Significant risk factors in the etiology of arterial ischemic stroke in children

Ilona Kopyta[1], Mikołaj Zimny[2]*

[1]School of Medicine in Katowice, Medical University of Silesia, Department of Paediatrics and Developmental Age Neurology, Chair of Paediatrics, Katowice, Poland, [2]School of Medicine in Katowice, Medical University of Silesia, Department of Paediatrics and Developmental Age Neurology, Chair of Paediatrics, Student Scientific Association, Katowice, Poland.

ABSTRACT

Stroke is a sudden loss of brain function due to disturbance in the cerebral blood supply with symptoms lasting at least 24 hours or leading to death with vascular background as its only cause. Stroke can be caused either by rupture of a blood vessel or aneurysm (hemorrhagic stroke, HS), or by thrombosis or embolisms (ischemic stroke, IS). In children stroke is defined as any neurological event related to an acute brain ischemia shown by the brain imaging technique. The incidence of arterial ischemic stroke (AIS) in children (about 2–13 / 100,000 children per year) is much lower than the incidence in the adult population. Still, adverse outcomes of acute brain ischemia in childhood include death, neurological sequel, epileptic seizures, and recurrence. The knowledge of childhood stroke etiology is still insufficient and the diagnostic and therapeutic procedures remain underdeveloped. Ischemic stroke is a heterogeneous condition with many different risk factors, both genetic and biochemical. The authors have reviewed the recent literature on risk factors of childhood ischemic stroke with the focus on biochemical factors like dyslipidemias, protein C deficiency and homocysteine, lipoprotein(a) and fibrinogen excess, and genetic factors like polymorphisms of 5,10-methylenetetrahydrofolate reductase, factor V, and fibrinogen genes.

Key Words: arterial ischemic stroke, children, genetic, biochemical, risk factors.

*Corresponding author. E-mail: zimny.mikolaj@gmail.com, ilonakopyta@autograf.pl

INTRODUCTION

Stroke, according to the American Heart Association (AHA) definition, is a sudden loss of brain function due to disturbance in the cerebral blood supply with symptoms lasting at least 24 hours or leading to death with vascular background as its only cause. Stroke can result in both focal and global neurological impairments including asthenia, severe headaches, hemiparesis, and blackouts [1]. Stroke can be divided into hemorrhagic (hemorrhagic stroke, HS) and ischemic (ischemic stroke, IS), which are caused by rupture of a blood vessel or aneurysm, or by thrombosis or embolisms respectively. Unfortunately, this definition does not apply to children, because pediatric patients with transient IS can have brain imaging results indicating stroke occurrence despite temporary (lasting less than 24 hours) nature of their condition. Thus, pediatric stroke can be defined as any neurological event related to an acute brain ischemia shown by the MRI [2,3]. In the world about 4.5 million people die of stroke each year and in developed countries it is the third most common cause of death in the adult population, but in children it is a rare condition [4]. The frequency of childhood stroke is reported to be as low as 2–13 / 100,000 per year and it regards all types of stroke: ischemic, hemorrhagic, and sinuvenous thrombosis (SVT) [5–9]. Pediatric stroke can be qualified as a genetic-based disease, because most of its risk factors are genetic conditions impairing homeostatic mechanisms preventing from thrombosis occurrence [10,11]. However, those conditions are hereditary, many of them might be acquired during lifetime. Thus, many of presented risk factors may be considered as both, genetic and biochemical [11]. In previous articles we have reviewed many factors considered as risk factors for pediatric IS: mutations in genes encoding factors II, V, VII, XIII, MTHFR, deficiencies of protein C (PC), protein S, antithrombin III and elevated levels of homocysteine, fibrinogen, cholesterol and its fractions. Among them only few showed association with IS occurrence in children.

