Title: Young Stroke

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Introduction

Stroke occurs when blood flow to the brain is disturbed, resulting in cell death and dysfunction in one or many parts of the brain. The two main types of stroke include ischemic, due to lack of arterial blood flow to the brain, and hemorrhagic due to bleeding (intracerebral hemorrhage). Although a majority of strokes occur in people aged above 65 years, when it occurs to an adult between the age of 18 and 65 years, it is referred to as a young stroke. A stroke may also occur in children, and its causes may be different from that In young adults and in individuals older than 65 years.

Generally, 80% to 85% of strokes are of ischemic origin and the remaining 15 to 20% are hemorrhagic, but in young stroke a greater proportion are hemorrhagic. A third main type of stroke occurs if venous blood flow from the brain is blocked, leading to cerebral venous thrombosis. This type of stroke generally causes only <1% of all strokes, but it causes about 5% of strokes in the young.

Young stroke should be viewed separately from older strokes for several reasons. The young have a different profile of risk factors and causes underlying their strokes compared with those seen in older stroke patients. Many causes or risk factors more common in young stroke patients are recognized, and include pregnancy and the postpartum period, genetic factors, migraine, illicit drug use, and patent foramen ovale. However, risk factors and causes that are commonly associated with older onset stroke can be present at younger ages as well.

Another important aspect that differentiates the young stroke patients from the older ones is their social and vocational situation. They often have family to take care of, are at the childbearing age, and their strokes often occur at a time of decisive career moves. Although the chances of surviving a stroke at a young age is much better than when it occurs at an older age, they still have to face an increased risk of recurrent strokes for years after the first event. Nevertheless, efficient acute treatment, rehabilitation, and stroke prevention can potentially lead to improved outcomes in individuals with young stroke.

1. Definition

There is no uniform criterion to define the entity “stroke in the young”. In the scientific literature on young adult stroke, the upper age cut-offs have varied from 30 to 65 years, being most commonly 50 or 55 in the recent literature. Although most of the scientific data come from studies using a lower age cut-off, in this article “stroke in the young” refers to ischemic or hemorrhagic strokes occurring in adult people aged less than 65 years, i.e. reflecting usual working age in most parts of the world. This is also the cut-off used in the World Health Organization’s Global Burden of Diseases analyses.

Synonyms to “stroke in the young” include “young-onset stroke”, “early-onset stroke”, and even “young stroke”. There is much less information available on young-onset hemorrhagic than ischemic stroke, and much less information is available on transient ischemic attacks (TIA)—i.e. symptoms originating presumably from a blood clot in an artery that rapidly resolves spontaneously without brain damage seen in imaging studies.

2. Epidemiology

Approximately one fourth of all strokes occur at age of less than 65 years and 1 out of 10 occur at age of less than 50 years.(Ferro, Massaro and Mas, 2010) Incidence is a measure of probability of occurrence of a disease in a population with a specified period of time. Incidence of first stroke increases virtually exponentially with age at younger ages, with the steepest phase of increase beginning in early midlife.(Putaala*, et al.*, 2009)

The incidence of ischemic stroke in people aged less than 50 years is about 10 per 100 000 inhabitants per year.(Naess*, et al.*, 2002; Putaala*, et al.*, 2009) Among those aged less than 35 years, women outnumber men in the incidence of ischemic stroke, but in those aged more than 35 years but less than 50 years, men outnumber women.(Putaala*, et al.*, 2009; Putaala*, et al.*, 2012)

Incidence of intracerebral hemorrhage in the young is about a half of that for ischemic stroke. One study showed an approximated incidence of 4.9 per 100.000 for nontraumatic intracerebral hemorrhage at age of 16 to 49 years.(Koivunen*, et al.*, 2014a)

Incidence of cerebral venous thrombosis is unknown, but it encompasses less than 1% of all strokes at all ages. Among younger patients, cerebral venous thrombosis cover up to 5% of all strokes.(Bousser and Ferro, 2007)

