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CLINICAL CASE OF ISCHEMIC STROKE IN A CHILD WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

Podchernyaeva N.S.*, Khachatryan L.G., Shpitonkova O.V., Kostina Y.O.

FSEI HT I.M. Sechenov First Moscow State Medical University MH RF, University Children's Clinical Hospital, Moscow, Russia

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Abstract

Ischemic stroke is one of the leading causes of disability and mortality in adult population. However, in recent years there is a trend towards an increased incidence of polyetiologic and polysymdromic manifestations of cerebral circulation disorders in children of different age. The most common and verified causes include non-inflammatory vasculopathy (local arterial dissection, moyamoya disease, drug vasculopathy, etc.), primary and secondary vasculitis with central nervous system involvement, embolization in children with cardiac diseases, acquired and congenital thrombophilia, metabolic disorders. It should be taken into account that the clinical manifestations of ischemic stroke in children are different from the common signs in adults. The latter usually have manifestations such as hemiparesis and speech disorders, whereas children might often face strong cephalgia (severe headaches), convulsive syndrome and impaired consciousness.

The article presents a clinical observation of ischemic stroke in a 7-year-old girl with systemic lupus erythematosus and antiphospholipid syndrome. The pathogenetic mechanism of thrombosis development was related to the presence of antiphospholipid antibodies secondary to hereditary thrombophilia. It also resulted in the severity of central nervous system damage and the formation of well-marked neurological deficit. Understanding of the pathogenetic mechanism allowed to give priority to anticoagulant therapy, particularly low molecular weight heparins for 6 months, followed by administration of indirect anticoagulants (warfarin) in combination with a number of repairing agents. Considering the fact of hereditary thrombophilia as well as the mutations in genes responsible for the metabolism of homocysteine in the folate cycle, folic acid was administered.

The significantly long-term anticoagulant therapy for more than 6 months after the stroke episode was justified, because there are unavoidable risk factors, in particular the persistence of antiphospholipid antibodies and the genetic predisposition.

Keywords: *systemic lupus erythematosus, antiphospholipid syndrome, ischemic stroke, polymorphisms of blood coagulation genes, warfarin, low molecular weight heparins.*

Introduction

Ischemic stroke is one of the leading causes of disability and mortality in adult population. It is believed that the incidence of ischemic stroke in children is rare. However, in recent years there are more facts, which demonstrate a shift in the age of ischemic stroke affecting young population. According to the Canadian Pediatric Ischemic Stroke Registry, the cases of arterial ischemic stroke in children is 2.7/100.000 children per year, with 25-30% of all cases occurring in the neonatal period, and 50% of cases up to 1 year of life [*DeVeber G, 2000*]. Ischemic stroke outcome in most children is

Address for Correspondence:
Podchernyaeva Nadezhda Stepanovna
Department of Children's Diseases
I.M. Sechenov First Moscow State Medical University
8 Trubetskaya Street, bld. 2, Moscow 105043, Russia
Tel.: 8 (916) 327-27-20
E-mail: n-cherny2011@mail.ru

malignant: 3-12% of children die during the acute period, 61-74% of children retain persistent neurological deficiency. In addition, episodic cerebral circulation disorders of ischemic forms are recurrent in 8-42% of patients on average [*DeVeber G, 2000; Fox C, Fullerton H, 2010*].

Pediatric ischemic stroke is a polyetiologic nosology. The most common and verified causes include non-inflammatory vasculopathy (local arterial dissection, moyamoya disease, drug vasculopathy, etc.), primary and secondary vasculitis with central nervous system involvement, embolization in children with cardiac diseases, acquired and congenital thrombophilia, metabolic disorders, and others [*Zykov V et al., 2011; Poisson S et al., 2014*].

