Brief Communication

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Ischemic Cerebral Infarction in an Infant Following Gonadotropin Treatment for Undescended Testes

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Cerebrovascular disorders are increasingly recognized as important causes of mortality and morbidity in the pediatric population. Risk factors for stroke in childhood are different from those in adults. Human chorionic gonadotropin is a polypeptide hormone produced by the human placenta and is composed of an α-subunit and a β-subunit. Pregnyl (human chorionic gonadotropin for injection) is a highly purified pyrogen-free preparation obtained from the urine of pregnant females. Ischemic cerebral infarction is seen in the young infertile male and female patients after gonadotropin treatment. The authors describe the case of a boy with right-sided hemiparesis following Pregnyl injection and discuss its possible pathogenetic mechanisms.

Keywords: cerebral infarction; gonadotropin; undescended testes

Introduction

Incidence of cerebrovascular disorders, including pediatric stroke, have increased and, depending on definitions and inclusion criteria, range from 2 to 13 per 100 000 children under age 18 per year in North America and Europe.[1,2] Cerebrovascular disorders are among the top 10 causes of death in children, especially in the first year of life.[3] Among survivors, more than half of the childhood stroke cases present with cognitive or motor disabilities.[4] Unfortunately, ischemic strokes are still underdiagnosed in infancy and childhood because of a lack of clinical suspicion and appropriate diagnostic testing. Variability of potential risk factors for stroke is the main difference between children and adults.

The action mechanism of human chorionic gonadotropin is virtually identical to that of pituitary luteinizing hormone. It stimulates production of gonadal steroid hormones by stimulating the interstitial cells of testis to produce androgens and the corpus luteum of the ovary to produce progesterone.[5] In general, human chorionic gonadotropin is used to induce testicular descent. Therapy is usually instituted in children between the ages of 4 and 9 or at early ages because of gonadal cancers and, thus, may help predict whether or not orchiopexy will be needed in the future.[5] We present a case of ischemic stroke in a 1-year-old boy with undescended testes following gonadotropin therapy, which is the first and only case reported in the literature.

Case Report

A 1-year-old male patient was admitted for sudden-onset right-sided hemiparesis and restlessness. He had a history of Pregnyl (human chorionic gonadotropin) 1500 U, $\frac{1}{2}$ ampoule, injection intramuscularly 3 times per week for undescended testes 2 weeks earlier. Physical examination revealed weakness in the right arm and leg. On laboratory examination, the following results were obtained: hematocrit 32.3%, hemoglobin 11 g/dL, white blood cell count 5600/μL, platelet count 244 000/μL, and normal prothrombin time, activated partial thromboplastin time, international normalized ratio, biochemical analyses, and blood gases. Cerebral magnetic resonance imaging revealed an acute infarct in the territory of the left middle cerebral artery, and magnetic resonance angiography showed occlusion of the left middle cerebral artery (Figures 1 and 2). Other investigations for the etiology of stroke were as follows: transthoracic echocardiography revealed small secundum atrial septal defect, but bubble study showed no intracardiac shunt that would be seen with patent foramen ovale; Doppler ultrasound of the carotid artery; hemoglobin electrophoresis, lupus anticoagulant assay, protein C, protein S, antithrombin III, factor V Leiden, activated protein C resistance, prothrombin

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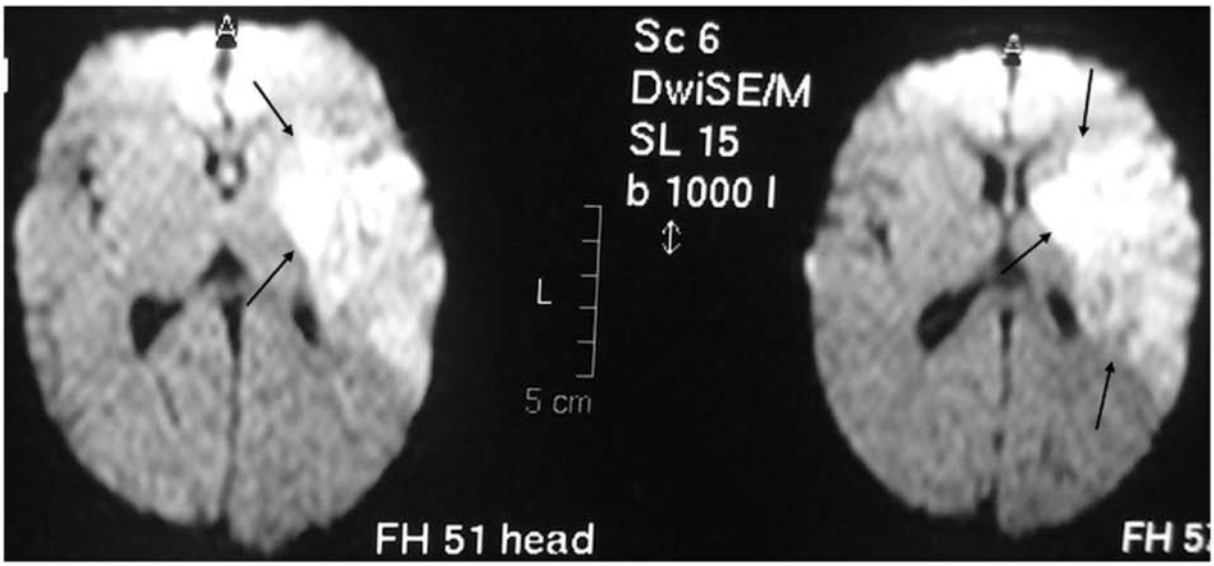

Figure 1. Axial diffusion weighted images show acute infarction in the left middle cerebral artery territory (black arrows).

