

**Progressive Intracranial Vascular Disease With Strokes and Seizures in a Boy With Progeria**

**ABSTRACT**

Progeria, a rare genetic disorder, is characterized by severe growth failure, premature aging, and very early atherosclerosis with coronary artery and cerebrovascular disease. There has been no detailed description of progressive cerebrovascular changes in progeria or any attempted neurologic correlation of those changes. A 5-year-old boy developed signs of progeria at 4 months and hypertension at 4 years, treated with atenolol and dipyridamole. Left-sided seizures with a left hemiparesis occurred at 5 years. Magnetic resonance imaging (MRI) showed bilateral acute, subacute, and chronic cerebral infarctions. Magnetic resonance angiography disclosed severe stenosis of the left internal carotid artery. The child was also found to have an aortic valve vegetation and was anticoagulated. He subsequently developed right-sided seizures, and treatment with gabapentin was started. Later, severe stenosis also of the right internal carotid artery was found. MRI showed new left cerebral infarction. The child's neurologic symptoms almost certainly were caused by cerebral infarctions from progressive atherosclerosis of major intracranial vessels, but clinical-neuroradiologic correlations were imprecise. There were multiple cerebral infarctions of different ages, some asymptomatic, others ipsilateral to the child's neurologic findings. No therapy has halted progression of the child's cerebrovascular disease. (*J Child Neurol* 2001; 16:212-215).

Progeria (Hutchinson-Gilford syndrome) is a rare genetic condition with a reported incidence of 1 in 8 million. Since probably half of the cases are unreported, the true incidence is likely closer to 1 in 4 million.<sup>1</sup> The first description of this disease was by Jonathan Hutchinson and Hastings Gilford in 1886, with approximately 100 additional cases reported since then. The nature of the genetic defect is unknown. Most cases are believed to result from a new autosomal-dominant mutation, a conclusion supported by a significant increase in paternal age. Siblings are usually not affected. Occasional sibships are felt to result from somatic mosaicism or stem cell mutation of ovary or testes. Several sets of affected identical twins have been reported. Males and females are affected with equal frequency.<sup>1</sup>

Progeria is characterized by the appearance of premature aging, heralded by the onset of severe growth failure in the first year of life, resulting in dwarfism. Additional findings include failure of growth of the facial bones and mandible; prominent eyes; sparseness of scalp hair leading to baldness; prominence of scalp veins; loss of eyebrows and eyelashes; loss of subcutaneous fat; failure of long bone growth; stiff and enlarged joints; coxa valga; thin, taut, and dry skin; small dystrophic nails; delayed dentition; a high-pitched voice; and premature atherosclerosis, including coronary

