Gorlin-Goltz Syndrome and Stroke: A Case Report

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SUMMARY We report on the case of a 32-years old male patient who was previously diagnosed with Gorlin-Goltz syndrome. The patient presented with sudden-onset right-sided hemiparesis, supranuclear facioparesis, and motor aphasia. He was treated with thrombolytic therapy, which successfully alleviated the symptoms. Subsequent radiologic work-up revealed anomalies in the vertebral arteries, a bifid rib, an ischemic lesion in the supply area of the left middle cerebral artery, and falx calcifications. Laboratory tests showed a 4G/4G polymorphism of the plasminogen activator inhibitor 1 (PAI-1) gene whose correlation with stroke is discussed in the article.

KEYWORDS: Gorlin-Goltz syndrome, stroke, PAI-1 gene polymorphism

INTRODUCTION

Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder with a prevalence of about 1:60000 (with estimations varying from 1:54000 to 164000 worldwide) (1). The Gorlin-Goltz syndrome has variable penetration and numerous manifestations, involving the following systems: skin, musculoskeletal and central nervous system, the eyes, and the endocrine system. It was described for the first time in 1894 but defined as a separate entity in 1960 by Robert J. Gorlin and Robert W. Goltz (2), who defined it as a syndrome consisting of multiple basocellular carcinomas (BCCs) and dysmorphic facial features due to multiple benign odontogenic keratocysts and musculoskeletal anomalies, most commonly bifid ribs (3,4). The major and minor diagnostic criteria for Gorlin-Goltz syndrome are well described (1,3,5-7).

The association between the syndrome and vascular incidents has not been described in the literature, but the association with tumors has been reported (eg. odontogenic keratocysts, cardiac fibroma, and medulloblastoma) (8).

The aim of this case report is to present a unique patient with Gorlin-Goltz syndrome and thrombophilia who was successfully treated for acute ischemic stroke.

CASE REPORT

A 32-year-old male patient presented with sudden-onset right-sided hemiparesis, supranuclear facioparesis, and motor aphasia. He was alert and responsive, showing no signs of meningeal irritation. He was afebrile and his vital signs were stable. His

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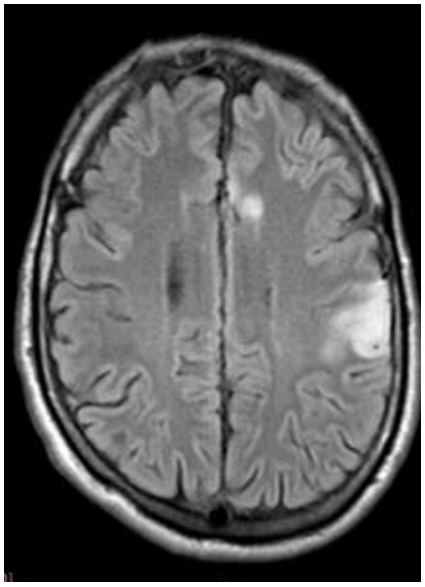

Figure 1. Brain magnetic resonance imagind (MRI) showing the ischemic lesions located frontally and frontoparietally (on the left).

score on the National Institute of Health Stroke Scale (NIHSS) was 10. As he arrived to the Emergency Department within a proper therapeutical window with no signs of ischemic and hemorrhagic lesions on the computerised tomography (CT) scan, thrombolytic therapy was administered according to the protocol, and the symptoms subsided to a NIHSS score of 2. Physical exams showed several shiny papulonodular skin lesions located on his face and upper trunk, varying in size from 2 to 8 mm in diameter. Some of them were ulcerated with a central crust. His facial features included a prominent supraorbital ridge, hypertelorism, and a small mandible. His lower jaw was small and asymmetric due to previous surgical removal of multiple odontogenic keratocysts.

He had been diagnosed with NBCCS at the age of 15 and had numerous BCCs removed from his trunk and face during childhood and adolescence. During hospitalization, a control brain magnetic resonance imaging (MRI) verified two separate ischemic lesions in the supply area of the left middle cerebral artery (Figure 1) and multiple falx calcifications. Further radiologic findings included a bifid rib and anomalies in the vertebral arteries which were verified by an MR angiography. Ultrasound imaging of the neck vessels indicated an occluded or possibly even hypoplastic left vertebral artery and an aberrant right vertebral artery, arising directly from the left side of the aortic arch (Figure 2). Both carotid arteries were patent, with a normal origin and course. After thrombolytic therapy had been provided, he was administered secondary stroke prevention therapy (statins, aspirin,

