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REVIEW

Risks associated with the stroke predisposition at young age: facts and hypotheses in light of individualized predictive and preventive approach

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Abstract

Stroke is one of the most devastating pathologies of the early twenty-first century demonstrating 1-month case-fatality rates ranging from 13 to 35% worldwide. Though the majority of cases do occur in individuals at an advanced age, a persistently increasing portion of the patient cohorts is affected early in life. Current studies provide alarming statistics for the incidence of "young" strokes including adolescents. Young stroke is a multifactorial disease involving genetic predisposition but also a number of modifiable factors, the synergic combination of which potentiates the risks. The article analyzes the prevalence and impacts of "traditional" risk factors such as sedentary lifestyle, smoking, abnormal alcohol consumption, drug abuse, overweight, hypertension, abnormal sleep patterns, and usage of hormonal contraceptives, among others. Further, less explored risks such as primary vascular dysregulation and associated symptoms characteristic for Flammer syndrome (FS) are considered, and the relevance of the FS phenotype for the stroke predisposition at young age is hypothesized. Considering the high prevalence of known genetic and modifiable risk factors in the overall predisposition to the young stroke, the risk mitigating measures are recommended including innovative screening programs by application of specialized questionnaires and biomarker panels as well as educational programs adapted to the target audiences such as children, adolescents, and young adults.

Keywords Young adults · Stroke · Risk factors · Individualized patient profile · Etiology · Vascular · Abnormal BMI · Blood flow · Microcirculation · Life style · Sleep patterns · Migraine · Hormonal regulation · Psychology · Stress · Screening program · Flammer syndrome · Phenotype · Questionnaire · Risk assessment · Baroreceptor sensitivity · Cardiac · Circadian rhythm · Tinnitus · Thermoregulation · Altered sensation · Body dehydration · Predictive preventive personalized medicine

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Introduction

Stroke belongs to the most devastating civilization diseases with a high impact on the health and quality of life with over 15 million new cases annually worldwide [1]. It is among the leading causes of death and disability demonstrating 1-month case-fatality rates ranging from 13 to 35%. From the European perspective, approximately 1.1 million individuals suffer a stroke each year [2, 3]. Further, the socio-economic consequences for the EU are dramatic by the total cost of stroke in 2015 as high as €45 billion.

Though the majority of all cases are diagnosed in elderly patients, there is a substantial number of individuals (approximately 10% of all cases) suffering from first-ever stroke below the age of 50 years, so-called "young" strokes [4]. Moreover, the incidence as well prevalence of stroke in young adults is dramatically increasing for the high-income as well as middle- and low-income countries representing a global challenge [5].

The dramatic burden of young strokes may be explained, at least in part, by an increasing incidence of the major vascular risk factors of stroke in youth and even in children [5, 6]. Specifically in young adults, the well-known risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, heavy episodic alcohol consumption, low physical activity, coronary heart disease, and obesity are common; some of them are increasingly prevalent. This actuality provides an opportunity for the targeted and personalized primary prevention of stroke in adolescents and young adults.

Further, about 20–30% of stroke cases in young adults remain of unknown etiology [4, 5, 7, 8]. The majority of young adults with stroke are presented to the hospital and diagnosed too late and outside the time window for intravenous fibrinolysis [9]. Therefore, specifically, the subgroup of young strokes should get subjected to the extensive medical research and improved medical services following a paradigm shift from reactive medicine to an appropriate predictive diagnosis, innovative screening programs, and targeted primary and secondary prevention linked to the treatments tailored to the person. Contextually, educational measures to the professionals and general population as well as novel strategies in the overall stroke management are needed [10, 11].

The actual article overviews the “traditional” stroke-related factors, which are acknowledged as contributing to increased stroke risks in both—elderly and young individuals. On the other hand, the article introduces possible novel risk factors and justifies their potential relevance particularly for the young stroke cases, contributing therefore to the clarification of the cases with currently unclear etiology. New mitigating strategies are discussed how to work specifically on the modifiable risk factors to efficiently combat the increasing incidence of young stroke cases by utilizing risk assessment within innovative screening programs applied to young populations.

Definition of young stroke

In the majority of studies, the young stroke is defined as the first-ever cerebrovascular event presenting in adults aged between 18 and 50 years [4, 12]. However, some studies dedicated to young strokes do refer to other age limits, which differs from that, e.g., 45 [13, 14] or 55 years [7, 15], as well as go for a wider range starting by 15 years of age [16]. Regarding the latter, however, because of distinct and more specific stroke etiologies in neonates, children, and young teenagers, these patient groups are discussed separately in the vast majority of studies [17–20].

Classification of young stroke

About 80% of young strokes are ischemic, while about 20% are hemorrhagic. The ischemic young strokes are classified (same as the strokes in general population) into the etiological subtypes by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification [21]. These subtypes are (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology also called cryptogenic. It is well documented that the stroke of other determined etiology (such as cervical arterial dissection, hematologic diseases, vasculitis, malignancies, Illicit drug use, pregnancy and puerperium, thrombophilia and others) is more prevalent in younger patients (< 45 years and even more < 35 years) compared to the older ones (> 45 years) [4, 8, 13, 22]. The proportion of cardioembolism (due to cardiomyopathy, atrial fibrillation/flutter and others) is also higher in younger patients. In contrast, the large-artery atherosclerosis occurs relatively rarely in very young adults but its incidence increases with the age enhancing the stroke risk.

In contrast to elderly, a large number of young strokes aged mainly between 18 to 35 years [4, 8] demonstrating unknown etiology reaches up to 39.6–42% in some studies [16, 22] that is extremely challenging for the healthcare sector and the society at large.

Rising incidence of young stroke

Young stroke incidence in high-income countries

The incidence of stroke in young adults was dramatically increasing during the last two decades. The burden of young stroke is observed in high-income as well as middle- and low-income economics demonstrating a global trend [5]. There is a substantial rise in the hospitalizations rate for ischemic stroke in contrast to relatively stable rates for intracerebral and subarachnoid hemorrhage.

The US study from The Greater Cincinnati/Northern Kentucky region showed trends towards increasing stroke incidence mainly at younger ages. The proportion of young strokes (aged < 55 years) increased from 12.9% in 1993/1994 to 18.6% in 2005 and was significantly increased in both black and white subpopulations [23]. Another US study evaluated the changes in acute stroke hospitalization rates for children and young adults aged up to 44 years in the time period 1995-2008 [24]. This study found that prevalence of hospitalizations of acute ischemic stroke increased among almost all age- and gender-stratified subgroups with the greatest increment in patients aged 35–44 years (28.2 vs. 38.6 per 10,000 hospitalizations, relative change of 36.9%).

French population-based study from the Dijon Stroke Registry examined changes in the incidence of stroke in individuals aged < 55 years old over the 27-year study period [25]. The incidence of ischemic stroke per 100,000 people/year was continually rising from 8.1 in the period 1985–1993 to 10.7 in the period 1994–2002, and up to 18.1 in the period 2003–2011, which was not the case for intracerebral hemorrhage (the incidence per 100,000 people/year 3.2 vs. 1.9 vs. 1.9 in the same time periods, respectively).