Systemic lupus erythematosus is a systemic connective tissue disease, in which the development of stroke is highly common. Individuals with systemic lupus erythematosus are at a 2 to 3-fold higher risk of ischemic stroke compared to the general population and the highest risks are observed in children 1-17 years of age and young adults [*Wang I et al., 2012; Holmqvist M et al., 2015*]. Risk factors of ischemic stroke in systemic lupus include: male gender, young age, family history burdened by cardiovascular diseases, hypertension, smoking, diabetes, hyperlipidemia, neurolupus, valvular heart disease, serositis, complement activity decrease, presence of autoantibodies, azathioprine intake [*Ballocca F et al., 2015; Fernández-Nebro A et al., 2015*].

Antiphospholipid antibodies have a large role in the genesis of many neuropsychiatric symptoms and particularly in ischemic stroke in systemic lupus erythematosus [*Yu H et al., 2006; Hawro T et al., 2015*]. Antiphospholipid antibodies are heterogeneous populations of antibodies, from which three groups – lupus anticoagulant, antibodies to cardiolipin and antibodies to β2-glycoprotein-1 are the diagnostic criteria of antiphospholipid syndrome. Antiphospholipid syndrome is an acquired autoimmune thrombophilia, which can be frequently associated with other autoimmune diseases, mostly with systemic lupus erythematosus, and is characterized by recurrent thromboses and obstetric disorders.

Clinical presentations of ischemic stroke in children differ from those in adults. Children often lack the common symptoms such as hemiparesis, speech disorder, incoordination. Primarily, along with hemiplegia/hemiparesis, children with ischemic stroke face severe headaches, consciousness disorders, convulsions. Central paresis of facial muscles and speech disorder may occur as well [*Zykov V et al., 2011; Mallick A et al., 2014*]. These clinical signs often get the wrong interpretation that leads to inaccuracies in therapy strategy, thus resulting in poor prognosis. Due to the variety of clinical symptoms of ischemic stroke in children, it is rather difficult to identify diagnosis, which therefore results in the delayed initiation of treatment and may consequently cause poor outcomes. According to the classification of American College of Rheumatology, there are 12 syndromes of central nervous system affection and 7 syndromes of peripheral nervous system affection [*ACR, 1999*]. Their pathogenesis is associated with thromboembolism, vasculopathy of small vessels, and rarely with true cerebral vasculitis [*Böckle B et al., 2014*]. The neurologic symptoms may be caused by metabolic disorders, infections, etc. Analysis of the pathogenetic mechanisms is an important condition of treatment strategy and has a large role in the prognosis of the patient.

Here is a clinical observation of central nervous system affection in a child with systemic lupus erythematosus and antiphospholipid syndrome.

Female patient A.V., 7 years of age, was admitted to the Children's Hospital of I. M. Sechenov First Moscow State Medical University in April 2014 with complaints of speech disorder and frequent headaches. Early history is without features. Heredity is not burdened by thrombosis.

The onset of disease was in September 2013. After tonsillitis the child began to complain of pain in the interphalangeal joints of the second finger of the right hand, wrist and left knee joints accompanied by febrile fever, once had an episode of tonic-clonic seizures. The patient was observed in the community hospital and was diagnosed with "acute condition of chronic tonsillitis, febrile seizures", and got antibacterial and symptomatic therapy, though without noticeable effect.

In February 2014 the patient was admitted to her community hospital with complaints of everyday high temperature above 39°C and arthralgia. The examination revealed lymphadenopathy, hep-

atosplenomegaly, polyserositis. The blood tests uncovered increase of erythrocyte sedimentation rate up to 40-52 *mm/h*, leukopenia (leukocytes 3.8×10^9/l), anemia (Hemoglobin – 92 *g/l*). In connection with fever, anemia, severe lymphadenopathy, hepatosplenomegaly, the oncohematological disease had to be ruled out. The biopsy of a bone marrow revealed no pathology. The second round of the prescribed antibiotic therapy (penicillin drugs, then macrolides) had no positive effect.

In March 2014, secondary to the acute fever the patient developed repeated episodes of generalized tonic-clonic seizures with loss of consciousness (the child was in a stupor for 5 days). The MRI revealed a well-marked cerebral edema. The results of EEG showed generalized epileptic activity. Laboratory tests revealed circulating lupus anticoagulant, a threefold increase in antibodies to cardiolipin titer and β2-glycoprotein-1, antibodies to DNA>200 *IU/mL*, antinuclear factor, 1:1280, leukopenia (leukocytes 2.8×10^9/l), hemolytic anemia (Hemoglobin – 76 *g/l*) with a positive Coombs test, increase of erythrocyte sedimentation rate up to 52 *mm/h*.