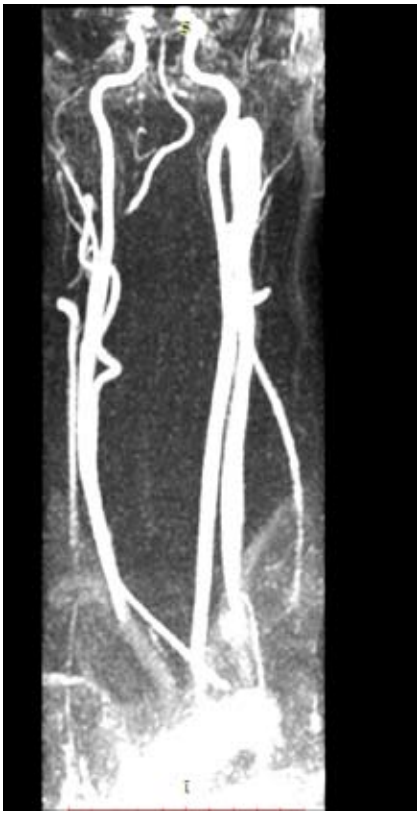

Figure 2. Magnetic resonance (MR) angiography (without contrast) of neck vessels showing both carotid arteries without signifficiant stenosis. The right vertebral artery originates from the left side of the aortic arch.

diet) and physical rehabilitation on the second day of hospitalization. By the end of his hospital stay, the patient was fully recovered. His laboratory tests for thrombophilia showed only a 4G/4G homozygosity for the plasminogen activator inhibitor 1 (PAI-1) gene. Other immunological and hematological laboratory testing did not show pathological values.

DISCUSSION

Thrombolytic therapy in our patient with Gorlin-Goltz syndrome was safe and successful. The ischemic lesions shown on the control brain MRI could have been related to embolism if as in our case thrombolysis has not been performed and if the cardiac evaluation showed any anomalities. Thus, our case was initially considered a cryptogenic stroke, with high likelyhood of thrombotic etiology. Further investigation concerning the underlying cause of early-onset cerebrovascular disease revealed only thrombophilia with 4G/4G homozygosity for the PAI-1 gene. A relationship between Gorlin-Goltz syndrome and PAI-1 gene polymorphism has not been reported. 4G/4G

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PAI-1 gene polymorphism can theoretically enhance the risk of thromboembolic incidents (9,10). Nevertheless, the relationship between the serum activity of PAI-1 and strokes is not simple. Many studies failed to prove correlation between the 4G/5G polymorphism or increased PAI-1 plasma levels and cerebrovascular disease risk under basal conditions (11-13). One study in particular has found higher reocclusion rates among 4G/4G patients undergoing fibrinolytic therapy (14). Another study compared two nested case-control studies, which both showed that the 4G allele is associated with an increased risk of ischemic stroke (15).

PAI-1 genotyping is a common test for thrombophilia and, considering its widespread use, further studies could be useful in revealing its precise role in stroke mechanisms and risk prediction. However, this may be most challenging in stroke patients with inherited diseases.

Our patient was known to have a hereditary syndrome (Gorlin-Goltz) affecting mesodermal and ectodermal tissues (16), and, therefore, neurologic manifestations were expected. Nevertheless, according to the literature, NBCCS has never before been associated with an increased risk of vascular incidents of any kind. Neurologic abnormalities associated with this syndrome include only otherwise benign multiple falx calcifications and certain radiologic finding such as bridging of the sella turcica, and none of these have been reported as clinically significant (16). In patients with Gorlin-Goltz syndrome there is an increased risk of medulloblastomas in early childhood (5) and rarely of congenital hydrocephalus (17) and epileptic seizures (18). No studies suggested an increased stroke risk and, to the best of our knowledge, there have been no reports of an early-onset stroke in an NBCCS patient.

Along with the aforementioned anomalies, radiologic examination revealed a hypoplastic left and aberrant right vertebral artery arising directly from the aortic arch. The right vertebral artery is normally the first branch of the ipsilateral subclavian artery, and this kind of aberrancy has been reported in only a few case reports so far. Anomalous origin is more commonly encountered with the left vertebral artery (19). Nevertheless, this congenital anomaly of vertebral arteries was not related to a current clinical picture and findings from the brain MRI.

In conclusion, selected patients with Gorlin-Goltz syndrome should be examined for vascular malformations and tested for thrombophilias and coagulopathies.

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