An increasing stroke incidence among patients aged 30 to 65 years is observed also in Sweden. The 3-year average incidence increased from 98.9 to 118.0 per 100,000 among men (by 19%) and from 48.4 to 64.4 among women (by 33%), between the time periods 1989-1991 and 1998–2000 [26].

The recently published US study examined temporal trends in hospitalization for acute ischemic stroke using the Nationwide Inpatient Sample among adults older than 25 years [27]. Whereas the hospitalization rates decreased for individuals aged above 65 years, the numbers increased for individuals aged 25 to 44 years by 43.8% (16 to 23 per 100,000) and 45 to 64 years by 4.7% (149 to 156 per 100,000) in years 2000 to 2010. Blacks demonstrated the highest hospitalization rates annually, followed by Hispanics and Whites.

Finally, the Danish study using National Patient Register identified all cases of first-ever hospitalized stroke and transient ischemic attack (TIA) in people aged by 15 to 30 years [28]. It was shown that the stroke hospitalization rates increased by 40%, and the TIA hospitalization rates increased by threefold during the time period from 1994 to 2012. A particularly dramatic increase in ischemic stroke incidence was observed after the year 2006. Consistent with other studies, the incidences of hospitalizations for intracerebral hemorrhage and subarachnoid hemorrhage remained stable during the study period.

Young stroke incidence in middle- and low-income countries

The stroke in young adults is on rise in middle- and low-income countries. This trend was observed in the recently published 10-year population-based study originated from Brazil [29]. Overall stroke incidence increased by 62% in subjects younger than 45 years and by 29% in those younger than 55 years. Similarly to the high-income economics, this study demonstrates rising incidence of ischemic young strokes, in contrast to the hemorrhagic ones.

Further, an increasing stroke incidence among the low-income young and middle-aged adults in rural China was observed during the time period between 1992 and 2015 years [30]. The rural areas of South Africa show very high young stroke incidence of 301.1 per 100,000 in the age subgroup 33–44 years and 723.2 per 100,000 for patients aged between 45 and 59 years. The stroke incidence is high (121.6 per 100,000) also in a very young population aged 15–29 years [31]. In consensus, a multicenter study involving 15 sites in Nigeria and Ghana showed a very high (24.3%) proportion of patients aged 18–49 years among all CT/MRI-confirmed stroke cases [32].

Changing milieu of young stroke risk factors

Originally, it was observed that the profile of risk factors in young stroke differs from that in the major stroke cohort, because of more frequent occurrence of so-called rare risk factors and etiology more specific for young patients (cervical arterial dissection, hematologic diseases, vasculitis, malignancies, Illicit drug use, pregnancy and puerperium, thrombophilia, infections, Fabry's disease, patent foramen ovale, among others) [4, 33].

However, the prevalence of traditional vascular risk factors originally identified mainly in old patients (hypertension, dyslipidemia, diabetes mellitus, smoking and others) is now dramatically rising also in the cohort of young stroke, as it is the case in young populations in general [7, 34–36]. Further, the pathogenic synergies of such risk factors seem to predominantly contribute to stroke specifically in young adults. The recently published results from the large international study including 32 countries in Asia, America, Europe, Australia, the Middle East, and Africa clearly show that the modifiable risk factors altogether represent 92.2% of population attributable risks (PARs) of stroke in patients aged below or equal to 55 years [37]. Similarly, an appearance of eight identified modifiable risk factors was well explanatory for as many as 78.9% of all first-ever young strokes from 26 clinical stroke centers in patients aged 18 to 55 years [6]. These observations are of a substantial relevance for the better primary prevention of stroke in young populations.

Genetics of stroke in young adults

It is generally accepted that a synergic interplay between genetic predisposition and environmental risk factors leads to the

stroke development. Genetic factors play more dominant role in young strokes than for elders [38] being more prevalent in patients younger than 70 years of age [39]. The heritability and phenotype that can be attributed to genetic factors of stroke was estimated of 40.3% for large-artery ischemic stroke, 32.6% for cardioembolic ischemic stroke, 16.1% for small artery occlusion ischemic stroke, 73% for lobar intracerebral hemorrhage, and 34% for deep intracerebral hemorrhage (heritability set for all stroke patients population) [40, 41].

Monogenic diseases associated with young stroke

Pathogenesis of stroke may develop due to disorders associated with a monogenic (Mendelian and mitochondrial) inheritance: about 5% of young stroke cases are estimated to be caused by that, in contrast to about 1% for elderly stroke patients [33, 42]. In monogenic disorders, the presence of one pathogenetic mutation is usually sufficient to manifest a phenotype. However, not all the subjects carrying the same mutation may manifest a complete pathology-related phenotype [38].

There are more than 50 monogenic diseases known, which phenotypic manifestation includes genetic predisposition to the stroke [33]. These diseases include some mitochondrial pathologies as well as Mendelian inheritance; for some of them, stroke is predominantly manifested, whereas in others, stroke occurs rather rarely. For instance, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is one of the most common mitochondrial diseases, the clinical features of which include early onset of migraine, seizures, cognitive impairment, hearing loss, and stroke-like episodes. Etiology of stroke-like episodes originates from vasogenic edema [43]. The A3243G and T3271C gene changes in tRNA Leu (UUR) are the most frequent mutations described as associated with MELAS [44–46].

With Mendelian inheritance, familial hemiplegic migraine may be responsible for stroke-like episodes observed specifically in children and teenagers. Typical clinical features are hemiparetic, sensory, visual, or dysphasic long-lasting aura, but also basilar migraine and cerebellar ataxia are common accompanied by the stroke-like episodes and coma as possible complications. Approximately 50% of all cases are caused by mutations in the CACNA1A gene which encodes the alpha1A sub-unit of the voltage-gated calcium channels in neurons [47].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common cause of hereditary cerebral small-vessel disease and vascular cognitive impairment in young adults [48]. Disease develops due to dominant mutations in the NOTCH3 gene [49, 50].

Fabry disease is the X-linked congenital lysosomal storage disorder with incomplete penetrance and variable expressivity caused by mutations leading to partial or total deficit of α-galactosidase A enzyme [51]. It is characterized by a progressive accumulation of glycosphingolipids in many tissues including vascular endothelial cells, heart, and neurons. The tissue damage, at least partly, is caused due to poor perfusion [52]; the clinical manifestation of the disease includes stroke [53, 54].

Ischemic stroke is one of the manifestations of several heritable connective tissue disorders. This group of disorders includes vascular Ehlers-Danlos syndrome (type IV) caused by dominant mutations in the collagen III gene (COL3A1), or Marfan syndrome caused by autosomal dominant mutations in the fibrillin 1 (FBN1) gene affecting the musculoskeletal and cardiovascular systems [38].

In Europe, rather uncommon but more prevalent in African and African American populations, hemoglobinopathy may also cause stroke. Further, the sickle cell disease may occur in combination with hemoglobinopathies. Generally, these patients can compensate hemolytic anemia and transient ischemic attacks; however, in a big portion of them, about 11% of patients by 20 years and 24% by 45 years of age, ischemic and hemorrhagic strokes do occur [47]. A timely diagnosis of the monogenic disease predisposing to the stroke allows for the targeted therapy avoiding the disease manifestation.

