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EARLY NEUROLOGICAL DETERIORATION AFTER ACUTE STROKE; MECHANISM AND PREDICTORS

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ABSTRACT

Neurological deterioration after acute ischemic stroke (AIS)is a common occurrence, leading to increased mortality, morbidity, and poor quality of life among stroke survivors. Recognition of the individuals at a greater risk for neurological deterioration may contribute to making early decisions and monitoring the therapy. Neurological deterioration arises in up to 40% of subjects after AIS during hospitalization and is followed by neurological and functional debility. Numerous predictors have been devised that predict this progression. This includes preliminary assessment of the severity of stroke, brainstem infarction, hyperglycemia, atrial fibrillation, diabetes mellitus and substantial fluctuations in blood pressure. Sequential observations, in depth analysis, and skilled professionals in specific stroke centers are crucial in early recognition, prevention and management of neurological deterioration in AIS patients. Recent advancements in the neurological and vascular imaging have contributed to providing a better understanding of the underlying mechanisms, though several questions remain unanswered. There is an immense need to evaluate the risk of neurological deterioration after AIS. This concise review summarizes the published data and highlights the causes, mechanisms and the risk factors that influence the incidence of neurological deterioration in patients with AIS.

KEY WORDS: stroke; outcome; deterioration; mortality; AIS; ischemic stroke.

INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of morbidity and mortality in adults.[1] AIS may be followed by neurological deterioration (ND) during the first 24-72 hours, also known as clinical worsening, progressive stroke, or stroke in evolution. Although various definitions of ND have been used across different studies, a more practical definition of the ND is an increase of 4 points in the National Institutes of Health Stroke Scale (NIHSS) in major acute stroke or 2 points in NIHSS in minor stroke admitted within 24 hours of stroke onset.[2,3] The incidence of ND may rise to 40% of AIS patients during hospitalization and is associated with both short-term and long-term neurologic and functional debility.[4] Multiple risk factors have been investigated to predict this progression in AIS patients, which comprise of preliminary assessment of stroke severity, blood pressure changes, brainstem infarction, hypoglycemia, hyperglycemia, atrial fibrillation, cardiac arrest, and diabetes mellitus (DM).[5,6] We categorized ND into early neurological deterioration (END), which occurs within 24 hours of AIS; and late neurological deterioration, which occurs within 24-72 hours of AIS, although some authors have defined END up to 7 days.[7] It has been noted that even a minor deterioration in NIHSS points has been related to a worse prognosis when compared to those patients who do not deteriorate.[6] There is limited data available regarding the association between stroke etiology and risk of ND, therefore, there is an immense need to evaluate the risk of ND after AIS. This concise review summarizes the published data from the literature and highlights the risk factors that influence the occurrence of ND in subjects with AIS.

METHODS

A detailed literature search was carried out using a combination of different keywords including "Neurological deterioration, early neurological deterioration, ND, END, acute stroke, acute ischemic stroke, and AIS" in various databases like Cochrane library, PubMed, Science direct, and web of science. Inclusion criteria were (1) Adult subjects > 18 years with AIS irrespective of vascular terrain or primary mechanism; (2) reflected END as any point of deterioration throughout 24 hours after hospital admission; and (3) studies available in the English language. The literature on ND following AIS and the

risks factors associated with its progression were critically reviewed. Randomized studies, retrospective studies, cohort studies, case series, and case reports were included in our study making it to a total of 20 articles that were searched and 10 were finalized for input. While editorials, commentaries, letters to editors, and abstract conferences remained in exclusion criteria. The citations of selected articles and reviews were also hand-searched.

INCIDENCE OF END

The actual incidence of END is difficult to assess because of variable definitions of END used across different studies.[3-11] Considering the eight studies in table 1 and excluding overlapping studies, the incidence of END varies broadly from 9.9% to 37.5%.[3-11] However, the rate of prevalence of END was almost similar in the two studies that used the definition ΔNIHSS ≥4 (18% and 18.9% and 20.6%).[8,12]

PREDICTORS OF END

Numerous papers have reported and proposed variable factors that could predict END after AIS. The risk of END increases with the severity of initial stroke.[13] Hyperglycemia, Hypoglycemia, higher or lower NIHSS, elevated blood pressure, history of diabetes, coronary artery disease, use of aspirin, and longer admission delays are some of the predictors reported in the literature.[3-6] Certain other factors like age, sex, and pre-stroke level of impartiality do not commonly seem to be substantial risk aspects for END.[14] Some studies reported age as one of the factors for the onset of END.[5]