There are also notable differences in the incidence between geographic areas and race-ethnic groups. For instance, in the Baltimore-Washington area, incidence of ischemic stroke for young white people was 10.5 per 100.000 while it was 21.7 per 100.000 for young blacks.(Kittner*, et al.*, 1996) As for ischemic stroke, higher rate of intracerebral hemorrhage has been found for young blacks than for young whites.(Kittner*, et al.*,1996)

Notably, incidence of ischemic stroke in the young has been increasing worldwide since 1980s to present.(Bejot*, et al.*, 2014; Kissela*, et al.*, 2012; Rosengren*, et al.*, 2013; Vangen-Lonne*, et al.*, 2015) The exact reasons for the increase remain unknown, but better awareness of the disease, improved diagnostics, increasing prevalence of overweight and diabetes, unhealthy diet and sedentary lifestyle may play a role. In conjunct with the increasing incidence and decreased stroke death rates, the number of prevalent cases has been increasing globally in the past 20 years. Recent epidemiological findings also suggest that the overall burden of young stroke represents globally now nearly half of the total stroke burden, with most of the burden in developing countries.(Krishnamurthi*, et al.*, 2015)

3. Risk Factors and Causes

Ischemic stroke or TIA

The same risk factors predisposing to ischemic stroke or TIA at older ages may also predispose to young-onset ischemic stroke or TIA. These include hypertension, dyslipidemia, smoking, diabetes mellitus, and cardiovascular disease. In fact, recent studies have shown that such traditional risk factors are common among young stroke patients.(Putaala*, et al.*, 2012; Rolfs*, et al.*, 2013; von Sarnowski*, et al.*, 2013)

There also are specific risk factors to young age. Some risk factors can exist only at young ages (e.g. pregnancy or postpartum period, oral contraceptive use). Other risk factors can exist at all ages, but their influence on the stroke risk has been shown to be stronger at younger ages (e.g. patent foramen ovale, migraine with aura, infections). The factor may also be related to lifestyle-related feature in the population, which is more common at younger ages (e.g. illicit drug use, heavy drinking, binge drinking, smoking, overweight).(Putaala, Heikinheimo-Connell and Tatlisumak. 2015)

The spectrum of causes underlying young-onset ischemic stroke differ markedly from those seen in the elderly patients.(Fromm*, et al.*, 2011) The major causes of ischemic stroke in the elderly, atherosclerosis in the large brain supplying arteries, atrial fibrillation, and small-vessel disease of the brain are rather infrequent among the young. This occurs probably because most traditional risk factors predisposing to these outcomes, such as hypertension, diabetes, and dyslipidemia, are either less common or less severe, or have not yet caused substantial damage to the cardiovascular system.(Ferro, Massaro and Mas, 2010; Yesilot Barlas*, et al.*, 2013)

The most common solitary cause of ischemic stroke in the young in high-income countries is a dissection of a neck artery (a tear within the wall of a blood vessel allows blood to separate the wall layers), involving carotid or vertebral artery. Sometimes a dissection can occur in or extend to an intracranial artery. Dissections alone cause about 15-20% of ischemic stroke in young people. (Debette and Leys, 2009) Other causes seen relatively often among young patients but rarely among elderly patients appear in the table:

- Dissection of a carotid, vertebral, or intracranial artery
- Systemic vasculitides
- Primary angiitis (vasculitis) of the central nervous system
- Systemic lupus erythematosus
- Primary antiphospholipid syndrome
- Sickle cell disease
- Genetic thrombophilic diseases (protein C, protein C, and antithrombin III deficiency; Factor V Leiden and prothrombin gene mutations)
- Sneddon's syndrome
- Moyamoya disease or syndrome
- CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Fabry disease
- MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

- HANAC (hereditary angiopathy, nephropathy, aneurysm, and muscle cramps)
- RCVS (reversible cerebral vasoconstriction syndrome)
- Migrainous infarction