Polygenic predisposition to young stroke

Polygenic predisposition is a more common cause of young strokes than the monogenic one. Moreover, in this case, the stroke pathogenesis is of multi-factorial nature by genetic and environmental interplay. RNA and proteins, as products of the stroke predisposition-related genes, are involved in homocysteine metabolism, coagulation and fibrinolysis, expression of platelet glycoproteins, renin-angiotensin-aldosterone system, lipid metabolism, inflammation, and in extracellular matrix remodeling (matrix metalloproteinases) [38]. Contextually, the role of and interrelationship between mutations and SNPs in a large number of candidate genes have been investigated utilizing genome-wide association study (GWAS) approach; however, the output is somewhat controversial as exemplified below.

Hyperhomocysteinemia is an independent risk factor for ischemic stroke [55]. The MTHFR C677T variant reducing by 50% the activity of MTHFR enzyme involved in the homocysteine metabolism was reported to be significantly associated with early onset of the ischemic stroke [56, 57]. Some studies indicate a synergistic interaction between C677T MTHFR variant and lipid metabolism in the development of atherothrombotic stroke [58]. Gene variants affecting coagulation and fibrinolytic system were the subject of a number of analyses and subsequent meta-analyses to investigate their association specifically with the young stroke. Here, the prothrombin G20210A variant is associated with increased prothrombin

levels and correlates with the stroke predisposition [59]. The Factor V Leiden (c.1691G4A) is a mutated form of human factor V resulting in a resistance to the activated protein C, proved to be a stroke predisposing condition [60]. A significant association between Factor V Leiden and early-onset ischemic stroke was found in studies, where cases were selected on the basis of having cryptogenic stroke or recruited from a subset of patients referred for a thrombophilic work-up [61, 62].

Lipoprotein lipase (LPL) is an important enzyme of lipid metabolism, hydrolyzing triglycerides from chylomicrons and VLDL, and removing chylomicron remnants as well as VLDLs from circulation. Mutations of lipoprotein lipase were described changing the protein sequence: Ser447Ter in exon 9, the Asn291Ser in exon 6, and p.Asp9Asn that may increase the risk of ischemic stroke [60].

Many other candidate genes are being studied with contradictory output, since the results are affected by the fact that specific gene mutation on the one hand and SNPs (discussed below) on the other hand are multiple and develop synergic interrelationships rather than affecting the risks individually. Based on the analysis of SNPs frequencies, GWAS provided indications that variants linked to the stroke risks are not necessarily located within the coding regions being therefore not the causal ones, but rather involved in the disequilibrium of the functionally relevant alleles located in close proximity to correspoding SNPs.

CHARGE Risk Score Project has included 2047 first-stroke > 55-year-old patients of the European origin, elaborating on a Genetic Risk Score matching 324 SNPs stroke-related risk factors; this project revealed a limited prediction power for the stroke predisposition [63]. In contrast, other studies found specific SNPs being significantly associated with the stroke particularly in young adult patients. Some of the associations seem to be specific for the stroke subtypes. Locus on chromosome 4q25 near the transcription factor PITX2 has been recorded as associated with cardioembolic stroke [64] as well as Rs1906591 and rs10033464 [65]. The rs505922 in the ABO gene has been associated with large-vessel and cardioembolic stroke. The SNP rs11984041 in HDAC9 gene has been associated with large-vessel atherosclerotic stroke [66, 67]. The rs12425791 and rs11833579 polymorphisms close to the NINJ2 gene have been associated with an increased risk for all types of ischemic strokes [68]. The rs660599 (on MMP12 locus) has been associated with the large-artery stroke [69].

In conclusion, permanently increasing genome-related knowledge clearly demonstrates that the reliable risk assessment for the stroke predisposition cannot be based solely on the genetic factors such as gene variants, the effect of which could be further modified by other conditions [60]. Consequently, a multi-level diagnostic approach is essential which is a promising to significantly increase the robustness of predictive power and the efficacy of the follow-up preventive measures.

Vascular risk factors associated with young stroke (Table 1)

Arterial hypertension

Arterial hypertension (HT) is one of the most important risk factors of stroke [90]: the risk of stroke is increasing by the duration of hypertensive period and age [91–93].

Further, arterial hypertension represents the major risk also for young strokes. The SIFAP1 (The Stroke in Young Fabry Patients) study composed of a large multinational European cohort of young strokes (4467 patients aged 18 to 55 years) observed very high prevalence of HT among the study participants (46.6%) [7]. Noteworthy, HT was observed in a significant portion (29.3%) of individuals aged below 45 years. To this end, the Dutch FUTURE study including young stroke patients aged 18 to 50 years and showing the high prevalence of HT (28.3%) among all strokes, has recorded the higher proportion specifically of the ischemic compared to hemorrhagic strokes (29.3% vs. 19.1%, resp.) [70]. Another recent study performed in Finland including 990 patients aged 15 to 49 years with first-ever ischemic stroke has identified HT in 39.3% of all cases [71]. Within the patient cohort, HT has been recorded also in the youngest subgroup of stroke patients aged 18 to 35 years (9%); HT prevalence was increased significantly in patients aged 36–45 years (25%) also in the other study [13]. The Korean study found the HT in 57 from 149 ischemic stroke patients (38.3%) aged 15 to 44 years, with higher incidence in men compared to women (42.9 vs. 24.3%, resp.) [14]. Considerably high prevalence of HT (44.4%) was observed among 1395 stroke patients aged 18 to 45 years by the study performed in Northern China [72]. The cross-studies analysis revealed a dramatic increase in the prevalence of HT among the young stroke patients over the age of 35 years [4].

In conclusion, an increasing prevalence of HT is an evident risk factor of young stroke cases [94]. Consequent mitigating measures by normalization of blood pressure may significantly decrease the lifetime risk of stroke [93].

Dyslipidemia

Dyslipidemia and, in particular, high levels of low-density lipoprotein cholesterol (LDL-C) accompanied by the reduced levels of high-density lipoprotein cholesterol (HDL-C) are known risk factors for ischemic stroke [95]. Dyslipidemia has been, further, associated with higher risk of ischemic stroke recurrence that is particularly evident in large-artery atherosclerosis subtype of stroke [96].