Based on clinical, laboratory and instrumental data the patient was diagnosed with systemic lupus erythematosus, subacute stage, 3rd degree activity, fever, arthralgia, lymphadenopathy, hepatosplenomegaly, central nervous system affection, high immunological activity. Assumption of antiphospholipid syndrome. The basic therapy included the following prescribed medications: prednisolone at a dose of 1 *mg/kg/day* (30 *mg/day*), cyclophosphamide pulse therapy at a dose of 250 *mg/day* intravenously, warfarin at a dose of 2.5 *mg/day* (INR 1.7-1.9). The anticonvulsant therapy included Valproic acid – Depakine-Chrono 600 *mg/day* (23 *mg/kg/day*). In post-intensive-care period no convulsive events occurred. Due to the therapy, the patient's condition improved significantly: fever, arthralgia, polyserositis were relieved, inflammation activity was decreased. The dosage of prednisolone was reduced to 20 *mg/day* and it was recommended to continue the warfarin therapy.

The patient was sent to University Children's Clinical Hospital for diagnosis confirmation, so as to organize further treatment. She was admitted to the department in March 2014 in the condition of moderate severity. Among the leading clinical symptoms were central nervous system dysfunctions. As for the neurological status, the patient was conscious, communicative, though asthenic, occasionally "froze" and fell into apathy or dysphoria; partially unwilling to answers questions. The cranial nerves: affected by a slight anisocoria characterized by unequal size of eyes (the left is larger), "flat" left nasolabial fold, hearing and visual acuity were without deficiency, presence of dysarthria, no tongue deviation. Cognitive dysfunctions included deficiency of sustained attention; perceptive abilities with a high latency, poor operational thinking characterized by a lack of summarizing ability, sensory aphasia, poor selective memory, poor orientation in time and space. Motor areas: residual movement asymmetry (the right prevails), elements of hemiparesis, incoordination, presence of atactic component in static and locomotor tests, vagotonic type of vegetative provision. The EEG reported multifocal symptomatic epilepsy. The real-time MRI (in dynamics) revealed increasing cerebral atrophy of the left hemisphere, residual ventriculomegaly.

Thus, the above-mentioned clinical and instrumental data are consistent with the picture of residual manifestations of ischemic affection of nervous system due to thrombosis in the middle cerebral artery (Fig. 1, 2).

According to laboratory research, no signs of systemic lupus erythematosus activity were found: antibodies to DNA – 24 *IU/ml* (normal 0-20 *IU/mL*), antinuclear factor – negative, however levels of serum antiphospholipid antibodies were higher than normal. Antibodies to cardiolipin-IgG – 15 *IU/ml* (normal is 0-7), antibodies to cardiolipin, IgM – 24 *IU/ml* (normal 0-10), lupus antibodies to cardiolipin – positive.

The patient's medical history, clinical, laboratory and instrumental research were assessed as a presentation of highly active systemic lupus erythematosus complicated by joint and serous membrane affection, Coombs-positive hemolytic anemia and leukopenia combined with antiphospholipid syndrome. The latter had clinical manifestation of ischemic stroke and laboratory markers, such as lupus antibodies to cardiolipin, anti-β2-glycoprotein-1 and antibodies to cardiolipin. Three types of antiphospholipid antibodies were detected, which indicated the risk of recurrent thrombotic complications.

An investigation was undertaken to study genetic polymorphisms of blood coagulation, so as to verify the risk of recurrent thrombosis and to determine the length and the intensity of antithrombotic therapy and preventive measures. The study revealed the heterozygous forms of mutations in methylenetetrahydrofolate reductase gene (MTHFR Ala 222Val CT) and plasminogen activator inhibitor-1 (SERPINE 675 5G/4G).