Cholesterol (total cholesterol—TC) is a sterol, a hydroxylated steroid molecule that is both assimilated from food and biosynthesized in the liver. Thanks to its bipolar structure, cholesterol builds cell membrane and maintains its fluidity. It also serves as a principal precursor for the biosynthesis of steroid hormones, bile acid, and vitamin D. Cholesterol, as a lipid, is a non-polar particle; thus it needs bounds with apoproteins to dissolve in water and pass through the membrane. Such complexes are called lipoproteins, a group which can be divided into four main groups depending on their density, size, and composition: VLDL (very low-density lipoproteins), IDL (intermediate-density lipoproteins), LDL (low-density lipoproteins), and HDL (high-density lipoproteins) which

are said to cause different cardiovascular diseases [12,13]. It was proven based on post-mortem examinations, that arteriosclerotic vascular disease (ASVD) begins in infancy and high TC started in childhood remains at a similar level in adulthood and is associated with risk of premature development of vascular disease, especially coronary and cerebral arteries. Additionally, rapidly developing ASVD depends on high lipid concentrations, especially low LDL and high HDL levels [12–14]. Moreover, research conducted on children from different populations confirmed that elevated levels of TC and LDL and decreased levels of HDL might contribute to AIS development during childhood [15–17].

Lipoprotein(a) (Lp(a)) is a complex molecule of the LDL particle attached by a disulfide bridge to apoprotein(a). Lp(a) concentrations in plasma are variable and due to its structural homology with plasminogen and lack of fibrinolytic activity elevated levels of Lp(a) may promote thrombosis. Additionally, elevated Lp(a) may lead to rapid development of atherosclerosis because of its high cholesterol content [18]. In the group of children with past medical history of heart or brain ischemia Lp(a) levels in the plasma were significantly higher than in the group without those diseases [19,20]. However, research carried out on the German children population [21–24] proved the weak role of Lp(a) elevated levels and childhood IS; in a case-control study conducted on the Polish population the middle level of Lp(a) in pediatric stroke patients was significantly higher than in controls [25]. Raised Lp(a) is an independent and confirmed risk factor for both cardiac and cerebral vascular diseases in children populations [26–29]. Thus, high Lp(a) level is a risk factor not only for the first stroke but also for its recurrence [30].

Protein C (PC) is a vitamin K-dependent coagulation factor synthesized in the liver as a single-chain polypeptide. After synthesis it undergoes different post-translational modifications with the assistance of thrombin-thrombomodulin complex and becomes an active, double-chain form called active protein C (APC). PC inhabits coagulation pathway by inactivating activated factors V and VIII, as well as promoting fibrinolysis by neutralizing plasminogen inhibitor activator-1. Although protein S (PS) is a cofactor of PC in this process [31,32], researches carried out on different children populations showed no relation between PS deficiency and AIS occurrence [21,23,24,33,34]. PC levels are age dependent [32] and PC deficiency is a disease-inherited autosomal dominant, where either both, PC activity and level, are decreased or only its activity is reduced due to invalid structure. Several studies showed that PC deficiency is a significant risk factor for AIS in pediatric patients [21,22,33,35,36]. Examinations carried out on pediatric patients indicate that screening PC levels tests may prevent commencing AIS occurrence.

Homocysteine (HCys) is an amino acid containing sulfur and remethylated to methionine by the vitamin B12-dependent enzyme, methionine synthase. This process uses levomefolic acid, as a methyl donor, which is generated from 5,10-methyltetrahydrofolate by the 5,10-methylenetetrahydrofolate reductase (MTHFR). Homocysteine can modify protein structure and function due to its incorporation into protein by disulfide or amide bindings. Protein N-homocysteinylation induces elastin degradation in the vascular wall and calcification process that may contribute to athreogenesis [37]. The elevated levels of HCys in plasma may result from mutations in genes encoding MTHFR [38,39]. The 677 (C > T) transition in the MTHFR gene increases the enzyme thermolability leading to its low activity which is the most common inherited cause of hyperhomocysteinemia [40]. Elevated levels of Hcys are reported to be toxic to the endothelium and can cause chronic inflammation. In the patients with hyperhomocysteinemia the beneficial effects of lowering plasma HCys levels by vitamins are not established yet, but receive increasing attention. Folate and vitamin B12 stimulate the rest activity of the MTHFR and in this way the vitamin supplementation seems to be the potential chance for both primary and secondary prevention of stroke in young patients [41]. Moderate hyperhomocysteinemia was observed to be associated with a quadrupled risk of childhood ischemic cerebrovascular disease [32]. Nowak-Gottl et al. [21] demonstrated that fasting HCys concentrations were significantly higher in cases than in controls. In few studies higher HCys levels were present in the group of pediatric patients with AIS compared to controls [38,39,43,44]. On the other hand, meta-analysis including a total of 3235 pediatric patients with a first AIS and 9019 controls revealed weak association between elevated HCys and AIS occurrence [45] and the study among Croatian patients with AIS did not demonstrate differences in HCys levels between patients and controls [15]. The latest data from meta-analysis evaluating over 800 pediatric IS patients proved that the 677 (C>T) mutation in the MTHFR gene is associated with the acute brain ischemia occurrence in children [46]. The patients with a MTHFR 677 (C>T) and 1298 (A>T) transitions had 25% higher HCys levels than the participants with only 1298 (A>T) mutation [47]. Hyperhomocysteinemia has been established as a risk factor of both venous and arterial thrombosis, leading to different neurological disorders with vascular background in adult and pediatric patients [40–43,48,49].