Dyslipidemia is an important risk factor among the group of young strokes as well. The high prevalence of dyslipidemia (34.9%) has been observed in the SIFAP1 young strokes study [7] demonstrating dyslipidemia as more common among men than women (39.3 vs. 28.5%, resp.) being diagnosed in 23.7%

Table 1 Summary of the risk factors, the association of which with young stroke has been demonstrated

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	Reference
Vascular risk factors			
Arterial hypertension	46.6% prevalence (29.3% under 45 years)	4467 patients, age 18 to 55 years	[7]
	28.3% prevalence (29.3% IS vs. 19.1% HES)	724 patients, age 18 to 50 years	[70]
	39.3% prevalence (9% under 35 years)	990 patients, age 15 to 49 years	[71]
	38.3% prevalence (42.9% men vs. 24.3%, women)	149 patients, age 15 to 44 years	[14]
	44.4% prevalence	1395 patients, age 18 to 45 years	[72]
Dyslipidemia	34.9% prevalence (39.3% men vs. 28.5% women), 23.7% under 44 years	4467 patients, age 18 to 55 years	[7]
	26.8% prevalence (26.2% IS vs. 5.9% HES)	724 patients, age 18 to 50 years	[70]
	45.5% prevalence in first-ever stroke 47.9% prevalence in recurrent stroke	837 patients, age 18 to 54 years	[22]
	52.7% prevalence	150 patients, age under 50 years	[73]
	48.2% prevalence	2118 patients, age 18 to 50 years	[32]
	7.5% prevalence	134 patients, age 18 to 45 years	[74]
Diabetes mellitus	10.1% prevalence (vs. 4.3% in controls)	2125 patients, age 18 to 55 years 8500 age-matched controls	[6]
	18.8% prevalence in first-ever stroke 9.7% prevalence in recurrent stroke	837 patients, age 18 to 54 years	[22]
	6.7% prevalence	150 patients, age under 50 years	[73]
	13.8% prevalence	1395 patients, age 18 to 45 years	[72]
Obesity and overweight	Higher risk (HR 1.57, 95%CI 1.28–1.94) for BMI > 30 kg/m^2	1201 patients, age of 15 and 49 years 1154 age-matched controls	[75]
	10.6% prevalence	990 patients, age 15 to 49 years	[71]
	16% prevalence	150 patients, age under 50 years	[73]
	19.5% prevalence (18 to 44 years) 24.1% prevalence (45 to 55 years)	4467 patients, age 18 to 55 years	[7]
	Higher risk with increased waist-to-hip ratio (third vs. first tertile HR 1.56, 99%CI 1.23–1.98)	4216 patients, aged ≤ 55 years 4234 age-matched controls	[37]
Abnormally low BMI—underweight	Higher risk (HR 1.44, 95%CI 1.431–1.450) for BMI < 18.5 kg/m^2	491,773 participants	[76]
	Higher risk (men HR 1.29, 95%CI 1.01–1.49; women HR 1.92, 95%CI 1.49–2.47) for BMI < 18.5 kg/m^2	104,928 participants	[77]
Lifestyle risk factors			
Cigarette smoking	Higher risk (HR 1.88) for current smokers vs. never smokers (HR 5.66 for more than 40 cigarettes/day)	615 patients and 530 controls	[78]
	Higher risk (HR 2.6, $P < 0.0001$) for current smokers vs. never smokers	466 patients, age 15 to 49 years 604 age-matched controls	[79]
	44.6% prevalence	990 patients, age 15 to 49 years	[71]
	41% prevalence (16 to 45 years) 45% prevalence (46 to 55 years)	624 patients, age 16–55 years	[8]
Excessive alcohol consumption	Higher risk (HR 2.20, 99%CI 1.49–3.23) for heavy episodic alcohol intake vs. never or former drinkers	4216 patients, aged ≤ 55 years 4234 controls	[37]
	33.0% prevalence (41.9% men vs 20.1% women)	4467 patients, age 18 to 55 years	[7]

Table 1 (continued)

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	Reference
	17.5% prevalence in first-ever stroke 13.5% prevalence in recurrent stroke	837 patients, age 18 to 54 years	[22]
	41.6% prevalence	1395 patients, age 18 to 45 years	[72]
Low physical activity	46.6% prevalence in men and 50.4% in women	4467 patients, age 18 to 55 years	[7]
	higher risk (HR 5.8, 95%CI 5.1–6.7)	2125 patients, age 18 to 55 years 8500 age-matched controls	[6]
Abnormal sleep duration (either too short or too long)	Dose-response relationship (U-shaped) between sleep duration and stroke, higher risk either for shorter or longer sleep duration compared to 7 h	218,155 participants, aged > 45 years	[80]
	17.9% prevalence (less than 6 h)	4467 patients, age 18 to 55 years	[7]
Illicit drug use	12% prevalence (18% under 35 years)	215 patients, age 18 to 45 years	[13]
	12.1% prevalence	422 patients, age 15 to 44 years	[81]
	Higher risk (HR 2.30, 95%CI 1.08–5.08) for cannabis users	218 patients, age 18 to 55 years	[82]
	Higher risk (IS HR 2.03, 95%CI 1.48–2.79; HES HR 2.33, 95%CI 1.74–3.11) for cocaine abuse	1935 patients, age 18 to 44 years	[83]
Other potential risk factors			
Migraine/migraine with aura	18.8% prevalence in men and 37.8% in women	4467 patients, age 18 to 55 years	[7]
	17% prevalence	990 patients, age 15 to 49 years	[71]
	5.7% prevalence (10.3% under 35 years)	150 patients, age under 50 years	[73]
Hormonal contraceptives (COC)	Higher risk of IS (pooled HR 1.7, 95%CI 1.5–1.9)	meta-analysis including 24 independent studies, age 18 to 50 years	[84]
	Higher risk of IS (pooled HR 1.8, 95%CI 1.2–2.8)	meta-analysis including 14 studies	[85]
Pregnancy, puerperium and associated complications	Higher risk (HR 11.9, 95%CI 5.5–25.6, for age 15 to 24 years) during peripartum period early postpartum (up to 6 weeks)	2,046,048 participants, age 15 to 49 years	[86]
	Higher risk (HR 3.51, 95%CI 1.08–11.35) for multiple (≥ 3) pregnancy loss Higher risk (HR 2.06, 95%CI 0.81–5.23) for presence of stillbirth	165 patients, age 18 to 50 years 743 age-matched controls	[87]
Psychosocial factors	Higher risk HR 2.20, 95%CI 1.78–2.72	4216 patients, aged ≤ 55 years 4234 controls	[37]
	57.2% prevalence of psychosocial stress	110 patients, aged ≤ 55 years	[88]
	higher risk (pooled HR 1.39, 95%CI 1.27–1.51)	Meta-analysis including 41 cohort studies and 5 case-control studies	[89]

IS Ischemic stroke, *HES* Hemorrhagic stroke, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *COC* combined oral contraception

of the youngest subgroup of stroke patients aged 18 to 44 years. The Dutch FUTURE study, further, showed the high prevalence of dyslipidemia (26.8%) among all young strokes, with the higher proportion in ischemic compared to hemorrhagic ones (26.2 vs. 5.9%, resp.) [70]. The Estonian study of young stroke patients aged 18 to 54 years has identified high prevalence of dyslipidemia among first-ever stroke subjects (45.5%) as well as among patients with stroke recurrence (47.9%) [22]. Dyslipidemia was the most common risk factor (52.7%) in Italian study of young stroke involving patients younger than 50 years [73]. Similarly, hypercholesterolemia was identified in a big portion (35%) of young stroke patients aged 16 to 45 years and even more prevalent (58%) in the group aged 46 to 55 years as recently published by Swiss study [8]. In consensus, the high prevalence of dyslipidemia (48.2%) has been demonstrated by the West African SIREN study involving 2118 young strokes aged 18 to 50 years [32]. In contrast, only a small portion (7.5%) of Brazilian ischemic young strokes suffers from dyslipidemia [74]. The cross-study analysis has demonstrated an increasing association of dyslipidemia prevalence with young stroke onset [4]. To this end, an increasing incidence of dyslipidemia and obesity is currently monitored within the subpopulations of children, adolescents, and young adults worldwide [97, 98] that is alarming in the context of lifetime increased stroke risks.

