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Review Article

Long-Term Prognosis of Ischemic Stroke in Young Adults

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There is limited information about long-term prognosis of ischemic stroke in young adults. Giving the potentially negative impact in physical, social, and emotional aspects of an ischemic stroke in young people, providing early accurate long-term prognostic information is very important in this clinical setting. Moreover, detection of factors associated with bad outcomes (death, recurrence, moderate-to-severe disability) help physicians in optimizing secondary prevention strategies. The present paper reviews the most relevant published information concerning long-term prognosis and predictors of unfavorable outcomes of ischemic stroke affecting young adults. As a summary, we can conclude that, in the long term, stroke in the young adult increases slightly the risk of mortality, implies higher risk of future cardiovascular events, and determines functional limitations in a significant percentage of patients. Nevertheless, in every individual case the prognosis has to be considered depending on several factors (stroke subtype, initial severity, cardiovascular risk factors) that determine the long-term outcomes.

1. Introduction

Ischemic stroke in young adults (15–45 years) is not exceptional and accounts for up to 12% of all first ischemic strokes, with a wide diversity of etiologies [1–8]. Moreover, the impact on years of potential life lost and on socioeconomic cost is very important in this range of ages.

Many series have reported a favorable prognosis, but only the short-term prognosis has been widely evaluated and there are few investigations about long-term functional recovery of young adults with first-ever ischemic stroke.

Most of the investigations in long-term prognosis have described good functional recovery in young adults with ischemic stroke, since most patients are independent and at least 50% return to work [8–12]. Moreover, some predictive factors for mortality, recurrence, and good/poor functional recovery have been identified [12].

In the main series, the mean followup after the initial episode ranges between 1 and 16 years (Table 1) [9–33]. The most important methodological limitations in most of these studies are the retrospective design, but it is not so important to evaluate the long-term consequences of stroke, since events as recurrence, death, and disability can be easyly and accurately evaluated with this methodology. The review of the clinical records (including periodic outpatient reviews) complemented with telephone interviews is the main tools for obtaining information about the patients' functional status after the stroke in the main studies about consequences of stroke in the young [9–14], including prospective series [10, 11].

The prognosis of ischemic stroke in the young is much better than in the elderly, with lower mortality and recurrence and better functional recovery [12]. Thus, prognosis of stroke in young as a whole has been described as favorable in most of the series [12, 17–21], but the long-term prognosis is notably worse when compared with the general population of the same age, with higher death rate, higher risk of cardiovascular events, and significant limitations in quality of life [12]. Moreover, in our series (with a mean followup of almost 12 years and mean age of 36 years old), only 57% of the patients followed for more than 3 years are alive, free of significant disability, stroke recurrence or other vascular event [12].

2. Mortality

The overall risk of long-term death after an acute ischemic stroke in young adults is low. The reported cumulative risk

Table 1: Long-term followup series in young adults with ischemic stroke.

	Number of patients	Mean followup [years]	Type of study
Varona et al. [12]	272	11.7	Retrospective
Putaala et al. [31]	731	5	Prospective
Hindfelt and Nilsson [13]	74	16	Prospective
Marini et al. [10]	330	8	Prospective
Kappelle et al. [9]	296	6	Retrospective
Lanzino et al. [20]	155	5.8	Prospective
Camerlingo et al. [21]	135	5.7	Prospective
Bogousslavsky and Regli [18]	38	3.8	Consecutive cases
Ferro and Crespo [14]	215	3.5	Prospective
Leys et al. [11]	287	3	Prospective
Chancellor et al. [29]	59	3	Retrospective
Matias-Guiu et al. [22]	386	2.8	Prospective
Grindal et al. [26]	34	2.7	Retrospective
Snyder and Ramirez-Lassepas [27]	52	2.4	Retrospective
Srinivasan [28]	46	2	Retrospective
Nedeltchev et al. [32]	136	2.1	Prospective
Musolino et al. [30]	60	6.1	Prospective
Naess et al. [33]	232	5.7	Retrospective

Table 2: Annual and cumulative rates of mortality and recurrent stroke in young adults after a first-ever ischemic stroke, based on data of study of Varona et al. [12].

