Case Report

Noonan Syndrome, Metabolic Syndrome and Stroke-in-the-Young: Coincidence, Causal or Contribution?

Jakris Eu-ahsunthornwattana MD, MSc*, Objoon Trachoo MD*,
Donniphat Dejsuphong MD*, Atchara Tunteeratum MD*,
Kanoknan Srichan RN*, Thanyachai Sura MD, MRCP*

** Division of Medical Genetics & Molecular Medicine and Academic Center for Medical Genetics, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

A 34-year-old Thai woman developed acute left hemiparesis with dysarthria from subcortical infarction of the right MCA territory eighteen months after being diagnosed with Noonan syndrome, diabetes mellitus, dyslipidaemia, and hypertension. Further investigations suggested atherosclerosis as a cause. Modifying her risk factors was difficult, partly because of limited adherence. Three years later, she had another attack of ischaemic stroke in the same area. Unlike the three previously reported cases, the causation of strokes in this patient appeared to be a more 'complex' interaction between genetic defect and environment including possible subtle arterial abnormalities, metabolic risk factors, and mental insufficiency.

Keywords: *Noonan syndrome, Cerebral infarction, Metabolic syndrome, Diabetes mellitus, Multifactorial causality*

J Med Assoc Thai 2010; 93 (9): 1084-7
Full text. e-Journal: *http://www.mat.or.th/journal*

Noonan syndrome is an autosomal dominant dysmorphic syndrome with variable expressivity and penetrance, and with locus heterogeneity. Patients have characteristic facial features, as well as associated physical features and cardiac anomalies[1]. The classic example of the latter is pulmonary valve stenosis as originally described by Noonan and Ehmke in 1963[2], although many other cardiac anomalies have also been reported. Mental retardation and other developmental or behavioral problems can also be found.

Recognized haematological complications in Noonan syndrome included susceptibility to leukaemia, thrombocytopenia and bleeding diathesis[1,3], but not thromboembolic events. To our knowledge, there were only three previously reported cases of ischaemic stroke in Noonan syndrome; all occurred in childhood (Table 1)[4-7]. The authors present another patient from a substantially older age group, and in whom the contribution of Noonan syndrome to the causation of stroke appeared to have followed a different and more 'complex' path.

Correspondence to:
Eu-ahsunthornwattana J, Division of Medical Genetics & Molecular Medicine, Department of Medicine, Ramathibodi Hospital, Rama VI Rd, Phaya Thai, Bangkok 10400, Thailand.
Phone & Fax: 0-2201-1374
E-mail: jakrise@gmail.com

Case Report

A 34-year-old woman from a neighboring province of Bangkok came to Ramathibodi Hospital in 2002 after having been diagnosed with diabetes mellitus, hypertension, and dyslipidaemia by her local hospital. A cardiac murmur as well as several abnormal physical features was noted on her first visit, prompting the first physician to refer her to the authors' unit.

She first attended her local hospital not long before that because of tiredness. There was not much else in terms of history, apart from that she was mentally 'slow' and could not finish her primary education. She was living with her mother, who was also her main caretaker. She did not smoke, consume alcohol, or use oral contraception. There was no significant history of cardiovascular disease in her family.

When the authors first saw her, she was 145 cm tall, weighed 55.2 kg (BMI = 26.3 kg/m^2), and had features of Noonan syndrome including a triangular face, low hair line, low-set ears, strabismus, high arched palate, webbed neck, cubitus valgus, and shield chest. These features in fact somewhat resembled her mother's, although more prominent. She had fully developed secondary sexual characteristics. Initial ophthalmological examination revealed mild non-proliferative diabetic retinopathy. A perimembranous ventricular septal defect was demonstrated on

Table 1. Characteristics of the ischaemic strokes in patients with Noonan syndrome

Case	Reference	Sex, Age	Site	Contributing factors
1	Hinnant, 1994[6]; Hinnant, 1995[7]	F, 15 year	Pons, right side of cerebellum, medulla	Trauma; hypoplastic posterior vessels
2	Robertson et al, 1997[4]	M, 4 month (1st attack) and 5 month (2nd attack)	Left temporo-parietal, occipital (1st attack), right cerebral hemisphere (2nd attack)	None identified
3	Wilms et al, 2002[5]	F, 6 year	Left putamen and caudate nucleus	Stenosis of middle cerebral arteries and left anterior cerebral artery
4	This patient	F, 34 year (1st attack) and 37 year (2nd attack)	Right cerebral hemisphere	Diabetes mellitus, hypertension, dyslipidaemia; atherosclerosis of anterior vessels; limited adherence to treatment

echocardiogram. The doppler ultrasound of her renal arteries was normal. She was given oral treatment for diabetes, hypertension, and dyslipidaemia. Nevertheless, despite the continual medication adjustment, her diabetes and dyslipidaemia control remained demonstrably poor−partly due to limited adherence to medication and life-style modification.