Diabetes mellitus

The history of diabetes mellitus (DM) is rather linked to ischemic but less to hemorrhagic stroke [37]. DM has been diagnosed in 5.9% of young stroke patients with the higher incidence (7.2%) of the ischemic stroke [70]. The SIFAP1 study observed the higher prevalence of DM in stroke patients compared to healthy controls (10.1 vs 4.3%, resp.) [6]. The relatively low prevalence of DM has been identified in the young stroke patients aged 16 to 45 years, however, with an increasing prevalence in older groups (aged 46 to 55 years) by Swiss study (2.5 vs 13%, respectively) [8]. The significantly higher prevalence of DM has been observed in recurrent strokes compared to first-ever strokes in Estonian young stroke study (18.8 vs. 9.7%, resp.) [22]. Another study showed 6.7% prevalence of DM among young stroke patients [73]. Among 1395 young adults aged 18 to 45 years investigated in Northern China, DM has been diagnosed in 13.8% [72]. Further, whereas DM prevalence among young stroke patients recorded in high-income countries is relatively low, significantly bigger portion of young stroke patients suffering from DM is demonstrated for the low-income African population by the West African SIREN study [32].

In conclusion, DM is a global healthcare and socio-economic burden demonstrating an epidemic character and being linked to a cascade of severe collateral pathologies [35, 99] including evidently increased lifetime stroke risks [100, 101]. However, being frequently linked to the modifiable risk factor of overweight and obesity (see more details in the below sub-chapter), specifically the dominating type 2 DM requires specialized screening population programs followed by the targeted preventive measures focused specifically on the needs of young subpopulations which may significantly benefit the healthcare sector and society as a whole [99].

Abnormal body mass index (BMI)

Obesity and overweight

Overweight (BMI $\geq$25 to <30 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) significantly increases cardiovascular risks in general and specific risks of stroke including young stroke cases [102–104].

The population-based multivariate analysis adjusted for age, sex, and ethnicity involving 1201 stroke patients aged 15–49 years and 1154 controls has demonstrated significantly increased stroke risk (HR 1.57, 95%CI 1.28–1.94) for obese individuals (BMI > 30 kg/m^2) [75]. This association, however, has been attenuated after adjustment by other pathology-relevant risk factors such as smoking, hypertension, and diabetes mellitus, which obviously are interrelated by synergic effects. Other research groups have investigated 990 patients aged 15 to 49 years with first-ever ischemic stroke demonstrating 105 individuals (10.6%) with the obesity [71]. Another study involving 150 ischemic stroke patients younger than 50 years has recorded 16% obesity prevalence in the patient cohort examined [73]; thereby, higher prevalence was observed in patients older than 35 years compared to the patients equal or below 35 years of age (18.8 vs. 4.3%, resp.). The SIFAP1 study has monitored the high prevalence of obesity in the subgroup of stroke patients aged 18 to 44 years (19.5%) and only slightly higher in the older group aged 45 to 55 years (24.1%) [7]. The Estonian study has recorded obesity in both—the first-ever (9.7%) and in recurrent (7.3%) young strokes [22]. In addition to the BMI monitoring, an increased waist-to-hip ratio has been clearly associated with an increased stroke risk in the large INTERSTROKE study involving 26,919 stroke patients [37]. To this end, particularly in the younger subgroup of patients (aged $\leq$ 55 years) an enhanced waist-to-hip ratio has been associated with a significantly increased stroke risk (second vs. first tertile HR 1.42, 99%CI 1.15–1.75; third vs. first tertile HR 1.56, 99%CI 1.23–1.98).

As prevalence of childhood and young adulthood obesity has increased dramatically over the past three decades [105], innovative screening programs and effective preventive measures are urgently needed to work on this modifiable factor, in order to reduce the stroke risks [106, 107].

Abnormally low BMI

The recently published population-based study involving 3.6 million adults from the UK clearly showed U-shape risks associated with the abnormal BMI, which means health risks for both overweight and underweight individuals, including cerebrovascular diseases [108]. Moreover, large analysis involving 491,773 US adults has identified an increased risk of stroke (HR 1.32, 95%CI 1.313–1.328) among underweight individuals (BMI < 18.5 kg/m^2) compared to those with normal weight (18.5 to 24.9 kg/m^2) [76]. Even higher stroke risk in underweight individuals (HR 1.44, 95%CI 1.431–1.450) has been showed after adjustment for age, sex, presence of diabetes or prediabetes, hypercholesterolemia, hypertension, smoking status, and physical inactivity. Relative risk estimates remained increased in the underweight population especially among the younger population (aged under 40 years). In consensus, the other study involving 104,928 subjects has demonstrated higher stroke risk for underweight (BMI < 18.5 kg/m^2) men (HR 1.29, 95%CI 1.01–1.49) and even more pronounced risk for underweight women (HR 1.92, 95%CI 1.49–2.47) [77].

In conclusion, although the stroke risk by low BMI is less extensively investigated than the risks by high BMI, the recent studies indicate high relevance of this area for the stroke research and clinical implementation in terms of innovative screening programs, prediction and targeted mitigating measures, particularly focused on the needs of young populations.

Lifestyle risks associated with young stroke

Cigarette smoking

Cigarette smoking is generally acknowledged stroke risk factor; the strong correlation between the dose and stroke risks has been described [37, 109]. Moreover, cigarette smoking demonstrates synergic effects with other stroke-relevant risk factors such as hypertension and multi-faceted stroke risks linked to the poor socio-economic situation and educational level of the affected individuals [110].

Specifically in young populations, cigarette smoking remains an important risk factor: substantially higher risk (HR 1.88) of stroke among the current smokers versus never smokers has been observed in the population-based case-control study dedicated to the risks of ischemic stroke in men aged 15 to 49 years [78]. Contextually, a dose-response relationship between smoking and stroke risk has been recorded, ranging from HR 1.46 for those smoking less than 11 cigarettes compared to HR 5.66 for more than 40 cigarettes daily. Similarly for females, the population-based case-control study involving 466 stroke patients and 604 healthy controls aged 15 to 49 years has recorded significantly higher stroke risk in current smokers compared to never smokers (HR 2.6, $P < 0.0001$) [79]. Also regarding the dose-response relationship, here, the highest risk of stroke was demonstrated for those who smoked 40 and more cigarettes per day (HR 9.1). In consensus, the cross-studies analysis has concluded the smokers prevalence over 50% among men and 40% among women in the youngest subgroup of patients aged 18 to 24 years [4]. The high prevalence of smokers (44.6%) has been monitored among 990 young adults aged 15 to 49 years with first-ever ischemic stroke in the study performed in Finland [71]. The Swiss study has observed high prevalence of smokers among both age-stratified subgroups of young stroke patients, namely 16–45 and 46–55 years of age (41 vs. 45%, resp.) [8]. Here, the portion of smokers was similar between first-ever and recurrent young stroke patients indicating the low efficiency of the smoking cessation as the secondary preventive measure against young stroke (34.7 vs. 28.1%, resp. $P = 0.202$) [22].