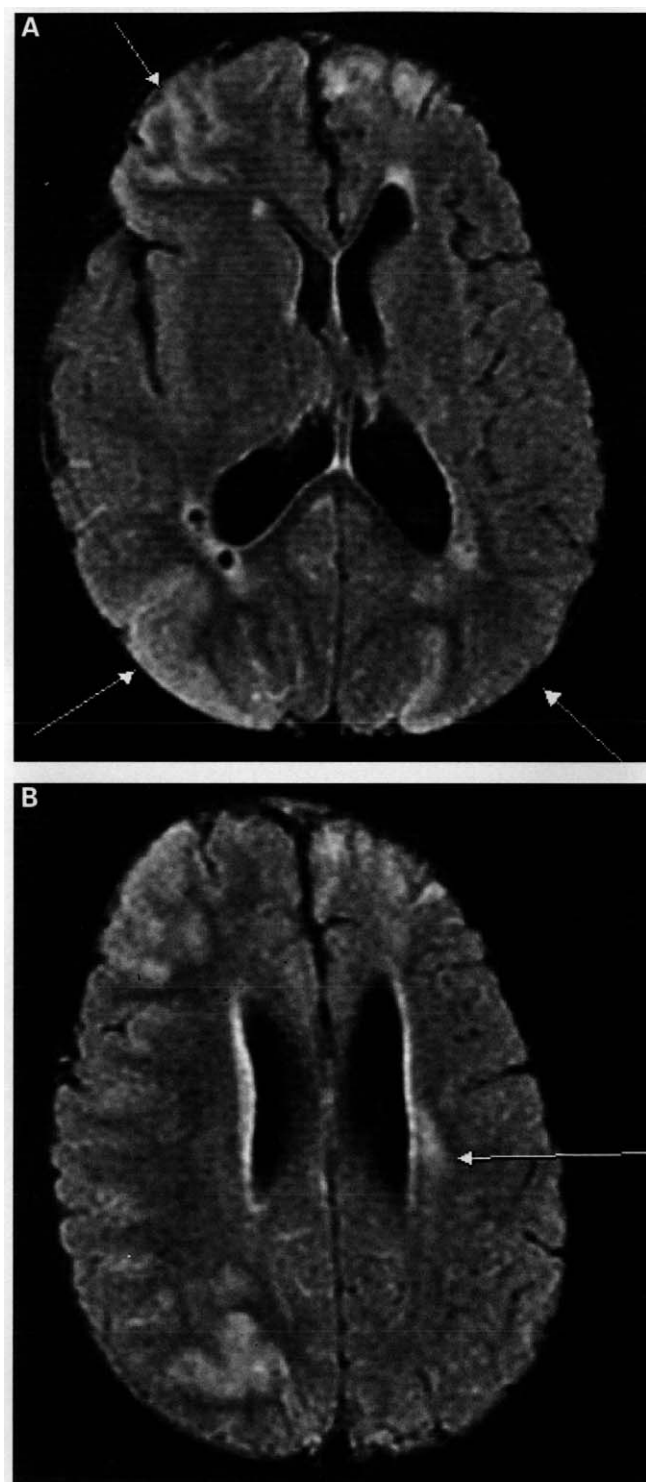


Figure 1. A, Fluid attenuation inversion recovery image. There is acute/subacute infarction in right anterior cerebral artery/middle cerebral artery, right middle cerebral artery/posterior cerebral artery, and left middle cerebral artery/posterior cerebral artery watershed territories (arrows). A left frontal anterior cerebral artery infarct is also seen. B, Fluid attenuation inversion recovery image. The areas of watershed infarction noted above are again visualized. Additionally, an infarct is seen in the deep left periventricular white matter (arrow).

artery disease. Most patients with progeria die in adolescence from cardiac complications of their disease, including myocardial infarction. The median age of death is 13.4 years.<sup>2</sup>

There have been only a few reports of cerebrovascular disease complicating progeria. We report here the first description of a case of progeria with detailed neuroradiologic study of progressive intracranial cerebrovascular disease complicated by multiple strokes and seizures.

### Case Report

The patient was a 5<sup>1</sup>/<sub>2</sub>-year-old African-American boy who was diagnosed with progeria at the age of 3 years. He was born at term after an uncomplicated pregnancy. Delivery was by cesarean section because of a breech presentation. At 4 months, joint stiffness was noted, and he was thought to have arthrogryposis. As a part of the work-up, he had a brain magnetic resonance imaging (MRI), which was normal. It later became apparent that he had progeria with severe growth failure, loss of subcutaneous fat, and physical features of premature aging. He developed hypertension at age 4<sup>3</sup>/<sub>4</sub> years and was begun on atenolol and dipyridamole. His first neurologic symptoms were at age 5 years when he developed three left-sided clonic seizures, each lasting about 1 minute, with about 1<sup>1</sup>/<sub>2</sub> hours between seizures; following the third seizure, he was noted to be plegic in his left arm with some accompanying weakness of the left face. MRI of the brain showed acute/subacute watershed infarcts between the anterior cerebral artery/middle cerebral artery and middle cerebral artery/posterior cerebral artery territories on the right and in the middle cerebral artery/posterior cerebral artery territory on the left. In addition, there was an old left frontal anterior cerebral artery territory infarct and an infarct in the deep left periventricular white matter (Figure 1A and B). Magnetic resonance angiography showed decreased flow in the left internal carotid artery (Figure 2A). There was occlusive disease in both cavernous carotid arteries, with focal occlusion of the right internal carotid artery, whereas the left internal carotid artery could not be visualized (Figure 2B). Because the narrowing of the left cervical internal carotid artery was uniform, diminished flow was felt to be secondary to distal intracranial vascular disease rather than to intrinsic disease in the cervical internal carotid artery. The vertebrobasilar system was normal. Electroencephalography showed bilateral slowing but no epileptiform discharges. Cardiac echocardiography showed a small patent foramen ovale, without a right-to-left shunt, and a mass under the aortic valve (vegetation or thrombus). The patient's left-sided weakness improved, but some weakness remained. He was anticoagulated with heparin and then warfarin; atenolol and dipyridamole were continued. He was not placed on anticonvulsant.