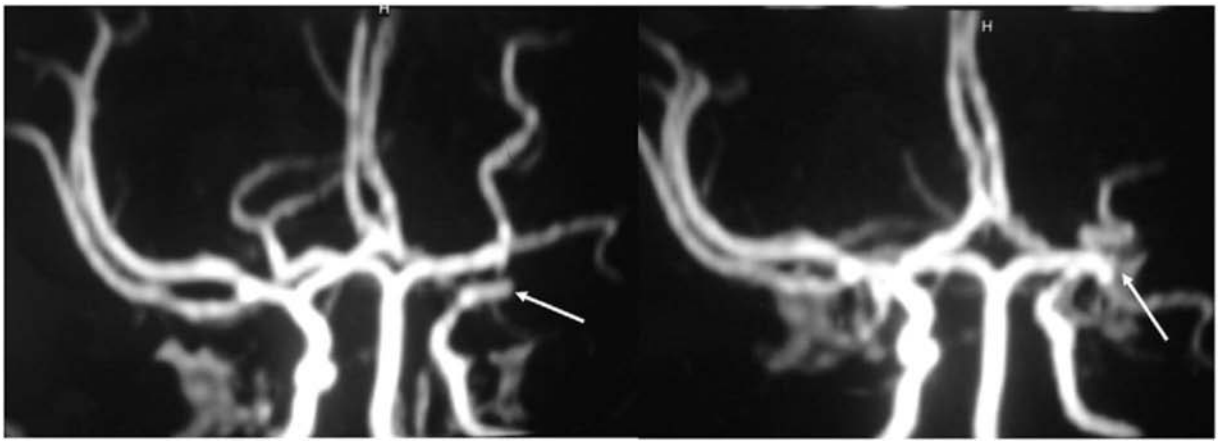

Figure 2. Magnetic resonance angiography shows occlusion of the left middle cerebral artery at its proximal segment (white arrows).

G20210A assessment, anticardiolipin, antinuclear antibody, homocysteine, and factor VIII, IX, and XII levels all were normal. Methylenetetrahydrofolate reductase was found heterozygote.

For initial treatment, a bolus of 75 U/kg heparin was started and then followed by a daily dose of 25 U/kg/h. After 2 days, warfarin was given at a dose of 0.13 mg/kg/day. Heparin was discontinued on day 5. Physical therapy was also applied. At 2 months of warfarin therapy, control cerebral magnetic resonance imaging and magnetic resonance angiography were performed. Cystic encephalomalacia was now demonstrated in the previously infarcted area in addition to recanalization of the left middle cerebral artery (Figures 3 and 4). Hemiparesis of the patient started to resolve. Warfarin therapy was continued for 6 months. The patient is still on aspirin therapy.

Discussion

Childhood arterial ischemic stroke is not rare. In an earlier study the incidence was 2.6 per 100 000 children per year, with the clinical presentation including hemiparesis 51%, speech disorder 17%, and seizures 48%.[6] Strokes in the pediatric population have many risk factors. At initial presentation, half of childhood stroke cases have a known predisposing cause, such as sickle cell disease, congenital heart disease, or infection.[7] For the remaining, a careful

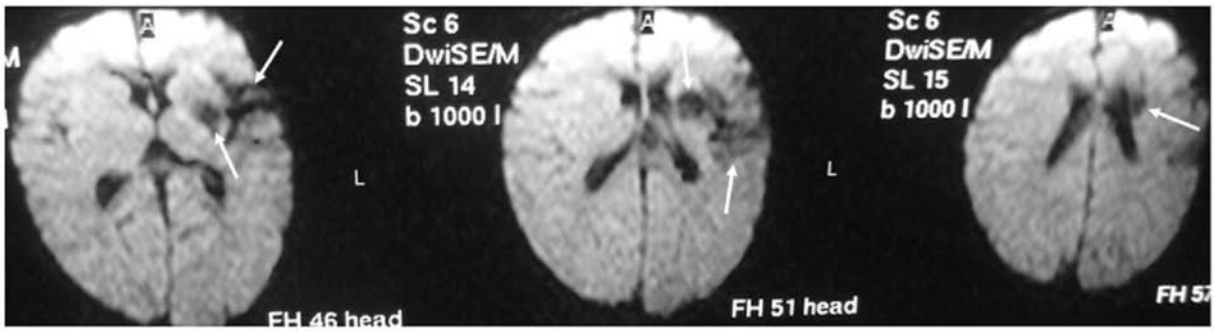

Figure 3. Follow-up axial diffusion weighted images show resolution of acute infarction to volume loss and cystic encephalomalacia (white arrows).