Migraine attack resulting in ischemic stroke (migrainous infarction) is a rare occasion with unknown mechanisms, and the diagnosis necessitates exclusion of other potential causes.(Laurell*, et al.*, 2011) Many diseases and conditions caused by a mutation in a single gene may underlie young-onset ischemic stroke, although known mutations are causing each only a fraction of all ischemic strokes in the young.(Cheng*, et al.*, 2014)

Cardiomyopathies, endocarditis, congenital cardiac malformations, atrial fibrillation, endocarditis, and cardiac tumors are examples of high-risk heart conditions that may lead to ischemic stroke at young age. These conditions encompass together about one tenth of all young-onset ischemic strokes.(Yesilot Barlas*, et al.*, 2013) Notably, rheumatic valvular disease of the heart is among the most frequent causes of young-onset ischemic stroke in many non-industrialized countries.(Ghandehari and Moud, 2006)

The reason for the ischemic stroke in the young remains unexplained (i.e. cryptogenic or undetermined) in up to 50% of patients, being more frequent the younger the patient's age.(Yesilot Barlas*, et al.*, 2013) Patent foramen ovale (PFO), a remnant of the fetal circulation that may cause venous blood to enter into arterial side via a shunt between atriums of the heart, is frequently found by cardiac ultrasound examination in these patients.(Kizer and Devereux, 2005) As PFO is also present in about a fourth of healthy individuals, determining when PFO is causally relevant to the ischemic stroke remains a major challenge, however.(Alsheikh-Ali, Thaler and Kent, 2009)

Intracerebral hemorrhage

As in older stroke patients, hypertension and smoking are the most frequent risk factors for young-onset hemorrhagic stroke. However, among the young, illicit drug use, hematologic disorders, and genetic conditions may be predisposing to hemorrhagic stroke in the young more often than in older patients.(Koivunen*, et al.*, 2014a)

As for ischemic stroke, the spectrum of causes for hemorrhagic stroke at younger ages is variable and different from that in the elderly. Arteriopathy related to hypertension is less frequent and amyloid angiopathy absent, while vascular malformations, hematologic disorders, illicit drug use, moyamoya disease, and vasculitides are more commonly causing intracerebal hemorrhage in young adults. Also for intracerebral hemorrhage, the cause remains unknown in relatively many young patient.(Koivunen*, et al.*, 2014a)

Causes atypical in elderly but relatively often underlying hemorrhagic stroke among young adults include:

- Arteriovenous malformation
- Cavernoma
- Coagulopathies and hematologic disorders
- Systemic vasculitis or primary angiitis (vasculitis) of the central nervous system
- RCVS (reversible cerebral vasoconstriction syndrome)
- Illicit drug use

- Moyamoya disease
- Cerebral venous thrombosis
- Pre-eclampsia or eclampsia

Cerebral venous thrombosis

Risk factors and reasons for cerebral venous thrombosis include pregnancy and puerperium, infections, systemic inflammatory conditions, genetic prothrombotic conditions, hematologic conditions, certain drugs (e.g. oral contraceptives, hormone replacement therapy, steroids), mechanical causes and trauma, as well as dehydration and cancer. Cerebral venous thrombosis can cause both ischemic or hemorrhagic lesion in the brain.(Bousser and Ferro, 2007)

4. Diagnosis

The basic diagnostic work-up does not differ in young stroke patients from that in older patients. However, due to the extensive array of different causes, a vigorous interview of patient and family history, clinical examination, and specific ancillary tests are often needed besides routine brain and vascular imaging, laboratory tests, and cardiac ultrasound.

