Ipsilateral Stroke in a Patient With Horizontal Gaze Palsy With Progressive Scoliosis and a Subcortical Infarct

Adeline S.L. Ng, MRCP; Yih-Yian Sitoh, FRCR; Yi Zhao, PhD; Esther W.L. Teng, BSc; Eng King Tan, FRCP; Louis C.S. Tan, FRCP

Background and Purpose—Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare congenital disorder caused by mutation in the ROBO3 gene. It is characterized by absent horizontal eye movements with progressive scoliosis developing in childhood and adolescence. To our knowledge, both diffusion tensor imaging evaluation in HGPPS patients who present with stroke and truncating stop codon mutation in the ROBO3 gene have yet to be reported.

Summary of Case—We present a man with HGPPS who experienced a left pure motor stroke as a result of a left corona radiata infarct on diffusion-weighted imaging. Diffusion tensor imaging tractography confirmed the presence of uncrossed corticospinal tracts, accounting for the ipsilateral deficit. He was also found to possess a novel ROBO3 stop codon mutation on genetic testing.

Conclusions—Patients with HGPPS may present with stroke symptoms on the ipsilateral side of the infarct in view of uncrossed corticospinal tracts. Truncating mutation in ROBO3 may provide additional pathophysiologic insights. (Stroke. 2011;42:e1-e3.)

Key Words: acute stroke ■ genetics ■ neuroradiology

A 55-year-old ambulant Indian man with a history of hypertension and scoliosis since childhood was admitted to our stroke unit with a 4-day history of sudden-onset left lower and upper limb weakness. Examination revealed a left motor stroke of Medical Research Council grade 4 out of 5 power in both upper and lower limbs, with a left upper motor neuron facial palsy. There were no sensory signs. Significantly, he had complete absence of extraocular movements horizontally with impaired convergence, but pupillary reflexes were preserved. Horizontal Doll’s maneuver was absent. Vertical eye movements and Doll’s maneuver were normal. He revealed that the horizontal gaze paralysis had been present since birth. He was also found to have severe scoliosis of his thoracolumbar spine that had remained stable since adolescence and did not impair him functionally. Before admission, he was employed as a security guard and did not require the help of any walking aid. He was cognitively intact and had a Mini Mental State Examination score of 30.

He had a significant family history in that his sister and paternal uncle had scoliosis from childhood. His parents, who had both died, were of a consanguineous marriage as first cousins and neither had scoliosis or gaze palsies.

MR imaging revealed a left putamen and corona radiata nonhemorrhagic infarct (Figure 1) as well as features suggestive of horizontal gaze palsy with progressive scoliosis (HGPPS), brain stem hypoplasia resulting in the split pons sign, “butterfly” configuration of the medulla (Figure 2A, B), and brain stem volume reduction. MRA showed irregularity in the supraclinoid left internal carotid artery and the M1 segment of the left middle cerebral artery, suggestive of atherosclerotic change. Ultrasound scan of his carotid arteries were unremarkable and 2-dimensional cardiac echocardiography revealed a decreased ejection fraction of 30% with segmental wall motion abnormalities and posterior mitral valve leaflet prolapse. Ischemic heart disease was diagnosed by a cardiologist and he was started on relevant cardiac medications. Because his stroke was likely cardioembolic in nature, he was started on aspirin initially and subsequently anticoagulated with warfarin.

In view of the clinical features suggestive of HGPPS, diffusion tensor imaging was performed to evaluate the corticospinal pathways. Diffusion tensor imaging tractography confirmed the presence of uncrossed corticospinal tracts (Figure 3) that explained hemiparesis on the same side as the infarct. Sequence analysis of all the coding regions of the roundabout axon guidance receptor homolog 3 (ROBO3) gene revealed a novel homozygous stop codon mutation (GAG to TAG) as a result of a G>T substitution in exon 17.

His condition improved with physiotherapy and he was back to his premorbid functional state on discharge.
HGPPS is a rare autosomal recessive condition attributable to mutation of the ROBO3 gene on chromosome 11 characterized by congenital absence of conjugate horizontal eye movements, preservation of vertical gaze and variable convergence, and progressive scoliosis developing in childhood and adolescence. The syndrome also includes a distinctive brain stem malformation and defective crossing of some brain stem neuronal pathways. Patients are otherwise neurologically intact and have little functional consequences; however, little is known about neuropsychological function and language lateralization in this syndrome. Amoiridis et al1 examined 2 brothers with HGPPS who performed normally on complex sensory and visuospatial functions, reading, and general intelligence tests.