Three months later, the patient developed five focal seizures, affecting his right arm, each lasting 5 minutes, followed by a right Todd paralysis that later improved. MRI showed a significant interval enlargement of the lateral and third ventricles, secondary to parenchyma loss; there were no areas of new infarction. Cardiac echocardiography showed the subaortic valve mass to be unchanged. Warfarin, atenolol, and dipyridamole were continued. The patient was started on gabapentin for seizure control.

Two months later, the patient experienced a recurrence of right-sided seizures with two episodes, each lasting a few minutes, of twitching of the right thumb and right cheek, with accompanying dysarthria. MRI showed a new left temporoparietal infarct in the distribution of the left middle cerebral artery (Figure 3). Extracranial magnetic resonance angiography showed progressive intracranial carotid disease, with complete occlusion of the left internal carotid artery, markedly diminished flow in the right internal carotid artery (Figure 4A), and increased flow through the posterior communicating arteries to the anterior circulation. The A1 segment of the right anterior cerebral artery was not visualized (Figure 4B). Repeat cardiac echocardiography showed no changes in the subaortic valve mass.

On a follow-up examination 3<sup>1</sup>/<sub>2</sub> months later, the patient still had a mild left hemiparesis, unchanged from after his first stroke. His dysarthria had improved but was not completely resolved. He had remained seizure free on gabapentin. His anticoagulants were unchanged from before.

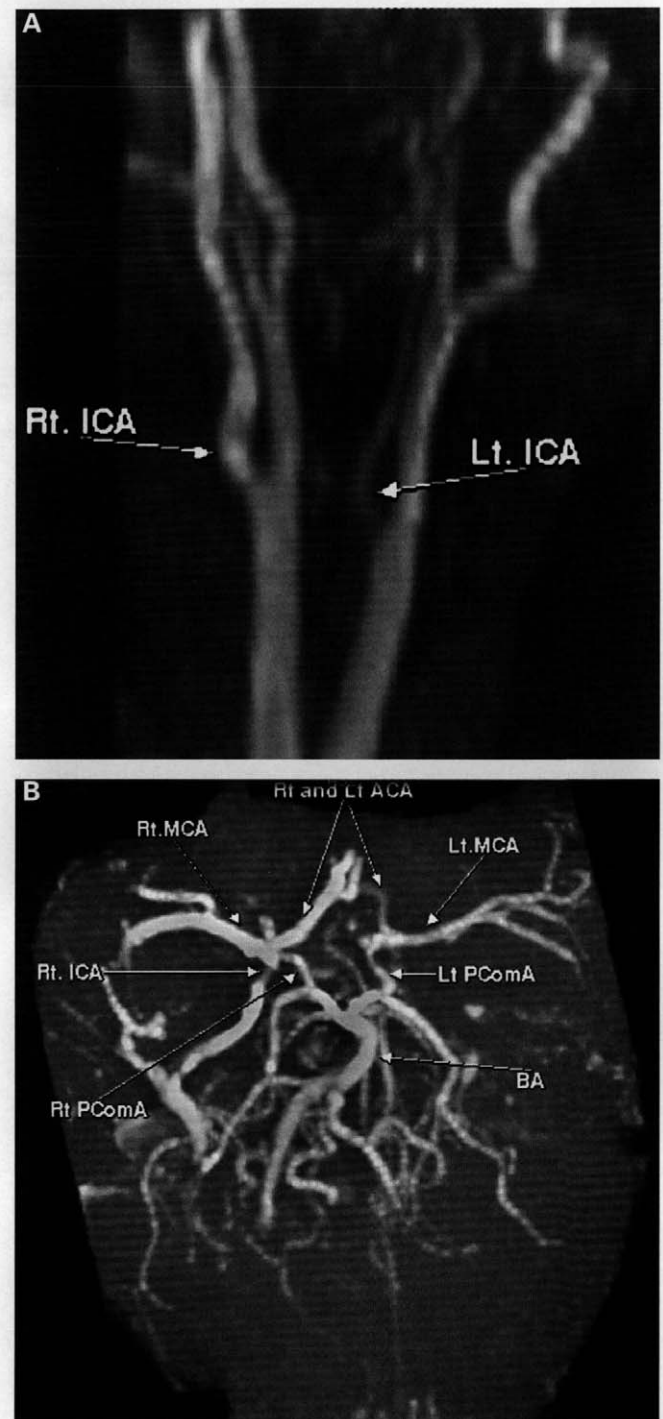


Figure 2. A, Two-dimensional time of flight magnetic resonance angiography of the extracranial carotid arteries shows a normal flow signal in the right internal carotid artery (arrow) and a uniformly decreased and narrowed flow signal in the left internal carotid artery (arrow). B, Three-dimensional time of flight magnetic resonance angiography of the circle of Willis shows occlusive disease of both cavernous carotid arteries, as reflected by an area of focal occlusion in the right internal carotid artery (ICA) (arrow) and nonvisualization of the left ICA. ACA = anterior cerebral artery; BA = basilar artery; MCA = middle cerebral artery; PComA = posterior communicating artery.