So, central nervous system damage in this patient was caused by the thrombotic process within thrombophilia due to the carriage antiphospholipid antibodies and the presence of genetic polymorphisms of blood coagulation. As there was a high

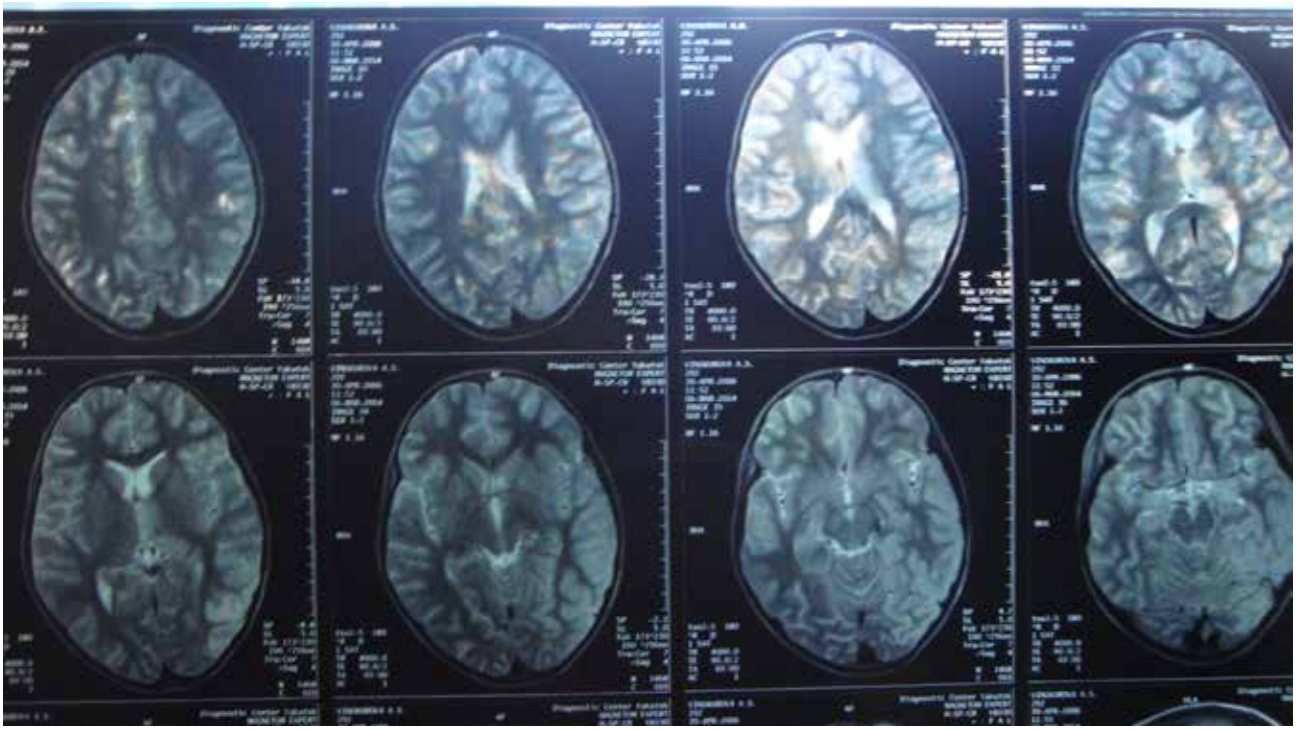

Figure 1. *Image of ischemic lesion in the parietal-temporal part*

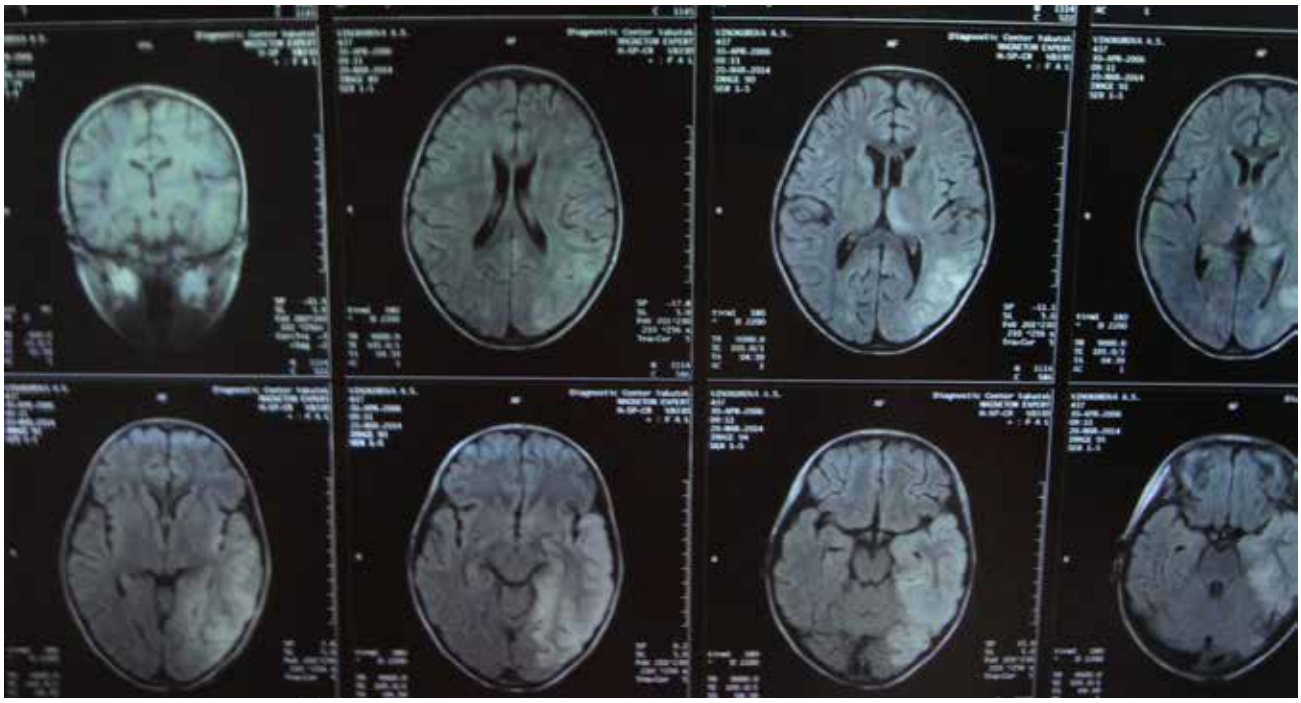

Figure 2. *Image of vicarious ventriculomegaly on the background of cerebral atrophy*

risk of recurrent thrombosis, the patient's further therapy strategy was aimed at the improvement of microcirculation and prevention of thrombosis recurrence. Thus, active antithrombotic therapy of low molecular weight heparin (Fraxiparine – subcutaneous 0.3 *ml/day*) was prescribed. In addition to this, vascular, metabolic and neurotrophic treatment of central nervous system disorders was conducted.

On rehospitalization 4 months later, the girl's condition was estimated as satisfactory. A significant improvement in neurological status was notable. The patient was conscious, alert, ready to answer questions and communicated well. Emotional and behavioral spheres were age appropriate, sometimes with asthenic reactions. Cranial nerves: slightly affected by anisocoria on the left. Cognitive sphere: improvement in expressive and receptive language; increased level of mechanical and associative memory, though, there was partial lack of thinking and attention with elements of asthenia. At the same time, the girl goes to school, assimilates sufficient amount of information. Motor areas: the tonus is closer to the physiological, amplitude of movement is not limited, minor signs of right-sided hemiparesis manifested by pyramidal signs and fatigue from physical exertion. The coordination tests revealed no deficiency in the static test, though there was slight right-side dysmetria in the locomotor test. Pelvic functions: central regulation is developed, the peripheral regulation is not impaired, presence of vagotonia in vegetative function. During the reporting period since the last hospitalization no seizure activity has been recorded.