In 2002, Jen et al2 described 6 patients from 2 nonconsanguineous families and mapped the disease locus to chromosome 11q23-25. ROBO3 encodes a protein that shares homology with the roundabout family of transmembrane receptors important in axon guidance and neuronal migration. Therefore, a normal functional ROBO3 gene is important in axon guidance activity and aids in regulation of hind brain axonal midline crossing. ROBO3 helps in directing cell migration and specifies the lateral position of longitudinal pathways. In addition, its interactions with other cell molecules aid in the modification of cytoskeleton assembly and regulation of growing axons.4 Our patient was confirmed to have a novel ROBO3 stop codon mutation.

Although close to 20 different mutations in the ROBO3 gene have been reported in HGPPS, this is the first description of a truncating stop codon mutation. Different mutations have been postulated to alter the structure of the ROBO3 protein. Our report provides the most direct evidence that a loss-of-function mechanism underpins the pathophysiology in HGPPS, whereby a lack of functional ROBO3 protein impedes brain stem development. It would be interesting to determine if truncating mutations are associated with a more severe disease phenotype when more of such cases are reported. Currently, it is unclear why the effects of ROBO3 mutations are restricted to horizontal eye movement and why there is progressive scoliosis.

Previous reports on MR imaging findings in HGPPS have described the following characteristics that are variable in axon guidance activity and aids in regulation of hind brain axonal midline crossing. ROBO3 helps in directing cell migration and specifies the lateral position of longitudinal pathways. In addition, its interactions with other cell molecules aid in the modification of cytoskeleton assembly and regulation of growing axons.4 Our patient was confirmed to have a novel ROBO3 stop codon mutation.

Although close to 20 different mutations in the ROBO3 gene have been reported in HGPPS, this is the first description of a truncating stop codon mutation. Different mutations have been postulated to alter the structure of the ROBO3 protein. Our report provides the most direct evidence that a loss-of-function mechanism underpins the pathophysiology in HGPPS, whereby a lack of functional ROBO3 protein impedes brain stem development. It would be interesting to determine if truncating mutations are associated with a more severe disease phenotype when more of such cases are reported. Currently, it is unclear why the effects of ROBO3 mutations are restricted to horizontal eye movement and why there is progressive scoliosis.

Previous reports on MR imaging findings in HGPPS have described the following characteristics that are variable
among affected individuals: brain stem hypoplasia involving reduction in volume of the pons and medulla; butterfly-like medulla; absence of the facial colliculi; and the split pons sign. These features were well-demonstrated in our patient. Diffusion tensor imaging can be used to identify specific fiber tracts and their directionality. In HGPPS, diffusion tensor imaging has demonstrated a widespread lack of crossing fibers in the brain stem, supported by evoked potential studies showing uncrossed descending motor and ascending sensory pathways.

A recent report of 7 individuals with genetically proven HGPPS described 1 individual with a right subdural hematoma and right hemiparesis, which is the first clinical confirmation of uncrossed corticospinal tracts in the literature. Our case is interesting and unique in that this is, to the best of our knowledge, the first clinical confirmation of uncrossed corticospinal tracts resulting in an ipsilateral ischemic stroke.

Conclusion
In summary, we present an interesting case of clinical and radiological features of HGPPS, confirmed genetically with a novel ROBO3 mutation, presenting with a stroke that highlights an important characteristic of this syndrome. Clinicians should be aware that patients with HGPPS may present with stroke symptoms on the ipsilateral side of the infarct in view of uncrossed corticospinal tracts found in this congenital condition.

Sources of Funding
The authors acknowledge the National Medical Research Council, Singapore General Hospital, and Singapore Millennium Foundation for their support.

Disclosures
None.

References
Ipsilateral Stroke in a Patient With Horizontal Gaze Palsy With Progressive Scoliosis and a Subcortical Infarct
Adeline S.L. Ng, Yih-Yian Sitoh, Yi Zhao, Esther W.L. Teng, Eng King Tan and Louis C.S. Tan

*Stroke*. 2011;42:e1-e3; originally published online November 18, 2010; doi: 10.1161/STROKEAHA.110.591271

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/1/e1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/