MECHANISMS OF END

Various mechanisms have been suggested to explain END after AIS. They comprise of 1) recurrent stroke As patients with AIS are at a higher risk of re-stroke in the first week but recurrent strokes noticed on diffusion-weighted MRI scans may not always produce new and discrete clinical manifestations. 2) Failure of collateralization; Occlusion of main cerebral vessels is one of the utmost significant predictors of END that leads to distal hypoperfusion unless actual circulation recanalizes. The development of collateral vessels helps in limiting the ischemic brain damage and further ensures quick recovery after an AIS. Inadequate collaterals with the resultant metabolic significances on the ischemic penumbra were reported as the most common mechanism of END. Other mechanisms of END include elevated intracranial pressure, clot progression, cerebral edema, seizures, and intraparenchymal hemorrhagic transformation. Advancements in cerebral vascular imaging have delivered a pronounced understanding of their role in END after AIS.[3-11,14]

CAUSES OF END

A limited number of studies have described the causes of END. Overall, based on the studies included in this review, only one has discussed the other causes of END apart from symptomatic intracerebral hemorrhage (sICH). Many factors have been reported so far that cause END. Malignant edema has been reported as one of the important causes of END. The prevalence of 14 % to 17 % was reported among all END patients which demonstrating -2–3% of the overall AIS sample.[8] Early recurrent ischemic stroke is reported to be an uncommon cause of END, with a prevalence of 0.6% and 1.8% in patients of acute strokes in which thrombolysis was done.[15] However, it is vital to underline the significance of an early recurrent ischemic stroke as a 100% mortality rate was reported following ND these patients.[15] Early symptomatic seizures have also been reported as the cause of END. In a vast cohort study of AIS patients treated with endovascular therapy, the prevalence of early seizures (24h) was 3.2%.[8]

RISK FACTORS ASSOCIATED WITH END

Huang et al. [16] suggested that certain factors like hyperglycemia, endovascular therapy (EVT), and hyperuricemia may be independently associated with END in AIS. Out of 213 patients attended after AIS, the prevalence of END was found in 31.9% (n=68) of the patients. Multivariate analysis revealed that END was certainly related to the glucose level in the blood, uric acid level, and treatment techniques. The most significant finding outcome was that a higher risk of END occurrence is closely associated with EVT when compared with those patients who received intravenous recombinant tissue-type plasminogen activator (rt-PA). Heck and Brown reported a greater prevalence of symptomatic transformation in patients treated with EVT when compared with IV rt-PA.[17] Another study reported an END incidence of 35.2% (44 out of 125) of the AIS patients within seven days post-stroke who underwent EVT. The majority of which (86.4%; n=38) occurred with 72 hours.[7]

Helleberg et al. [8] reviewed numerous studies to observe an association between END after AIS and the functional level of these patients at 3 months post-stroke. The authors concluded that END measured by the change of at least 2 points in Scandinavian Stroke Scale (SSS) and/or NIHSS predicted poor short-term and long-term outcomes in AIS patients and reported that SSS is not inferior to

NIHSS in measuring the END or predicting outcome in these patients. Many reasons for clinical deterioration were also reported, including vascular pathology, weakened physiological homeostasis, local effects, and biochemical disorders.[8]

Siegler et al. [6] conducted a study on 961 AIS patients to look for END and its association with the stroke etiology (as per the TOAST classification). 323 patients (34%) experienced END. The large artery strokes, particularly involving the internal carotid artery (ICA), had an independent three-time higher risk of END (OR: 3.0; 95% CI, 1.4-6.6), whereas strokes of unidentified etiology were least often associated with END (OR= 0.6; 95% CI 0.4-1.0).[6]

Another study reviewed the association of different causes of stroke, reversible and non-reversible, with the time of onset of END.[5] They had a cohort of 350 patients with AIS, 71 (20.28%) of which experienced ND and approximately half of these patients experienced END within 48 hours of a stroke. The patients with increased severity of the stroke experienced END early as compared to the patients with milder stroke. A one-point increase in the NIHSS score on admission resulted in a 3.1% shorter time to END (p=0.0034). The authors also noted that age has an inverse relation to the median onset of END, even after adjusting for different confounders, including NIHSS score on admission. For each one-year increase in patient's age, a shorter time of 3.9% to ND (p=0.0257) was reported.[5]