5. Management

General acute management of young-onset stroke is similar to that in older patients. Acute treatment strategies of ischemic stroke include immediate transport to a hospital providing acute stroke care, administration of intravenous thrombolysis with or without endovascular thrombectomy within the first hours after symptom onset, followed by treatment in a stroke unit.(Jauch*, et al.*, 2013; Powers*, et al.*, 2015) Younger patients may benefit from intravenous thrombolysis with greater extent compared with older patients with similar symptom severity.(Toni*, et al.*, 2012)

In very large middle cerebral artery infarctions, a neurosurgical procedure called hemicraniectomy may be lifesaving, and, in the best scenario, affect favorably to functional outcome (i.e. ability to move, independency in daily living). In this procedure, part of the skull is removed to allow a swelling brain to expand without being squeezed to the opposite side of the brain.(Vahedi*, et al.*, 2007) Also for hemicraniectomy, younger patients may have more benefit from the procedure than older patients.(Juttler*, et al.*, 2014; Vahedi*, et al.*, 2007)

Treatment of intracerebral hemorrhage also follows the same principles as for older patients.(Hemphill*, et al.*, 2015) Because vascular malformations more often underlie intracerbral hemorrhage in the young, surgical or endovascular treatments may be more often warranted.(Koivunen*, et al.*, 2014b)

Cerebral venous thrombosis is usually treated with oral anticoagulants for 3 to 6 months. Depending on the underlying cause, the need for anticoagulation treatment may occasionally be permanent.(Bousser and Ferro, 2007)

6. Rehabilitation

Individuals with young stroke have unique rehabilitation needs. Both physical and cognitive skills are impacted by stroke, which has profound effects on a young individual's quality of life.(Keppel & Crowe 2000; O'Connor*, et al.,* 2005; Röding*, et al.,* 2009) This is because they are at a stage in life when employment is important, and are more likely to be caring for children.(Dixon*, et al.,* 2007; Stone 2007) However, few studies have assessed the specific needs of young stroke patients.(Low*, et al.,* 2003) As a result, many of the needs of young stroke patients are unmet in the context of inpatient rehabilitation which tends to focus on older stroke patients.(Röding*, et al.,* 2003; Stone 2005)

Furthermore, young stroke survivors have a longer period of disability to contend with due to their impairments which creates a socioeconomic challenge.(Bjorkdahl & Sunnerhagen 2007; Mehndiratta*, et al.,* 2004, O'Connor*, et al.,* 2005) The cost of stroke in young people exceeds that of stroke in older people due to a loss in productivity and more psychosocial complications.(Jacobs*, et al.,* 2002; Nayak*, et al.,* 1997) These complications include stress in the family, institutionalization, return to work and future needs.(Teasell*, et al.,* 2000) Thus the rehabilitation of young stroke patients presents distinct rehabilitation challenges.

Young stroke patients have been shown to demonstrate greater neurological and functional recovery and have a better prognosis and long-term survival rate compared to older stroke patients.(Adunsky*, et al.,* 1992; Hindfelt & Nilsson 1992; Marini*, et al.,* 2001; Nedeltchev*, et al.,* 2005, Black-Schaffer & Winston 2004) However, they are at increased risk for experiencing reduced cognitive performance, anxiety and depression compared to stroke-free age and sex matched controls.(Schaapsmeerders*, et al.,* 2013, Waje-Andreassen*, et al.,* 2013)

Traditional rehabilitation is generally the same for younger and older stroke patients.(Teasell*, et al.,* 2000) Rehabilitation starts in the acute care hospital, and continues on inpatient rehabilitation units, then in outpatient therapy programs, and eventually progress to vocational rehabilitation. Following stroke there can be a period of natural recovery which is characterized by a non-linear pattern of improvement. This can look like a stairstep pattern of improvement across different areas. It is now well-established that recovery may continue for many years after the stroke.(Sabini, *et al.,* 2012) Specialty guidelines for stroke rehabilitation have been developed (www.carf.org, and www.strokebestpractices.ca/). Return to work or to other life activities such as school, or parenting are important goals of rehabilitation. The unique issues associated with younger stroke rehabilitation pertain to the nature of family support, the presence of young dependents, marital stress, and return to work.(Dixon*, et al .* 2007)

