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# JOURNEY OVER FOUR DECADES TO DISCOVER NEW DEFINITIONS OF STROKE AND TIA FOR 21<sup>ST</sup> CENTURY: ARE WE READY FOR THE CHANGE?

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Stroke was the second most frequent cause of death worldwide in 2012, accounting for 6.7 million deaths.<sup>(1)</sup> Approximately 17 million people had a stroke in 2010 and 33 million people have previously had a stroke and were still alive making total population of 50 million with stroke in the world.<sup>(2)</sup> Stroke is the number one preventable cause of permanent disability.<sup>(3)</sup> Projections show that by 2030, stroke prevalence will increase by more than 20% over 2012.<sup>(3)</sup> The World Health Organization (WHO) definition (1970) of stroke “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” is still frequently used.<sup>(4)</sup> This definition has been accepted by neurology community for more than 40 years despite many pitfalls. Firstly, this definition stresses on focal or global cerebral dysfunction and did not include stroke caused by brainstem, retinal or spinal cord vascular events. Secondly, few vascular events may present with headache without causing focal or global cerebral dysfunction such as mild cases of cerebral venous thrombosis and subarachnoid hemorrhage and would not fulfill this WHO definition. Thirdly, old definition also did not address silent infarction and silent cerebral hemorrhage found on neuroimaging or neuropathological examination. Fourthly, another component of this definition i.e. “global cerebral dysfunction” occurs only in special setting such as severe hypotension and after a period of cardiac arrest causing global cerebral ischemia and, in strict sense, is not a stroke syndrome. As a result oldest WHO definition of stroke has become outdated, obsolete and needed reformulation. First definition of transient ischemic attacks “TIAs” was proposed in 1964 by J. Marshall and defined such attacks as “a disturbance of neurological function of less than 24 hours’ duration occurring in the territory of supply of the carotid or vertebrobasilar arteries.”<sup>(5)</sup> In 1975, an Ad Hoc Committee on Cerebrovascular Disease published the following definition: “Transient ischemic attacks are episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours). They leave no persistent neurological deficit.”<sup>(6)</sup> When this definition was formulated, diagnostic techniques were unavailable that could determine the presence of brain infarction. The definition of TIA that was used in the 1975 report was universally cited until the beginning of the 21st century. There were two pitfalls in old definition of TIAs: duration of TIAs and lack of imaging findings. As neurological deficit may recover completely clinically within 24 hours but imaging may show evidence of infarction. Frequency of DWI abnormality in patients with transient neurological episodes of different durations was found between 30-51% in a pooled analysis from 10 MRI Studies enrolling 818 patients.<sup>(7)</sup> During the last 40 years, lot of development and progress has been made in understanding stroke and therapeutic approaches to stroke. New techniques in imaging have been developed with better understanding of stroke syndrome that has prompted attempts at new redefinition of “Stroke” and “TIAs”. The Stroke Council of the American Heart Association/American Stroke Association convened a writing group to develop an expert consensus document for an updated definition of stroke for the 21st century. In this editorial I would highlight some of these new definitions of stroke related syndromes as formulated by expert panel and has already been published in journal of “Stroke”.<sup>(8)</sup> The updated definition of stroke incorporates clinical and tissue criteria especially imaging. The term “Stroke” is broadly applicable to include all cases of CNS infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury (i.e symptoms persisting  $\geq 24$  hours or until death, and other etiologies excluded). CNS infarction also includes hemorrhagic infarctions, types I and II. Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms. Almost 50 years ago, Fisher first described the presence of cerebral infarction in the absence of any clinically apparent stroke or transient ischemic attack.<sup>(9)</sup> It is only in recent years with major advances in imaging technology, however, that ‘silent’ brain infarcts (SBI) have been studied in any detail. Silent CNS infarction is defined as imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion. The prevalence of SBI ranges from 5% to 62% in population based cohorts, most estimates falling in the 10% to 20% range. Longitudinal studies suggest an annual incidence between 2% and 4%.<sup>(10)</sup> Silent

brain infarcts increase the risk of clinical infarction by 2 to 4 times in population-based studies.<sup>(11)</sup> This led to incorporation of brain infarction into the ABCD system (ABCD2I score) which improved prediction of stroke in the acute phase after transient ischemic attack.<sup>(12)</sup> The presence of hemorrhage in ischemic infarction has forced many treating physicians to stop ischemic treatment till hemorrhage is resolved. This hemorrhagic transformation of ischemic infarction has also been more clearly defined in two categories i.e. hemorrhagic infarction and parenchymal hemorrhage with clear guidelines regarding continuation or discontinuation of anti thrombotic treatment. "Hemorrhagic infarction" is defined as hemorrhage that may occur after infarction, either spontaneously or caused by antithrombotic or thrombolytic therapy. Hemorrhagic infarction is characterized by its lack of mass effect. Hemorrhagic infarction type I is defined by petechiae of blood along the margins of the infarction, whereas type II has confluent petechiae within the infarction but without a space occupying effect. Despite presence of hemorrhage these patients are treated according to ischemic protocol and are considered cerebral infarctions. In contrast, parenchymal hemorrhage is defined by the presence of mass effect, similar to the ICH definition of a focal collection of blood. Parenchymal hemorrhage type-I is a confluent hemorrhage limited to  $\leq 30\%$  of the infarcted area with only mild space-occupying effect, and type II is  $>30\%$  of the infarcted area and/or exerts a significant space-occupying effect. These parenchymal hemorrhages parenchymal hemorrhages should be considered ICHs and may require reversal of antithrombotic therapy, aggressive antihypertensive therapy, and/or anti-edema therapy'. Similarly stroke due to intracerebral hemorrhage, Subarachnoid hemorrhage, Cerebral venous thrombosis and Stroke, not otherwise specified has been redefined by the expert panel.<sup>(8)</sup> At the end I would like to highlight recent definitions of TIA. In 2002, an expert committee proposed a new definition: "A TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction".<sup>(13)</sup> In 2009, an expert committee of the American Heart Association/American Stroke Association published a scientific statement defining TIA and recommending evaluation. The definition of transient ischemic attack (TIA) proposed was: "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction".<sup>(14)</sup> Because of the variability of duration ; there is now general agreement that a fixed time designation should not be the primary distinguishing factor between stroke and TIA. Time should be a secondary consideration when adequate imaging is unavailable. Future implications of new definitions for physicians in Pakistan. The new definitions rely more on imaging techniques especially DWI and / or PWI MRI which can detect infarction within few minutes after the arterial occlusion and even in patients who had transient vascular event on clinical ground. In Pakistan, neurological services are available only in main teaching hospitals and MRI facilities are limited to major cities. More over the use of thrombolytic therapy for acute stroke is even rare in the country. Under these circumstances treating physician would have no choice to adhere to the older definitions which are more clinical than imaging or tissue based. How we need to develop the neurological services in the country and update the knowledge of physicians with new trends and development in the world.

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