Malignant edema is reported as one of the causes of END and its incidence among all END24 patients ranged from 14% to 27%. Given its interval progression, malignant edema is expected to occur in later stages of END.[8] This statement would be supported by the reported prevalence of 6.5 % fatal swelling of brain in a large group of patients admitted to the hospital with circulation strokes.[18]Various mechanisms of END include elevated intracranial pressure, clot progression, cerebral edema, seizures, and hemorrhagic transformation.[14]

Deranged blood sugar levels, both hyperglycemia, and hypoglycemia, are associated with END. Moreover, hyperglycemia on admission is related to sICH after EVT in AIS with resultant poor outcomes. In experimental models, it was proposed that an acute hyperglycemia leads to an increase in cerebral lactate production, followed by brain edema, which may contribute to the early development of END.[19] Apart from deranged blood sugar levels, other factors, for instance, elevated blood pressure, smoking, coronary artery disease, use of antiplatelet agents, and admission delays are some of the risk factors for END. In many patients, the cause of END cannot be determined despite detailed investigations, such cases are referred to as unexplained End (UnEND).

Girot et al. [20] studied the AIS patients with UnEND. A total of 1925 AIS patients were included in the study, out of which 128 (6.6%) experienced UnEND. They noticed that AIS patients with non-modifiable aspects are at greater risk to experience UnEND. The main predictors of UnEND were reported to be pre-stroke modified Rankin Scale ≥2 (OR, 2.22 [95% CI, 1.09–4.55]), initial NIHSS (OR, 0.65 [95% CI, 0.52–0.81]), general anesthesia (OR, 2.55 [95% CI, 1.51–4.30]), diabetes mellitus (OR, 2.17 [95% CI, 1.32–3.56]), and elevated blood pressure (OR, 1.10 [95% CI, 1.01–1.20]).[20]

Advances in specialized stroke care units greatly improve stroke care. The stroke care units categorize the stroke patients based on their stroke severity and take active measures in high-risk patients to prevent and manage END appropriately. Rapid initiation of antithrombotic therapy and EVT results in improves morbidity. Proper monitoring of hypotension, large vessel obstruction, atrial fibrillation, hyperglycemia, and high body temperature is crucially important to prevent initial neurological deterioration and to improve the patient outcome.

FUTURE DIRECTIONS

END is more common than previously thought in AIS patients. To establish the exact incidence and prevalence of END, the global stroke community should uniformly decide and implement a widely acceptable definition of END. This will help in promoting the END research and in comparison, of the different studies to evaluate the risk factors of END and the crucial steps to prevent and manage it. Since stroke is one of the leading causes of morbidity and mortality in adults, the knowledge, prevention, and management of END along with the establishment of ubiquitous stroke care units will significantly improve the stroke outcome.

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Table 1: Incidence of END after AIS in non-overlapping studies

No.	Study	Study Type	Delay of Inclusion	Total No. of Patients (n)	Percentage of END (total)	Percentage of END in 24h
1	Mori et al., (2012)	Retrospective multicenter study	<3h	566	9.9%	9.9%
2	Baizabal-Carvallo et al., (2014)	Retrospective study	<4h 30	34	18%	NA
3	Helleberg et al., (2014)	Prospective observational study	< 24h	368	18.9%	NA
4	Seners et al., (2015)	Different studies	< 8h	2870	2.2 to 37.5%	13.8%
5	Siegler et al., (2016)	Single-Centre retrospective study	NA	961	34 %	34%
6	Siegler et al., (2017)	Prospective study	<48h	350	54.95%	25.4%
7	Huang et al., (2018)	Retrospective single center case study	<4.5h	213	31.9%	NA
8	Girot et al., (2020)	Prospective observational study	NA	1925	6.6%	NA

Abbreviations: AIS = Acute ischemic stroke; END = Early neurological deterioration; NA = Not available; CI= Confidence Interval

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Bushra Ahmad Taimuri; data collection, data analysis, manuscript writing, manuscript review
Sajid Hameed; data collection, data analysis, manuscript writing, manuscript review
Hina Imtiaz; data analysis, manuscript writing, manuscript review
Mohammad wasay; data analysis, manuscript review