In conclusion, due to the high prevalence of smokers in young stroke patient cohorts, and the dose-response relationship between smoking and an increased stroke risk, cigarette smoking represents one of the most appropriate targets among modifiable risk factors for the primary prevention of young stroke [78, 79].

Excessive alcohol consumption

Light drinking and low alcohol intake was repeatedly associated with lower risk of ischemic as well as hemorrhagic strokes [111–113]. The J-shaped risk association between alcohol intake and stroke morbidity and mortality has been identified in a large meta-analysis including 27 prospective studies and 1,425,513 individuals in total [114].

Consequently, the high (more than 60 g of alcohol daily) and even more excessive alcohol consumption is clearly associated with an increased stroke risk as demonstrated by a number of studies [37, 111, 112, 114, 115]. Regular excessive alcohol intake elevates the risk of acute ventricular and supraventricular cardiac arrhythmias and atrial fibrillation predisposing to cardioembolic stroke, elevates blood pressure, activates platelets and humoral hyper-coagulation, which individually and synergically predispose to the ischemic stroke [116].

Excessive alcohol consumption increases the risk of young strokes as demonstrated for instance by the large INTERSTROKE study including young individuals aged below and equal to 55 years: excessive and heavy episodic alcohol intake versus never or former drinking has been compared (HR 2.20, 99%CI 1.49–3.23) [37]. In consensus, the SIFAP1 study has shown that the majority of men (63.1%) and a high portion of women (36.9%) among young stroke patients regularly consumed alcohol specifically in the youngest subgroup of patients aged 18 to 24 years [7]. The high

stroke risk by abnormal alcohol consumption has been identified in a big portion of patients (33.0%), further, pronounced in men against women (41.9 vs 20.1%, resp.). Noteworthy, Estonian study has showed that an excessive alcohol consumption was a prevalent risk among first-ever (17.5%) as well as recurrent young strokes (13.5%) [22]. The high prevalence of the abnormal alcohol intake (41.6%) has been identified among 1395 young stroke patients aged 18 to 45 who have been investigated in Northern China [72]. Moreover, the alcohol intoxication is associated with an increased risk of both—ischemic (HR 1.93, 95%CI 1.74–2.13) and hemorrhagic stroke (HR 2.92, 95%CI 2.51–3.40) [117].

In conclusion, excessive alcohol consumption represents an important modifiable risk factor for young stroke. As the alcohol consumption at early age has long-term consequences in life [118], corresponding preventive and educative programs should be considered for children and youth.

Low physical activity

Regular physical activity reduces the risk of stroke generally and for people younger than or equal to 55 years (HR 0.60, 95%CI 0.45–0.80) [37]. As recommended by the American Heart Association, exercising 2.5 h or more per week is associated with a significant reduction of stroke risks (HR 0.41, 95%CI 0.35–0.48).

In contrast, low physical activity and sedentary lifestyle belong to the prevalent stroke risk factors including young strokes (HR 5.8, 95%CI 5.1–6.7) [6]. For instance, as reported by SIFAP1 study, low physical activity (defined as walking less than 1 mile per day) has been identified as a risk factor in a big portion of young stroke patients—both males (46.6%) and females (50.4%) [7]. On the other hand, the jobs which require working in a standing position as well as of higher intense physical activity significantly increase risks of TIA and stroke [119, 120], demonstrating the need of well-balanced physical activities for an effective prevention of stroke.

In conclusion, the propagation of well-balanced physical activities under professional supervision is an issue for innovative preventive programs focused on reducing the incidence of young strokes in general populations.

Abnormal sleep duration

The abnormal sleep duration, both too short and too long, is associated with an increased risk of stroke [121–124]. However, this association varies by race and sex [125]. By the meta-analysis of 16 prospective studies, an approximate U-shaped risk has been identified for stroke, stroke-related mortality, and dose-response [123]. Compared with 7 h sleep duration per day, each 1-h decrease or increase of the sleep duration enhances the stroke and stroke-related mortality risks (pooled HR 1.17, 95%CI 1.13–1.20). The same U-shaped dose-response risk has been observed in another study including 218,155 Australian adults older than 45 years [80]; the risks reported were especially prominent at the younger age but not evident in individuals older than 75 years. In SIFAP1 study, less than 6-h night sleep duration has been observed in 17.9% of young stroke patients, being more pronounced in men compared to women (20.6 vs. 13.9%, respectively) [7]. On the other hand, the long sleep duration (≥ 9 h) has been identified in 18.5% of men and 27.2% of women. Thereby, the most prevalent long sleep duration (≥ 9 h) has been reported for the youngest subgroup of patients aged 18 to 24 years (50% of women and 26.1% of men). Though much rarely, some sleeping disorders such as obstructive sleep apnea have been reported for young stroke cases [71, 126].

In conclusion, 7–8 h per night is the recommended normal duration of the good-quality sleep. However, in case of individual deviations, a consultation by an expert in sleep medicine is essential to analyze the causality followed by the mitigating measures tailored to the person, in order to avoid potential adverse health effects including young stroke cases.

Drugs abuse

Especially among adults, drug abuse represents an important global health and social problem [127, 128]. Regular illicit drug users are in a higher risk of stroke as recorded specifically for cocaine, ecstasy, methamphetamines, and cannabis [4, 12]. One of the studies has reported on the Illicit drug use for 12% of young stroke patients aged 18 to 45 years [13]; thereby, in the youngest subgroup (aged 18 to 35 years), the prevalence was even higher (18%). Another USA study has published similar statistics for the prevalence by 12.1% of illicit drug use in the cohort of young stroke patients aged 15 to 44 years [81]. Noteworthy, the drug-associated stroke in young adults has been linked specifically to the vascular mechanisms rather than to other risk factors such as hypertension, diabetes etc.

Further, the substantially increased risk of ischemic stroke is systematically reported for young cannabis users [129]. The study that investigated stroke patients aged 18 to 55 years has clearly demonstrated the cannabis use association with an increased risk of transient ischemic attack (TIA) and ischemic stroke (HR 2.30, 95%CI 1.08–5.08) [130]. The cannabis intake leads to multifocal intracranial vasoconstriction strongly associated with the stroke risks [82]. Contextually, another study has demonstrated significantly increased risks of stroke and TIA especially for patients using cannabis on a weekly basis and more frequently (incidence rate ratio 4.7, 95%CI 2.1–10.7) [131]. Similarly, cocaine abuse is associated with an increased risk of ischemic strokes (HR 2.03, 95%CI 1.48–2.79) but also of hemorrhagic ones (HR 2.33, 95%CI 1.74–3.11) in young patient cohorts [83]. Methamphetamine abuse is related mainly to hemorrhagic young stroke [83, 132].

Hypertension, vasculitis, direct vascular toxicity, and vasospasm are the mechanisms underlying methamphetamine-associated strokes [132].