	0-1 year	2–5 years	2–10 years	2–20 years
Mean annual mortality (%)	4.9	1	0.8	0.9
Cumulative mortality (%)	4.9	9	12.1	21.7
Mean annual recurrence (%)	3.6	3	2.3	1.7
Cumulative recurrence (%)	3.6	15.4	24.2	36.4

of mortality is about 2% (95% confidence interval [CI], 1.5% to 3.9%) at 1 month, about 5% (3.1% to 6.5%) at 1 year, 9%-10% (8.5% to 11.5%) at 5 years, and 12% (11.2% to 13.0%) at 10 years [12, 31] (Table 2).

The mortality rate is higher in the first year (about 4%-5%; 95% CI: 1.8% to 6.0%) and decreases in following years (about 1.0% annually; 95% CI: 0.3% to 1.7%) [10–12, 21, 34]. Also the risk of vascular mortality is higher in the first year after stroke and then falls to lower risk in subsequent years. Thus, the mean vascular mortality rate is lower as longer is the followup.

The cumulative risk of mortality at 10 years in young adults with ischemic stroke is about almost 10 times higher than in the general population of the same age [12, 34], as shown in Figure 1, which compares the survival of young

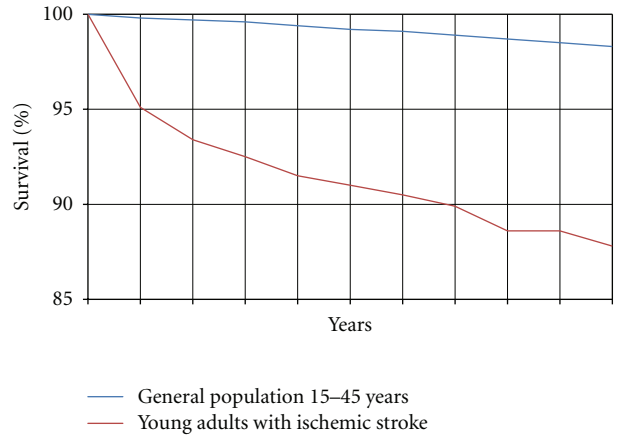

Figure 1: Graph showing a comparative approximation of the different probabilities of survival at 10 years in young adult patients (15–45 years) with ischemic stroke and the general population aged 15–45 years. (based on data of study of Varona et al. [12]).

patients with ischemic stroke in our series against the survival of persons between 15–45 years in the Madrid Community [35, 36], indicating the negative impact on survival for suffering from ischemic stroke in the young [12].

However, the mortality of young adults with ischemic stroke is much lower than in older patients, since survival at five years is more than 90% in the young and only 40% in the elderly [37].

Among the survivors after a first-ever ischemic stroke, the main causes of death are stroke recurrence (20%–30%), other cardiovascular events (20%–50%), malignancies (15%–35%), and infections (10%) [9, 12, 31].

2.1. Risk Factors for Mortality. Apart from patients with malignancies, several subgroups of patients and some factors have been identified as associated with notably higher risk of death: increasing age (above 35 years; relative risk [RR] of 2.0 and hazard ratio [HR] of 2.5), male gender (RR of 1.9; HR of 2.1), the presence of cardiovascular risk factors, in particular arterial hypertension (HR 1.3), completed stroke, with total anterior circulation involvement (HR: 3.3), heart failure (HR: 5.2), heart and/or vascular disease (HR: 1.7), heavy drinking (HR: 2.8), large artery atherosclerosis (HR: 4.4), smoking (HR: 1.4), and severe neurological deficit at presentation (RR of 5.1) have been associated with mortality in young adults with ischemic stroke [10, 12, 31, 33]. The majority of these factors are associated with an atherosclerotic risk profile, which is present in older and male patients in whom premature atherosclerosis is much more prevalent [38] and prognosis is worse.