Fibrinogen is an acute-phase plasma glycoprotein consisting of three polypeptide chains (α, β, and γ) attached via disulfide bounds. The genes encoding the polypeptides (FGα, FGβ, and FGγ) are localized on chromosome 4q28 in a cluster. The mRNA is synthesized independently for each of the chain, but the synthesis of β chain is the rate-limiting step in fibrinogen synthesis [50] and that seems to be the most important factor affecting plasma serum level [51,52]. Plasma fibrinogen levels were reported as heritable traits [53], while the FGβ gene is related to elevated level of fibrinogen and FGα and FGγ genes were found to be important in fibrin structure [54,55]. Numerous studies analyzed the possible relations between fibrinogen levels and both, cardiac and cerebral vascular diseases, although data are inconsistent [56–58]. In a large individual participant meta-analysis, moderately strong relationships between

plasma fibrinogen level and the risks of coronary heart disease, stroke, other vascular mortality as well as nonvascular mortality were found [95]. In Polish pediatric patients with AIS, high levels of fibrinogen were observed and established as a significant risk factor for AIS and following the occurrence of neurological deficits [17]. Nowak-Göttl et al. underlined the heritability of the elevated fibrinogen levels in the IS children but also indicated the importance of their life-style leading to the high serum fibrinogen concentration [25].

Factor V (FV) is a proenzyme which under the influence of thrombin becomes its active form (FVa). FVa is a cofactor of active factor X in the prothrombinase complex of the coagulation cascade, crucial for the transformation of prothrombin to thrombin. FV is encoded by the FV gene (1q23) and the transition in the position 1691 (G > A) (Leiden mutation) is responsible for the production of factor V Leiden which causes APC resistance. The Leiden mutation causes replacement of arginine by glycine in the FVa which leads to less efficient degeneration by APC and increased thrombin generation/production/concentration as a result. The large meta-analysis showed that the presence of FVa Leiden is associated with IS both in neonates and in older children [59–62]. The mutation is associated not only with the arterial ischemic incidents, but also with SVT occurrence [63]. The author's investigation of the group of 81 AIS children and 149 controls, did not confirm the data, possibly because of the comparatively small group of patients [64]. The comparable research done by Kenet and Haywood presents different strength of the association between the Leiden mutation and childhood stroke [45,65]. Probably, the accidental selection of group members and its size play the most important role in the achieved results. Analyzing the data regarding European pediatric AIS population, we find the results confirming the association between the presence of Leiden mutation and AIS (in the German, Austrian, Croatian, and Portuguese children groups) as well as denying it (in the Serbian, Estonian, and Polish groups) [60,65, 67–69]. However, the association between FVa Leiden and AIS occurrence was found; in many pediatric AIS groups it was not present.

CONCLUSION

Ischemic stroke is a heterogeneous condition with many different factors as its cause. In many cases, more than one risk factor can be established in stroke patients. This implies high demand for multiple diagnostic tests for every child after AIS. There are few meta-analyses which perform the role of the described genetic polymorphisms (MTHFR, FV and FG genes) in the pathogenesis of pediatric IS. Data from international literature on dyslipidemias, PC deficiency and HCys, Lp(a) and fibrinogen excess are often contradictory, though most experts on the field agree that these are important risk factors for childhood AIS and due to that it is necessary to develop unique screening procedures for all pediatric patients with the family history of stroke.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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