In conclusion, the prevalence of illicit drug use as an acknowledged risk factor is steadily increasing among young stroke patients [15]; to this end, even occasional drug misuse significantly elevates the risk of stroke [133]. Consequently, well-designed educational programs focused on the needs of adolescents and children are essential to mitigate the danger of the drug misuse and related adverse health effects in young populations.

Other potential risk factors associated with young stroke

Migraine

Personal history of migraine, in particular with aura, is associated with increased risks of both—ischemic and hemorrhagic strokes (HR 2.26 and HR 1.94, resp.) [134–136]. The migraine-associated risks of stroke are higher for women (HR 2.08, 95%CI 1.13–3.84) than men (HR 1.37, 95%CI 0.89–2.11) [135]. Women aged below 45 years, who suffer from migraine with aura, smokers using oral contraception are particularly predisposed to the stroke development [135, 137].

Further, in the SIFAP1 study, the lifetime history of migraine has been reported for 18.8% of men and 37.8% of women with stroke; the highest prevalence has been monitored specifically in the subgroup of patients aged 25 to 34 years [7]. Similarly, another study has reported on the history of migraine for 17% of young stroke patients aged 15 to 49 years [71]. Noteworthy, higher migraine prevalence has been observed in patients with no any other well-documented stroke risk factors compared to patients with at least one additional stroke risk factor (23.6 vs. 16%, $P = 0.032$). The history of migraine with aura has been demonstrated as more prevalent specifically in the subgroup of very young stroke patients aged below and equal to 35 years [73].

In conclusion, young individuals, particularly females, suffering from migraine with aura are at an increased risk of stroke, which is, further, strengthened by smoking and using of hormonal contraception. This evidence should be incorporated into the dedicated information campaign to increase awareness among young people.

Hormonal contraceptives

Hormonal contraceptives to protect young women against undesirable pregnancies are broadly used as oral, transdermal, or vaginal drugs containing either combined estrogen and progestogen (combined oral contraceptives—COC) or progestogen alone. By evidence, COC demonstrates prothrombogenic effect sufficiently increasing the risks of cardiovascular diseases [138, 139].

Further, using COC is associated with an increased risk of stroke in young female subpopulations. The large meta-analysis including 24 independent studies among young women in the reproductive age (18 to 50 years) has demonstrated an increased risk of ischemic stroke (pooled HR 1.7, 95%CI 1.5–1.9) among COC users compared to non-users [84]. Thereby, the stroke risk has not been linked to the progestogen-based drugs. In contrast, the dose-dependent stroke risk has been clearly demonstrated for users of the estrogen-based contraceptives with the highest risk by pills containing ≥ 50 μg of estrogen.

The use of COC is associated with an increased risk of ischemic (pooled HR 1.8, 95%CI 1.2–2.8) but not hemorrhagic strokes [85]. The risk of stroke is persistently elevated also for the second and third generation of COCs as well as non-oral hormonal contraceptives [140]. Though for the progestogen-based contraceptives no risk elevation is so far demonstrated, the data used are limited and further research is needed to confirm their potential safety regarding the stroke risks [141].

In conclusion, the use of hormonal contraceptives generally increases the stroke risks, which are further potentiated by synergic effects of other risk factors such as smoking, history of migraine with aura etc. This evidence should be incorporated into the dedicated information campaign to increase awareness among young people.

Pregnancy, puerperium, and associated complications

Pregnancy and puerperium are both associated with an elevated risk of stroke with the predominance of hemorrhagic stroke type [142, 143]. The study involving more than 2 million women in England aged 15 to 49 years clearly showed ninefold higher incidence of stroke during peripartum period (2 days before and 1 day after delivery) and threefold higher incidence during early postpartum (up to 6 weeks after delivery) compared to non-pregnant women [86]. Noteworthy, the highest risk of stroke during peripartum and early postpartum has been identified among the youngest subgroup of pregnant women aged 15 to 24 years (HR 11.9, 95%CI 5.5–25.6).

The risk of ischemic stroke among women aged 18 to 50 years is significantly increased by the multiple (≥ 3) pregnancy loss (HR 3.51, 95%CI 1.08–11.35) and stillbirth (HR 2.06, 95%CI 0.81–5.23) that acts an independent risk factor [87]. Further risk by delivery of a preterm or small-for-gestation-age-infant has been associated with an occurrence of cardiovascular diseases and stroke later in life even after adjustment for socio-economic factors, smoking, and pregnancy-related complications [144]. The risk of stroke is, further, significantly elevated by specific pregnancy-associated pathologies such as pregnancy-inducted hypertension, gestational diabetes mellitus, and preeclampsia [145–147].

In conclusion, innovative screening programs, predictive diagnostics, and proper management of complications linked to pregnancy would significantly contribute to stroke prevention in young women and women in general.

Psychosocial factors

The psychosocial stress is another modifiable risk factor associated with the stroke risks: the case-control INTERSTROKE study involving 32 countries has demonstrated an increased risk of stroke (HR 2.20, 95%CI 1.78–2.72) by evidence of psychosocial stress (measured as combination of stress at home and work, life events, and depression) [37]. Thereby, the highest risk of stroke has been observed for China (HR 5.79, 95%CI 3.39–9.87), whereas the lowest risk—for Western Europe, North America, and Australia (HR 1.19, 95%CI 0.72–1.96). To this end, men were more affected than women (HR 2.59 vs. HR 1.77, resp.).

Further, the psychosocial stress is demonstrated as the stronger risk of stroke for young individuals aged below or equal to 55 years compared to older ones (HR 2.36 vs. HR 2.06, resp.) [37]. In consensus, another study has demonstrated high prevalence of psychosocial stress (57.2%) among young stroke patients (age ≤ 55 years) [88]. Being highly attractive from view point of predictive and preventive medical approaches, this risk factor has been reported for stroke prestage in the study [88]. The cross-study meta-analysis has concluded that psychological factors increase the risk of stroke by 39% (pooled HR 1.39, 95%CI 1.27–1.51) [89].

Hypothesized relationship between Flammer syndrome phenotype and young stroke risks—potential utility of specialized questionnaires for the risk assessment

As discussed in the previous sections, the proportion of stroke cases without any known etiology or identifiable risk factor among the youngest subgroup of patients reached up to 39.6–42% in some studies [16, 22]. No history of risk factors associated with atherosclerosis such as hypertension, dyslipidemia, diabetes mellitus, obesity, or smoking was evident for these patients. Also neither cardiac disease nor classical "rare" etiology is identified and therefore, the etiopathogenesis of such strokes in young adults remains currently unexplained.

Keeping in mind an urgent need of innovative screening programs which would enable to provide young populations with an effective targeted prevention against clinical manifestation of the pathology, a risk assessment specifically for young stroke should be considered in the context of suboptimal health conditions demonstrating the relevant risks and predisposing the affected individuals to pathology manifestation early in life.