As "protective" factors, the following have been reported as associated with lower long-term mortality: stroke due to dissection of extracranial arteries, stroke associated with migraine, permanent poststroke anticoagulation therapy (in patients with cardioembolic stroke or potential cardiac sources of emboli and patients with hypercoagulable states) (RR 0.3), and hypercholesterolemia (RR 0.3). The protective role of hypercholesterolemia therapy has been reported in

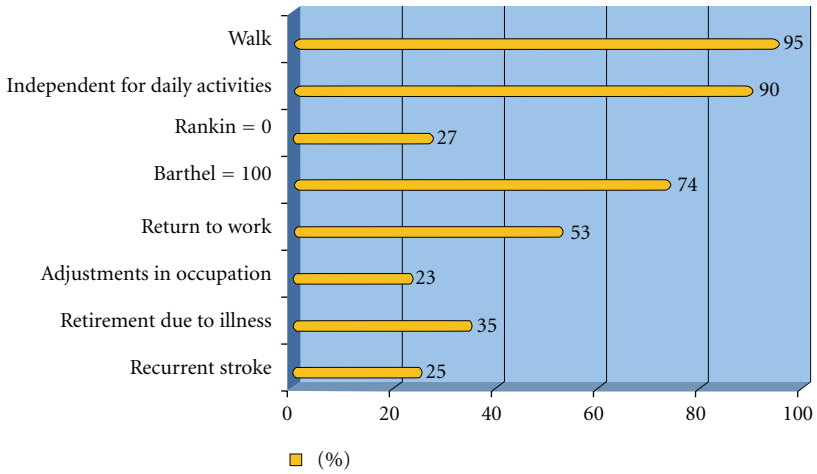

Figure 2: Functional outcome after long-term followup of young adults with ischemic stroke (number of patients: 240; mean followup time: 11.7 years), based on data of study of Varona et al. [12].

young [10, 12] as well as in elderly [39]. This is due to the neuroprotective effect of drugs such as statins or fibrates, which are prescribed in young adults with stroke and hypercholesterolemia.

Ischemic stroke in relation to atherothrombotic (HR: 4.4) and cardioembolic (HR: 2.8) causes has been associated in some series with a poor prognosis. Conversely, several etiologies have been associated with better prognosis and lower percentages of mortality: lacunar infarct, nonatherosclerotic vasculopathy, hypercoagulable state, and undetermined/unknown etiology [9, 10, 31, 40].

3. Long-Term Functional Deficits

With respect to functional recovery, the prognosis for young adults with stroke is good, especially compared with the elderly. Some series have reported that up to 90% of patients with a long-term followup are independent for all activities of daily living and 95% are able to walk without any assistance in spite of previous stroke (Figure 2) [9–12].

Functional recovery and residual disability outcomes are often rated with modified Rankin scale (MRS), Barthel Index (BI), and Glasgow Outcome Scale (GOS). According to these scales, in the long-term followup even more than 70%–80% of the patients report no significant problems for daily activities (MRS = 0–2; IB = 100), about 10%–20% report moderate handicaps (MRS = 3), and only about 10% report major handicaps and residual dependency after ischemic stroke (MRS score higher than 3 and/or BI score less than 90) [12, 30, 41].

These figures contrast with the figures in the elderly, in whom 35%–40% of patients with stroke are dependent on other persons after the stroke [42, 43].

The reported predictive factors for better long-term functional recovery have been: age below 35, transient ischemic stroke, favorable initial course without severe handicaps at discharge, and stroke associated with migraine and/or oral contraceptives [11, 12]. No etiology has been significantly associated with a better or poorer functional recovery, but lacunar infarct and unknown etiology have been associated to a slightly better prognosis.