### Discussion

Premature atherosclerosis is a well-known complication of progeria.<sup>3</sup> Its cause is unknown. In the last several years, it has become clear that cerebrovascular atherosclerosis may play a role in the

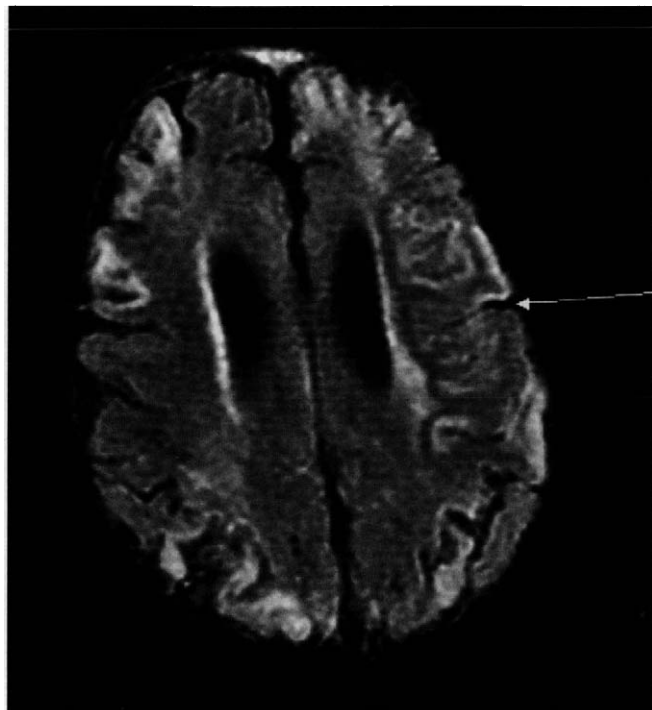


Figure 3. Fluid attenuation inversion recovery images show an acute temporoparietal infarct in the territory supplied by the left middle cerebral artery (arrow), not present in the earlier study (see Figure 1B).

morbidity and probably the mortality of patients with progeria, although, to date, there have been no reported deaths from progeria ascribed to complicating cerebrovascular disease. Dyck et al<sup>4</sup>

reported a girl with progeria who at ages 7 and 9 years had episodes of transient right hemiplegia, followed by recurrent vertigo. Cerebral angiography showed complete occlusion of the left internal carotid artery and severe atherosclerosis of the vertebral system. Angina pectoris began at age 9 years; it progressed, culminating in myocardial infarction at age 11 years. At age 14 years, she was experiencing 20 to 30 episodes of angina a day. Coronary angiography showed extensive disease, and she underwent coronary bypass surgery. Naganuma et al<sup>5</sup> reported a 7-year-old boy with progeria, transient ischemic attacks, and a right hemiplegia. Cerebral angiography showed complete occlusion of the left carotid artery and vertebral artery narrowing. Cranial computed tomographic (CT) scan showed multiple low-density contrast-enhancing lesions in the left frontal and parieto-occipital areas. Wagle et al<sup>6</sup> described a case of left hemiparesis in an 8-year-old girl with progeria who, on MRI, had infarction in the distribution of the superior division of the right middle cerebral artery. Magnetic resonance angiography showed the carotid artery bifurcations and the large intracranial arteries to be normal. Carotid duplex ultrasonography and cardiac ultrasonography also were normal. Smith et al<sup>7</sup> reported a 4-year-old boy with progeria with transient headaches, drooling, and right arm weakness; 1 month later, he developed a right-sided seizure followed by a flaccid right hemiparesis. Cranial CT scan showed bilateral supratentorial subdural collections and an acute left posterior parietal infarct, confirmed by MRI, which also showed diffuse periventricular white matter and basal ganglia ischemic disease and a right posterior parietal infarct. Magnetic resonance angiography showed bilateral occlusion of the proximal internal carotid arteries and of the origins of the vertebral arteries. There were multiple cervical collateral vessels seen, reconstituting the cavernous portion of the left internal carotid artery and both cervical-