Due to symptoms characteristic for the Flammer syndrome (FS) [148, 149], we hypothesize here a potential relationship between FS phenotype and increased risks of the young stroke predisposition. FS describes a phenotype characterized by the presence of primary vascular dysregulation accompanied by a cluster of symptoms and signs, among others including frequently cold extremities, low blood pressure, prolonged sleep onset, shifted circadian rhythm, reduced feeling of thirst, altered drug sensitivity, and an increased sensitivity towards stress and pain sensation. The FS phenotype is prevalent in several patient cohorts demonstrating hypoxic, ischemic, and /or neurodegenerative features such as normal-tension glaucoma, anterior ischemic optic neuropathy, retinal vein occlusions, Sicca and Susac syndromes, central serous chorioretinopathy [150], as well as multiple sclerosis and metastatic breast cancer [151–156]. Regarding the latter, systemic hypoxic effects have been demonstrated as being particularly relevant for the development of an aggressive metastatic disease such as brain metastasis frequently observed in young breast cancer patients [155] with FS phenotype [154].

The individuals with FS are less prone to atherosclerosis but exhibit signs of endothelial dysfunction [157]. The systemic imbalance by an increased release of endotelin-1 acting as the vasoconstrictor against the endothelial vasodilator NO is considered to be the key driver in the FS and related pathologies; due to the systemic effects, the mechanism may affect the functionality of the brain vessels [158]. Other FS characteristic symptoms and signs analyzed below may further synergically contribute to the cerebrovascular events being potentially indicative for the stroke predisposition in young individuals.

The hypothesis is strongly supported by evidence provided in the recently (2016–2018) published articles which we refer in the below paragraphs to and becomes systematically evaluated in the currently run multicenter studies under participation of the clinical and research groups presented by the authors of this paper.

Cluster of the FS symptoms potentially relevant for screening programs focused on young stroke

Compromised cerebral blood flow, disturbed microcirculation, cold extremities

Regulation of the cerebral circulation is very complex which relies on the interplay between cardiovascular, respiratory, and neural physiology. Compromised cerebral blood flow is a well-acknowledged risk factor of stroke; consequently, cerebral circulation monitoring is suggested as critical for the stroke prediction, prognosis, and management [159]. On the other hand, FS-affected individuals frequently demonstrate strongly compromised and disturbed microcirculation that is evident by their cold extremities even during the summer time

and/or in situations, when non-FS individuals feel comfortable with the actual temperature [148, 160].

Baroreceptor sensitivity and altitude sickness

Increased baroreceptor sensitivity has been demonstrated in the context of compromised cerebral blood flow and predisposition to the ischemic stroke [159]. On the other hand, FS-affected individuals demonstrate a prolonged adaptation to the changing altitude and a tendency towards altitude sickness [161, 162].

Cardiac component

Arterial blood pressure is one of the key players in the stroke pathomechanisms, and the cardiac component plays an important role in the regulating processes [159]. Further, the intraoperative hypotension has been demonstrated as a risk factor for adverse outcomes in stroke patients [163]. On the other hand, low blood pressure and/or even cardiomyopathy have been reported for the FS individuals [148, 164].

Hormonal (dys)regulation: estrogen level, migraine with aura, and vascular risks

Hormonal (dys)regulation linked to the estrogen levels in blood and vascular risks plays an important role in cerebrovascular pathologies as demonstrated for young stroke patients suffering from migraine with aura [165–168]. On the other hand, migraine with aura is frequently observed in individuals with FS phenotype [161] with higher prevalence of this phenotype in females [148].

Dizziness

Increased prevalence of stroke has been demonstrated for patients with isolated vertigo and vascular risk factors [169]. On the other hand, dizziness is a characteristic symptom of the FS phenotype [170]. Both vascular dysregulation and increased baroreceptor sensitivity play a role in the appearance of the symptoms.

Tinnitus

Tinnitus is highly prevalent in individuals with FS phenotype [170], FS-affected patients diagnosed with xerostomia [156] and/or metastatic breast cancer [154]. On the other hand, the association between the appearance of tinnitus and increased risks of ischemic cerebrovascular disease has been demonstrated specifically in young and middle-aged patients [171].

Altered thermoregulation and feeling inappropriately cold

Although cerebral thermoregulation remains poorly understood, recent studies demonstrate detectable brain temperature disturbances and brain-systemic temperature decoupling involved in the stroke pathology [172]. Moreover, based on the evidence, an altered brain thermoregulation is proposed to serve as a neuroimaging biomarker in CNS injury. On the other hand, altered thermoregulation in FS-affected individuals has been demonstrated as potentially linked to FS-associated pathologies [160].

Reduced thirst perception and body dehydration

Robust statistical data demonstrate that nearly half of acute stroke patients are dehydrated at the time of admission [173]. The state of dehydration can play a role in CNS perfusion and lead to hemoconcentration and vascular sludging, exacerbating the stroke. On the other hand, a reduced thirst perception is characteristic for the FS individuals; consequently, if their daily liquid intake is not properly controlled, these deficits may cause significant body dehydration as discussed in recent publications [160]. Moreover, in young individuals demonstrating symptoms of xerostomia, FS phenotype is highly prevalent [156].

Further, Sjögren syndrome has been demonstrated as associated with prevalent cerebrovascular disease [174, 175]. Finally, similarities between Sjögren and Flammer syndromes such as Sicca symptoms, among others, have been analyzed in the literature [176].

Low BMI

Slim body shape is characteristic for FS-affected individuals [170]. On the other hand, the BMI < 25 has been demonstrated as a general risk factor of an increased mortality by cerebrovascular disorders [108].

Altered circadian rhythms and sleep patterns

Altered circadian rhythms and sleep patterns are characteristic for the FS-affected individuals [170, 177]. On the other hand, sleep-wake disorders have been demonstrated as the risk factor of stroke and deteriorated recovery [178]. The necessity for targeted prevention and personalized treatments has clearly been stated.

Psychologic factors and stress

FS-affected individuals demonstrate obsessive personality and tendency to perfectionism frequently linked to increased psychologic stress [170] that has been extensively discussed in context of several pathologies potentially linked to FS

phenotype including both neurodegenerative eye disorders [179] and oncologic diseases [152–154], and corresponding molecular mechanisms and targets for stress response have been clearly identified [180, 181]. Similarly, chronic stress and mood disorders have been proposed to play a significant role in the pathomechanisms of the multifactorial stroke predisposition [182, 183].

Conclusions and expert recommendations

Young stroke is a multi-factorial disease which may involve the genetic component but also many of modifiable factors, the combination of which potentiates the risks of the pathology onset. Particularly, a series of modifiable risk factors analyzed here as known and highly prevalent in the patient cohort of young strokes motivate a reconsideration of the currently persisting reactive approach to the stroke management in favor of predictive diagnostics and personalized mitigating measures for individuals at risk, together composing the advanced strategy of targeted prevention. The proposed instruments are

- Specialized questionnaires providing the initial information about potential risks and indicating the necessity of follow-up laboratory tests
- Biomarker panels for multi-level diagnosis demonstrating high predictive power
- Mathematical algorithms to estimate the level of risks based on the individualized patient profiles
- Innovative screening programs strongly promoted by the state and focused on the groups in general population stratified by risks such as children and adolescents in poor socio-economic situation, family history of the genetic predisposition, persons with abnormal weight, and pregnant women
- Well-designed educational measures adapted to the target audiences such as children, adolescents and young adults
- Educational programs for the care-relevant professionals such as general practitioners, psychiatrists, gynecologists, and neurologists, among others.

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