Cognitive impairment from stroke can complicate a young stroke patient's reintegration back into the community and return to work.(Malm*, et al.,* 1998, Hommel*, et al.,* 2009) Almost half of young stroke patients are diagnosed with some degree of post-stroke depression ,(Kappelle*, et al*., 1994; Neau*, et al*., 1998) which is associated with a poor rehabilitation outcome (Neau*, et al.,* 1998). A better understanding of cognitive deficits is required for more effective age-adapted rehabilitation programs.(Röding*, et al.,* 2003) Young stroke patients also expressed a need for communication with other stroke patients their age that had been affected by similar experiences.(Dixon*, et al.,* 2007; Röding*, et al .* 2003) Furthermore, rehabilitation for young stroke survivors should emphasize participation in fitness activities, as they are necessary for well-being and secondary stroke prevention ;(Naess*, et al.,* 2004) unfortunately these activities are often given up following a stroke. (Wolf*, et al.,* 2012) Post stroke fatigue in young adults can negatively affect scholastic, vocational, and social pursuits. It is associated with higher mortality rates, depression, and lower functional outcomes in older patients,(Naess*, et al.,* 2005) but is relatively understudied in young survivors.

Individuals interested in rehabilitation services should seek consultation from a neurologist or rehabilitation physician specializing in stroke rehabilitation. Due to the interaction between

physical symptoms, changes in thinking skills, and emotional changes, persons with stroke can benefit from broad-based specialty rehabilitation therapies by an interdisciplinary team, including physical, occupational, speech, recreational therapists and specialists in physical medicine and neuropsychology. Common rehabilitation regimes include some combination of physiotherapy, speech language therapy, occupational therapy, and pharmacological therapy. (Stein 2004; Young & Forster 2007) Strategies to improve motor recovery in young stroke patients include: Constraint-induced movement therapy, robot-aided rehabilitation, virtual reality training, EMG-biofeedback, functional electrical stimulation, increased exercise intensity, and acupuncture.(Stein 2004)

A stroke affects the entire family. Caregivers of stroke survivors suffer from higher rates of depression and greater rates of deterioration in their own health.(Kinsella & Duffy 1979) Caregivers report more emotional distress when caring for individuals with stroke who exhibit more depressive symptoms and cognitive impairment, and when caregivers were younger, female, in poorer physical health, and experienced more interference with their lifestyle. (Cameron*, et al.,* 2011) In the case of younger strokes, where the primary caregiver is the spouse, added responsibilities of caring for children create further adjustment problems.(Visser-Meily*, et al.,* 2005, Martinsen*, et al.,* 2012) The relationship between parents post-stroke and their children is complex, and the stroke event can add stress to the family environment.

Vocational and return to work issues are a major facet of rehabilitation unique to the young stroke population.(Malm*,* et al., 1998) Significant predictors of return to work include age, sex, functional status, absence of psychiatric illness, and education level.(Bergmann*,* et al., 1991; Glozier*, et al.*, 2008; Howard, *et al*., 1985; Peters, *et al*., 2013) Individuals in managerial positions and white collar occupations are most likely to return to work.(Howard 1995, Saeki*, et al.,* 1993; 2010) The higher success rate for white collar positions may be attributed to better education, work conditions, pay and less physically demanding tasks. The side of hemiplegia or weakness has not been consistently associated with the ability to return to work in young stroke patients.(Black-Schaffer & Osberg 1990; Heinemann*,* et al., 1987; Howard*, et al.,* 1985; Kotila*, et al .* 1984; Weisbroth*, et al.,* 1971) However, those with better upper extremity use, ambulation, and abstract reasoning are more likely to return to work. Right hemiplegics with milder communication and cognitive deficits also have better vocational outcomes. There is a distinct negative correlation between aphasia and return to work.(Black-Schaffer & Osberg 1990) Neuropsychological testing may be required in order to accurately delineate the extent of cognitive problems and determine how they might impact the patient's eventual return to work.(Lindberg*, et al*., 1992; Ljunggren*, et al.,* 1985). The inability to return to work frequently leads to emotional and financial hardships for stroke survivors and their families.(Churchill 1993) To address this issue, The Stroke Association & Different Strokes published Getting Back to Work after Stroke.(Barker 2006) Employers and professionals within the community should try to focus on meeting the needs of stroke survivors and their families in order to facilitate participation and independence for stroke patients.(Kersten*, et al.,* 2002) Young stroke patients need to be connected with support organizations and those who share similar experiences (see www.youngstroke.org).