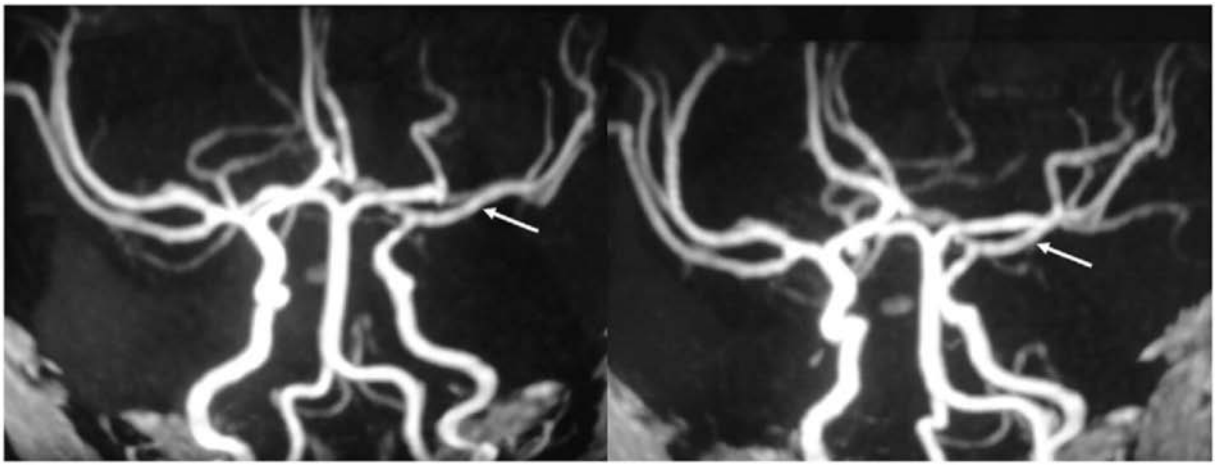

Figure 4. Follow-up magnetic resonance angiography shows recanalized left middle cerebral artery (white arrows).

evaluation is needed. Variability of risk factors and multifactorial potential in childhood stroke are the main differences from adult stroke. Cardiac disease, including congenital and acquired heart disease, is the most common cause of stroke in childhood.[8] Our patient had no cardiac disease. Hematologic or metabolic disorders can cause stroke, such as elevations in homocysteine and lipoprotein (a); deficiency of protein C, protein S, and antithrombin III; the presence of the factor V Leiden G1691A mutation or prothrombin mutation G20210A[9-12]; iron deficiency anemia[6,7]; Fabry disease[13]; mitochondrial myopathy encephalopathy; and strokelike syndrome. None of them was present in our patient. Other factors causing stroke include vascular disorders such as arterial dissection,[7] Moyamoya syndrome,[14] and transient cerebral arteriopathy.[15] In a recent prospective cohort of patients with arterial ischemic stroke in the United Kingdom, vascular abnormality was found in 79% of patients on cerebral arterial imaging.[6,7] The most common abnormalities in this study were occlusion or narrowing of the proximal large arteries. However, risk factors were identifiable in only 72% of the cases.[6] In another study, association with infection was shown in at least one third of the childhood stroke cases.[7] In our patient, there were no signs and symptoms of infection.

Known side effects of human chorionic gonadotropin are headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, and pain at the site of injection.[5] A serious adverse reaction during infertility treatment is arterial thromboembolism.[16] A hypercoagulable state with secondary supraphysiological hyperestrogenemia and hemoconcentration after ovarian hyperstimulation may induce attacks of thromboembolism. In the literature, there are many reports about cerebral infarction during gonadotropin treatment of infertility.[17-21] In those cases, thrombosis was described especially in the left internal carotid artery, right middle cerebral artery, or intracranial venous system and was thought to be because of the activation of the coagulation cascade system after human chorionic

gonadotropin administration. Pregnyl (human chorionic gonadotropin) was given to our patient for the treatment of undescended testes and might have affected the coagulation cascade system. Additionally, heterogeneity of methylenetetrahydrofolate reductase as in adults might be a predisposing factor to hypercoagulability.

No randomized controlled treatment trial is conducted in childhood stroke, except in the sickle cell disease, to establish safety and efficacy of acute interventions or secondary preventative strategies. Studies about antiplatelet (aspirin, clopidogrel) and anticoagulant (low-molecular-weight heparin, warfarin) treatments are ongoing. Most experts agree that aspirin use is beneficial in secondary stroke prevention in the pediatric population despite the aspirin failure rate being 17%.[6,7,22] Majority of the failure group is composed of patients with dissection, cardiac embolism, and prothrombotic disorders. Of more than 50% of patients receiving antithrombotic therapy, outcomes were normal in 34%, neurologic abnormality in 56%, and death in 10%. In our patient, anticoagulant and then antiplatelet treatments were applied, followed by improvements in clinical exam findings such as resolution of hemiparesis and imaging studies.

We, thus, describe the case of ischemic stroke in a 1-year-old boy with undescended testes following Pregnyl therapy, which is the first and only case reported in the literature to our knowledge.

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