Eighteen months after the initial consultation, she developed acute left hemiparesis with dysarthria. Computed tomogram showed subcortical infarction of the right middle cerebral artery territory. Laboratory tests for thrombosis tendency were negative. Carotid and vertebral duplex scans were both normal. No microembolic phenomenon was found on the Transcranial Doppler although stenoses in the anterior circulation were noted. Magnetic Resonance Angiogram of her brain further showed irregular narrowing of the right middle cerebral artery and mild irregularities in the left middle cerebral artery (Fig. 1). The general feeling from the sonologist and radiologists was that these resulted from an atherosclerotic process. She gradually recovered after anti-platelet therapy, and was switched to insulin injections for her diabetes.

Three years later, she again presented with left hemiparesis. The computed tomogram again showed subacute infarction in the right middle cerebral artery territory.

The control of her metabolic parameters remained difficult. She continued to gain weight. Over the last year, her renal function had quickly deteriorated. This was complicated by increasing

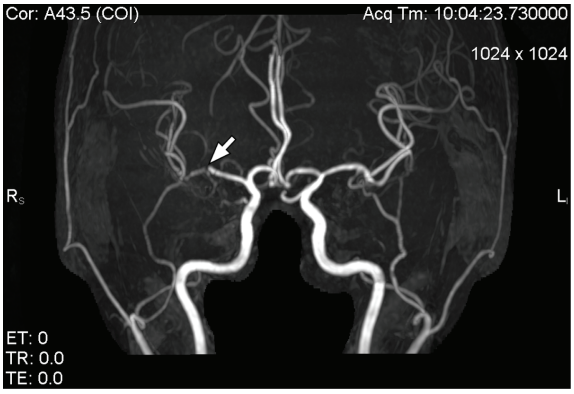

Fig. 1 Magnetic Resonance Angiogram after the first ischaemic stroke showing irregularly narrow right middle cerebral artery with downstream attenuation and mild irregularities in the left middle cerebral artery

tiredness and oedema in her legs, thus further limiting her activities. Due to a complex home and financial circumstance, she was not able to receive renal replacement therapy. She died in March 2008 from renal failure.

Discussion

This is the fourth reported case of ischaemic stroke in Noonan syndrome, and the first that the strokes occurred in adulthood. The cause of recurrent ischaemic strokes in the presented patient seemed very likely to have differed from that in other cases. In all

previous cases, the strokes occurred in childhood and were likely to be caused by some degree of vascular malformations. In the presented patient, the metabolic risk factors including diabetes mellitus, obesity, hyperlipidaemia, and hypertension appeared to have played a major role in the causal link.

The presented patient fulfilled the criteria for metabolic syndrome and was at an increased risk for vascular diseases including strokes[8]. That said, the onset of stroke was rather early even with these risk factors. The authors therefore suspect that there may also be other factors that contributed to the patient's strokes.

Most of the strokes reported in Noonan syndrome were hemorrhagic in nature and resulted from vascular malformations or bleeding diathesis. Two of the three childhood cases of ischaemic strokes also had vascular defects (Table 1)[5-7]. Arterial intimal thickening had been reported in Noonan syndrome[9], but the only vascular defects found in the presented patient were felt to be more compatible with atherosclerotic process. Nevertheless, the authors do not have the vascular imaging prior to the ischaemic events, and there could be some subtle arterial defects, which were later compounded by the atherosclerosis and caused the stroke.

The authors are not aware of any association between Noonan syndrome and diabetes mellitus, dyslipidaemia or metabolic syndrome. However, the former is a known complication of Turner syndrome, which shares many similar morphological features. Essential hypertension has been reported in a boy with Noonan syndrome[10], but could well be a coincidence. Nevertheless, the early onset of these conditions in this patient made the authors wonder if there is in fact a yet unknown contribution from Noonan syndrome. In addition, decreased mental capacity from Noonan syndrome had also resulted in less adherence to the modification of her metabolic risk factors. Arguably, her strokes were caused by Noonan syndrome, at least indirectly.