4. Occupational Status

Ischemic stroke in the young originates limitations in the quality of life and occupational status [9, 12, 20, 21, 40, 44]. Series have reported that between 50%–70% of young adults with stroke return to work, with a time period ranging from several days after stroke to 40 months, with a mean of 8 months. However, about 25% of them need adjustments [other job or part-time employment] in their occupation due to their inability after stroke to perform the prior activity, so less than half of the patients return to their previous work (Figure 2) [9, 10, 12, 30, 40, 45].

Transient ischemia (71%), undetermined stroke (69%), and nonatherosclerotic vasculopathy (64%) had been associated with a higher probability of returning to work [12].

5. Other Sequelae

In the reported series, between 20%–50% of patients have poststroke depression (using DSM-IIIR criteria and/or The Montgomery Asberg Depression Rating Scale). Most of these patients need specific psychiatric assistance. Stroke localization on carotid artery territory, a severe disability, and absence of return to work have been reported as associated with poststroke depression [12, 41].

The poststroke headache has been reported in about 15%–20%, while poststroke seizures have been reported in about 10% [12, 33, 41].

6. Quality of Life

Few studies have evaluated specifically the quality of life after ischemic stroke in young people. In a Norwegian report, stroke had only moderate effects on self-reported health-related quality of life (HRQoL) among young adults with

ischemic stroke as a group (the most affected domain was physical functioning), although some factors were associated with marked reduction in HRQoL: functionally dependant status, fatigue, depression, unmarried status, and unemployment [46]. Other series conclude that aside from residual disability (mainly rated by MRS scale and BI), other factors which affect the quality of life are unemployment, motor impairment, aphasia, dysarthria, and dysphagia [47].

Thus, early identification and improved therapy for conditions such depression, fatigue, and physical disability may improve quality of life among young adults with ischemic stroke [46].

7. Recurrence

Recurrent stroke is frequent in the young, but lower compared with older patients, so cumulative recurrence rate at 5 years is almost 2 times lower in young (15%) than in older (29.5%) patients (Table 2) [12, 48].

The recurrence rate is higher in the first year (3%–5%) and decreases in following years (2%–5%). Thus, the annual recurrence rate between the second and twentieth year after stroke is less than 2% [10–12, 21, 33, 49] (Table 2).

Recurrence is more frequent in patients with atherothrombotic stroke (about 5% annual) than in those with stroke due to non-atherosclerotic vasculopathy (about 2%) [12].

Recurrent stroke may result in an important limitation in vital and functional prognosis, so about 15%–20% of patients died as the result of the recurrence, 30%–40% had severe handicaps with residual dependent status, and more than 50% receive permanent disability pension as a result of the recurrent stroke. These findings underline the importance of a properly secondary prevention therapy to avoid recurrence.

The predictive factors for recurrence in most of the studies are age over 35 years (RR: 1.7), the presence of cardiovascular risk factors (especially, diabetes mellitus, RR: 2.5), previous transient ischemic attack (RR: 1.5), and atherothrombotic stroke in the carotid territory (RR: 1.7). Stroke associated with migraine, stroke due to extracranial artery dissection, and patients with an unknown etiology have been associated with lower risk of recurrence [2, 12, 13, 20, 32, 33].

8. Conclusions

Although global risk of long-term death is low, first-ever ischemic stroke in young people has severe prognostic implications. The mortality risk is higher than general population, the risk of recurrent vascular events is considerable, and only about 50% of patients recover fully (without significant disability) and return to work after first-ever ischemic stroke. Several subgroups have notably increased risk of unfavorable outcomes in the long term and therefore need special attention. Thus, while the atherosclerotic risk profile is associated with the highest risk of recurrent stroke and mortality, age under 35 years and the stroke associated with dissection, migraine and/or contraceptives are associated with a good long-term outcome. Regarding young people with a long expected life span ahead, identifying factors associated to higher mortality is essential, because we can modify some of these factors with strict pharmacological control and/or invasive cardiovascular procedures in selected patients.

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