebral palsy ultimately should be preventable to a large degree. Clearly, newer methods of fetal monitoring and definition of exact timing and mechanisms of perinatal brain injury are needed.

### Conclusions

This most interesting study by Truwit et al (1) shows that cerebral palsy in the premature infant is related primarily to periventricular white matter injury, perhaps occurring primarily in the neonatal period. Cerebral palsy in the term infant has a more heterogeneous basis; ischemic injury to cerebral cortex, basal ganglia and thalamus, and to myelin accounts for some, but by no means



all, cases. Timing is perinatal in approximately 17%–24% of such cases. Strikingly, cerebral cortical dysgenesis secondary to disordered neuronal migration appears to account for nearly one-third of cerebral palsy in term infants. MR is of major value in identification of the anatomic substrates for cerebral palsy.

## References

1. Truwit CL, Barkovich AJ, Koch TK, Ferriero DM. Cerebral palsy: MR findings in 40 patients. *AJNR* 1992;13:67–78
2. Volpe JJ. *Neurology of the newborn*. 2nd ed. Philadelphia: W. B. Saunders, 1987.
3. Zivin JA, Choi DW. Stroke therapy. *Sci Am* 1991;265:56–63
4. Hattori H, Wasterlain CG. Excitatory amino acids in the developing brain: ontogeny, plasticity, and excitotoxicity. *Pediatr Neurol* 1990;6:219–229
5. MacDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res Rev* 1990;15:41–70
6. Benveniste H. The excitotoxin hypothesis in relation to cerebral ischemia. *Cerebrovasc Brain Metab Rev* 1991;3:213–245
7. Barks JD, Silverstein FS, Sims K, Greenmayre JT, Johnston MV. Glutamate recognition sites in human fetal brain. *Neurosci Lett* 1988;84:131–136
8. Pryds O, Greisen G, Lou H, Friis-Hansen B. Vasoparalysis associated with brain damage in asphyxiated term infants. *J Pediatr* 1990;117:119–125
9. Volpe JJ. Current concepts of brain injury in the premature infant. *AJR* 1989;153:243–251
10. Paneth N, Rudelli R, Monte W, Rodriguez E, Pinto J, Kairam R. White matter necrosis in very low birth weight infants: neuropathologic and ultrasonographic findings in infants surviving six days or longer. *J Pediatr* 1990;116:975–984
11. Damska M, Laure-Kamionowska M, Schmidt-Sidor B. Early and late neuropathological changes in perinatal white matter damage. *J Child Neurol* 1989;4:291–298
12. Keeney SE, Adcock EW, McArdle CB. Prospective observations of 100 high-risk neonates by high-field (1.5 tesla) magnetic resonance imaging of the central nervous system. II. Lesions associated with hypoxic-ischemic encephalopathy. *Pediatrics* 1991;87:431–438
13. Volpe JJ, Pasternak JF. Parasagittal cerebral injury in neonatal hypoxic-ischemic encephalopathy: clinical and neuroradiological features. *J Pediatr* 1977;91:472–477
14. Volpe JJ, Herscovitch P, Perlman JM, et al. Positron emission tomography in the asphyxiated term newborn: parasagittal impairment of cerebral blood flow. *Ann Neurol* 1985;17:287–296
15. Pasternak JF. Parasagittal infarction in neonatal asphyxia. *Ann Neurol* 1987;21:202–203
16. Pasternak JF, Predey TA, Mikhael MA. Neonatal asphyxia: vulnerability of basal ganglia, thalamus and brainstem. *Pediatr Neurol* 1991;7:147–149
17. Flodmark O, Lupton B, Li D, et al. MR imaging of periventricular leukomalacia in childhood. *AJNR* 1989;10:111–118
18. Chattha AS, Richardson EP Jr. Cerebral white matter hypoplasia. *Arch Neurol* 1977;34:137–148
19. Hagberg B, Hagberg G. The changing panorama of infantile hydrocephalus and cerebral palsy over forty years: a Swedish survey. *Brain Dev* 1989;11:283–290
20. Hagberg B, Hagberg G, Olow I, von Wendt L. The changing panorama of cerebral palsy in Sweden. V. The birth year period 1979–82. *Acta Paediatr Scand* 1989;78:283–290
21. Hagberg B, Hagberg G, Zetterstrom R. Decreasing perinatal mortality: increase in cerebral palsy morbidity? *Acta Paediatr Scand* 1989;78:664–670
22. Riikonen R, Raumavirta S, Sinivuori E, Seppala T. Changing pattern of cerebral palsy in the Southwest region of Finland. *Acta Paediatr Scand* 1989;78:581–587
23. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. *N Engl J Med* 1986;315:81–86
24. Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr* 1988;112:515–519
25. Grant A, O'Brien N, Joy MT, et al. Cerebral palsy among children born during the Dublin randomised trial of intrapartum monitoring. *Lancet* 1989;1:1233–1235
26. MacDonald D, Grant A, Sheridan-Pereira M, et al. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. *Am J Obstet Gynecol* 1985;152:524–539