7. Prevention

Primary prevention of stroke at all ages includes generally healthy lifestyle, in particular regular physical activity, weight control, healthy diet favoring Mediterranean diet ingredients, and avoidance of tobacco smoking, excess alcohol use and illicit drugs.(Meschia*, et al.*, 2014)

Secondary prevention after a stroke or TIA at young age should generally follow the same principles as for older patients.(Kernan*, et al.*, 2014) Medication and preventive measures

should be tailored according to the underlying cause and therefore it is of utmost importance to carry out extensive and timely diagnostic investigations to decipher the cause for the stroke in a young patient.

If established vascular risk factors (e.g. elevated blood pressure, high cholesterol, diabetes mellitus) are present, their careful treatment is warranted. Medical treatment typically involves antiplatelet medication or anticoagulants. Depending on clinical features, these are combined with cholesterol and/or blood pressure lowering medications. If a specific cause—such as stenosis in a cervical artery due to atherosclerosis, cardiac myxoma, arteriovenous malformation, moyamoya disease—is present, the preventive treatment aims at removing such a source or creating a bypass in the brain circulation. When a systemic condition such as a hematologic disease or systemic vasculitis is primarily underlying the stroke, its efficient treatment forms a cornerstone of secondary prevention. Estrogen-containing hormonal product should be stopped. Other precipitants such as excess alcohol drinking, illicit drug use should be eliminated to minimize the risk of future strokes.

In many conditions related to young-onset stroke, there is uncertainty regarding the optimal secondary prevention. Patent foramen ovale is an example of such condition and currently it remains uncertain whether closure of patent foramen ovale, using a catheter device, is superior to best medical treatment.(Li*, et al.*, 2015) It also remains uncertain for many cases, how long secondary preventive medication should be continued, particularly if there are no known vascular risk factors present and the stroke remained cryptogenic.(Naess*, et al.*, 2005)

8. Prognosis

Age is the most important factor driving mortality after stroke. Young stroke patients thus generally survive their strokes more often compared with older patients. However, compared with background population of same age, young stroke patients face an about 4-fold risk of dying in the long-term after their stroke.(Rutten-Jacobs*, et al.*, 2013a) The most frequent causes of death include vascular diseases,(Putaala*, et al.*, 2009) so their efficient treatment is highly important to mitigate the risk of dying after young-onset stroke.

Observational studies show that young patients with ischemic stroke have a substantial risk of future nonfatal strokes and other cardiovascular events, depending primarily on the risk factors and cause of the initial stroke.(Pezzini*, et al.*, 2014; Putaala*, et al.*, 2010; Rutten-Jacobs*, et al.*, 2013b)

Functional outcome in young stroke patients is generally favorable, with about 4 out of 5 regaining independence in daily living measured with modified Rankin Scale.(Naess*, et al.*, 2002; Putaala*, et al.*, 2013) However, such scales are only crude measures of clinical outcome and they may not accurately consider for example subtle cognitive deficits, fatigue, and depression, which are rather common residual symptoms in young patients after stroke, and may hamper quality of life.(Koivunen*, et al.*, 2015; Maaijwee*, et al.*, 2015; Naess*, et al.*, 2006; Synhaeve*, et al.*, 2015)

Return to work and productive duties is among the most important outcome after young-onset stroke as mentioned above. Limited number of studies including patients from many decades indicates that rather high percentage of young stroke survivors is left without paid work in the long term.(Maaijwee*, et al.*, 2014) Work adjustments may also be needed for those returning to work.

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