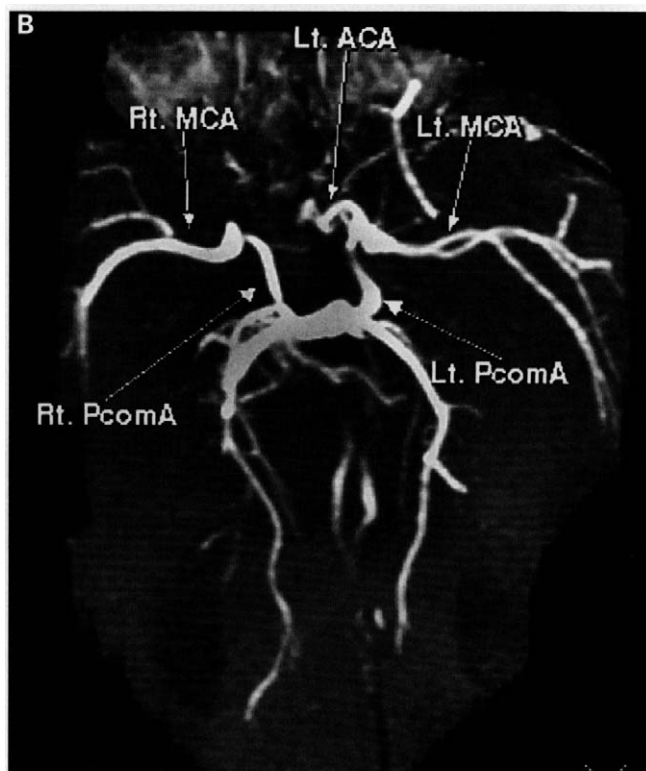
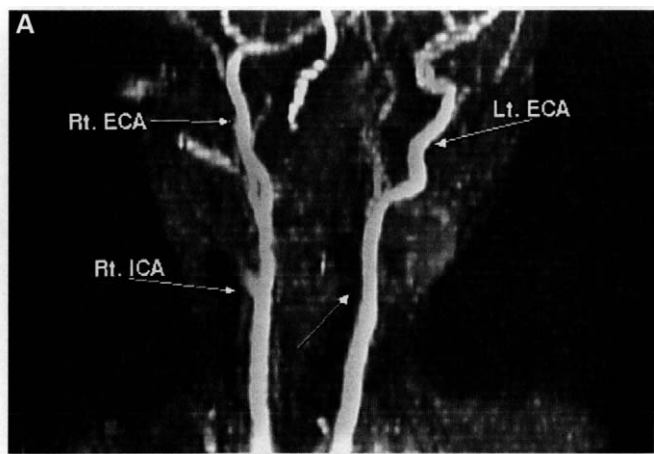


Figure 4. A, Two-dimensional time of flight magnetic resonance angiography of the extracranial carotid arteries shows complete occlusion of the left internal carotid artery and markedly diminished flow in the right internal carotid artery. B, Three-dimensional time of flight magnetic resonance angiography of the circle of Willis shows progression of the occlusive vascular disease when compared with Figure 2B. The previously visualized right internal carotid artery (ICA) and proximal segment of the right anterior cerebral artery (ACA) are no longer seen. Note enlargement of the flow signal in both posterior communicating arteries providing increased supply to the anterior circulation. ECA = external carotid artery; MCA = middle cerebral artery; PcomA = posterior communicating artery.



vertebral arteries. Flow was markedly diminished in the right anterior cerebral artery and in branches of the middle cerebral arteries, with increased flow in both ophthalmic arteries. Warfarin was begun. The patient's right hemiparesis slowly improved, but he developed transient episodes of left-sided weakness. MRI about 6 months later showed bilateral supratentorial subdural collections, increased size of the cerebral sulci and ventricles, and periventricular white-matter signal abnormalities with biparietal and right frontal infarction. Magnetic resonance angiography was unchanged.