The repeated MRI of the brain reported symptoms of ischemic stroke in the form of atrophy localized in the parietal-temporal part and residual ventriculomegaly. EEG report indicated moderately expressed epileptiform changes of epileptic activity prevailing in the posterior parts of the brain, hyperventilation-induced focal changes in the posterior temporal parts.

In the absence of clinical and laboratory activity of systemic lupus erythematosus, the dosage of prednisolone was reduced to 10 *mg/day* (0.3 *mg/kg/day*), the treatment was continued with warfarin (INR 1.8-1.9). Due to the identified mutations in folate cycle genes, folic acid was prescribed at the dose of 1 *mg/day*.

The girl's further monitoring for the period of a year and a half demonstrated a complete smoothing down of the neurological symptoms, which again proved significant reparative ability of a child's brain due to the appropriately selected therapy. Consistent implementation of antithrombotic preventive therapy made it possible to avoid new episodes of cerebral circulation disorders.

Present observation demonstrated the complexity of interpretation of severe neurological symptoms with underlying high clinical and laboratory activity of systemic lupus erythematosus and manifested by prolonged loss of consciousness, recurrent generalized tonic-clonic seizures and focal symptoms. Additional studies allowed identifying the type of central nervous system affection in the form of ischemic stroke in the middle cerebral artery and detecting its risk factors (the presence of antiphospholipid antibodies and gene polymorphisms of blood coagulation). Identifying the genesis of the existing disorders allowed to determine the therapeutic strategy, i.e. the use of direct and later indirect anticoagulants, which greatly influenced the reparative processes in the central nervous system, as well as to prevent thrombosis recurrence.

REFERENCES

1. *Ballocca F, D'Ascenzo F, Moretti C, Omedè P, Cerrato E., et al*. Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis. Eur J Prev Cardiol. 2015; 22(11): 1435-1441.
2. *Böckle BC, Jara D, Aichhorn K, Junker D, Berger T., et al*. Cerebral large vessel vasculitis in systemic lupus erythematosus. Lupus. 2014; 23(13): 1417-1421.
3. *DeVeber G*. Canadian pediatric ischemic stroke registry. Pediatric Child Health. 2000: A17.
4. *Fernández-Nebro A, Rúa-Figueroa Í, López-Longo FJ, Galindo-Izquierdo M, Calvo-Alén J.,*

et al. Cardiovascular events in systemic lupus erythematosus: a nationwide study in Spain from the RELESSER registry. Medicine (Baltimore). 2015; 94(29): e1183.

5. *Fox CK, Fullerton HJ.* Recent advances in childhood arterial ischemic stroke. Curr Atheroscler Rep. 2010; 12(4): 217-224.
6. *Hawro T, Bogucki A, Krupińska-Kun M, Maurer M, Woźniacka A*. Intractable headaches, ischemic stroke, and seizures are linked to the presence of anti-β2GPI antibodies in patients with systemic lupus erythematosus. PLoS One. 2015; 10(3): e0119911.
7. *Holmqvist M, Simard JF, Asplund K, Arkema EV*. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. RMD Open. 2015; 1(1): e000168.
8. *Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T., et al*. Childhood arterial ischemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol. 2014; 13(1): 35-43.
9. *Poisson SN, Schardt TQ, Dingman A, Bernard TJ*. Etiology and treatment of arterial ischemic stroke in children and young adults. Curr Treat Options Neurol. 2014; 16(10): 315.
10. *The American College of Rheumatology*. Nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999; 42: 599-608.
11. *Wang IK, Muo CH, Chang YC, Liang CC, Lin SY., et al.* Risks, subtypes, and hospitalization of stroke patients with systemic lupus erythematosus: a retrospective cohort study in Taiwan. J Rheumatol. 2012; 39(8): 1611-1618.
12. *Yu HH, Lee JH, Wang LC, Yang YH, Chiang BL*. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: a 20-year study. Lupus. 2006; 15(10): 651-657.
13. *Zykov VP, Komarova IB, Chuchin MY, Ushakova LV, Stepanishchev IL*. [Ischemic stroke in children] [Published in Russian]. Uchebnoe posobie. Moscow. 2011. 72p.