Traditionally, the manifestation of 'single gene' disorders such as Noonan syndrome is viewed as directly resulting from their genetic defects. However, as the patients become older, the manifestation of their disease could become more 'complex' involving both the direct and indirect contributions from their genes and environments.

Acknowledgements

The authors wish to thank the patient's mother who has kindly granted permission to present this patient's case.

References

1. Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. Annu Rev Genomics Hum Genet 2005; 6: 45-68.
2. Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. J Pediatr 1963; 63: 468-71.
3. Witt DR, McGillivray BC, Allanson JE, Hughes HE, Hathaway WE, Zipursky A, et al. Bleeding diathesis in Noonan syndrome: a common association. Am J Med Genet 1988; 31: 305-17.
4. Robertson S, Tsang B, Aftimos S. Cerebral infarction in Noonan syndrome. Am J Med Genet 1997; 71: 111-4.
5. Wilms H, Neubauer B, Deuschl G, Zunker P. Cerebral occlusive artery disease in Noonan syndrome. Cerebrovasc Dis 2002; 14: 133-5.
6. Hinnant CA. Thromboembolic infarcts occurring after mild traumatic brain injury in a paediatric patient with Noonan's syndrome. Brain Inj 1994; 8: 719-27.
7. Hinnant CA. Noonan syndrome associated with thromboembolic brain infarcts and posterior circulation abnormalities. Am J Med Genet 1995; 56: 241-4.
8. Gil-Nunez A. The metabolic syndrome and cerebrovascular disease: suspicion and evidence. Cerebrovasc Dis 2007; 24 (Suppl 1): 64-75.
9. Ishikawa Y, Sekiguchi K, Akasaka Y, Ito K, Akishima Y, Zhang L, et al. Fibromuscular dysplasia of coronary arteries resulting in myocardial infarction associated with hypertrophic cardiomyopathy in Noonan's syndrome. Hum Pathol 2003; 34: 282-4.
10. Rokicki W, Rokicka A. Noonan syndrome coexisting with essential arterial hypertension in 8 year old boy. Wiad Lek 2002; 55: 488-93.

กลุ่มอาการนูแนน, กลุ่มอาการเมตะบอลิก และโรคหลอดเลือดสมองขณะอายุน้อย: ความบังเอิญ, สาเหตุ หรือ ปัจจัยร่วม?

จักรกฤษณ์ เอื้อสุนทรวัฒนา, โอบจุฬ ตราชู, ดลนิภัทร เดชสุพงศ์, อัจฉรา ธัญธีรธรรม, กนกนันท์ ศรีจันทร์, ธันยชัย สุระ

หญิงไทยอายุ 34 ปี มีอาการอัมพาตซีกซ้ายร่วมกับพูดไม่เป็นความ ซึ่งเป็นผลจากภาวะเนื้อสมองตายจากการขาดเลือดในบริเวณหลอดเลือดแดงมิดเดิลซีรีบรัลด้านขวา 18 เดือน หลังจากที่ได้รับการวินิจฉัยกลุ่มอาการนูแนน เบาหวาน ไขมันในเลือดสูง และความดันโลหิตสูง การตรวจเพิ่มเติมชี้ว่า ภาวะหลอดเลือดแดงแข็งน่าจะเป็นสาเหตุของภาวะการขาดเลือด การควบคุมปัจจัยเสี่ยงของผู้ป่วยทำได้ลำบาก ส่วนหนึ่งเนื่องจากความร่วมมือที่จำกัด และสามปีต่อมา ผู้ป่วยก็เกิดภาวะเนื้อสมองตายซ้ำในบริเวณเดิมอีกครั้ง โรคหลอดเลือดสมองในผู้ป่วยรายนี้แตกต่างจากที่เกิดขึ้นในผู้ป่วยกลุ่มอาการนูแนนสามรายที่เคยมีการรายงานมาก่อนหน้า เนื่องจากดูเหมือนจะมีความซับซ้อนในแง่พยาธิกำเนิดซึ่งเป็นปฏิสัมพันธ์ระหว่างความผิดปกติทางพันธุกรรม และปัจจัย ทางสิ่งแวดล้อม เช่น สภาพวิรูปของหลอดเลือดแดง ปัจจัยทางเมตะบอลิก และภาวะบกพร่องทางสติปัญญา