Two main possibilities were considered in our case to explain the pathogenesis of the child's strokes. Initially, they were thought to be embolic, with the subaortic valve mass as the source of brain emboli. The child demonstrated extensive and progressive intracranial cerebrovascular disease, however, with strokes in the territories supplied by these vessels and in their watershed territories; also, there was no interval change in the size or configuration of the subaortic mass. Thus, we concluded that the patient's strokes were probably not embolic but rather caused by ischemic changes in brain secondary to progressive narrowing and occlusion of intracranial vessels. It is noteworthy that Caplan et al<sup>8</sup> found African Americans to be more prone to develop intracranial rather than extracranial atherosclerosis, whereas Caucasians more frequently had extracranial disease, which is what was found in our case. Ischemic changes in perivascular white matter and basal ganglia, as seen in the patient of Smith et al,<sup>7</sup> may well be secondary to occlusive disease of penetrating arteries.

In our patient, we found an imprecise correlation between the location and age of the cerebral infarctions and the laterality and time of onset of the child's symptoms. For example, the patient initially had new-onset left focal seizures and left-sided weakness, but his MRI then showed bilateral acute and subacute infarcts in both middle cerebral artery watershed territories. With subsequent right-sided seizures and transient right-sided weakness 3 months later, there was no acute infarction seen on MRI, only interval loss of deep parenchyma. Two months after that, however, right-sided seizures recurred, and MRI now showed new infarction in left middle cerebral artery territory.

Our patient experienced multiple episodes of seizure recurrence. The frequency of early seizures with acute brain infarction varies from 4.4% to 10%.<sup>10</sup> About one third of these patients will go on to have late seizures. About 10% of patients with acute brain infarction will have only late seizures.<sup>11</sup> Of the five cases of progeria with complicating cerebrovascular disease in childhood described above, ours was the only one in which seizures were the first neurologic sign.

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## References

1. Brown WT: Progeria, in Buyse ML (ed): *Birth Defects Encyclopedia*. Cambridge, MA, Blackwell Scientific, 1990, 1411-1413.
2. McKusick VA: Progeria. *Online Mendelian Inheritance in Man, OMIM*, Website. Baltimore, MD, Johns Hopkins University, 1999. <http://www3.ncbi.nlm.nih.gov/omim>.
3. Baker PB, Baba N, Boesel CP: Cardiovascular abnormalities in progeria. Case report and review of the literature. *Arch Pathol Lab Med* 1981;105:384-386.
4. Dyck JD, David TE, Burke B, et al: Management of coronary artery disease in Hutchinson-Gilford syndrome. *J Pediatr* 1987;111:407-410.
5. Naganuma Y, Konishi T, Hongou K, et al: A case of progeria syndrome with cerebral infarction. *No To Hattatsu* 1990;22:71-76.
6. Wagle WA, Haller JS, Cousins JP: Cerebral infarction in progeria. *Pediatr Neurol* 1992;8:476-477.
7. Smith AS, Wiznitzer M, Karaman BA, et al: MRA detection of vascular occlusion in a child with progeria. *AJNR Am J Neuroradiol* 1993; 14:441-443.
8. Caplan LR, Gorelick PB, Hier DB: Race, sex and occlusive cerebrovascular disease: A review. *Stroke* 1986;17:648-655.
9. Kilpatrick CJ, Davis SM, Tress BM, et al: Epileptic seizures in acute stroke. *Arch Neurol* 1990;47:157-160.
10. Asconape JJ, Penry JK: Poststroke seizures in the elderly. *Clin Geriatr Med* 1991;7:483-492.
11. Kilpatrick CJ, Davis SM, Hopper JL, Rossiter SC: Early seizures after acute stroke. Risk of late seizures. *Arch Neurol* 1992;49:509-511.

## Neurodevelopmental Delay Associated With Nonconvulsive Status Epilepticus in a Toddler

### ABSTRACT

Nonconvulsive status epilepticus is a prolonged and continuous state of increased unawareness without overt motor seizures linked with repetitive generalized epileptic discharges. In children, it may occur de novo but more commonly may complicate a preexisting epileptic disorder. We report on a 2-year-old female who presented with global developmental delay as the main manifestation of nonconvulsive status epilepticus. Following valproic acid treatment, her motor, cognitive, and speech delays had gradually subsided and nearly completely resolved, in concert with normalization of electroencephalography (EEG). Hence, given a possible, albeit rare, presentation of nonconvulsive status epilepticus with global developmental delay, we suggest that EEG should be recommended in any infant who manifests neurodevelopmental delay. (*J Child Neurol* 2001;16:215-217).

Convulsive status epilepticus is a life-threatening medical emergency that requires prompt and vigorous treatment. The term is usually used to describe prolonged or repetitive seizures without a period of recovery between attacks.<sup>1</sup> Nonconvulsive status epilepticus