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CNS TUBERCULOSIS AND STROKE, BURDEN, MANAGEMENT CHALLENGES AND FUTURE NEEDS FOR CARE AND RESEARCH

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An estimated 10 million cases of Tuberculosis (TB) and 1.6 million deaths due to this disease occurred worldwide in 2017 (1). About 1.7 billion people, 23% of the world's population are estimated to have latent TB infection and are thus at risk of developing active TB disease during their life time. TB is mostly common in developing countries and Pakistan ranks 5th among 30 high-burden countries and 5th for Drug Resistant TB (DRTB). The incidence of TB in Pakistan is 267 per 100,000 (1) with an estimated 525,000 cases in 2017 including 57,000 cases among those who were less than 15 years of age.

In this editorial, we draw attention to stroke related to CNS-TB and its management challenges including duration of TB treatment, choice of anti-tuberculous drug regimens and the need and opportunities for collaborative research.

Tuberculous Meningitis (TBM) is one of the severe forms of extra pulmonary tuberculosis. Diagnostic difficulty and under reporting means that the true burden of TBM in the population is not known. Some estimates suggest the global burden to be at least 100,000 cases per year (2). TBM causes death and permanent disability due to severe neurologic deficits in more than half of those affected despite anti-tuberculosis chemotherapy (3-4). Furthermore, the long duration of anti-tuberculosis chemotherapy, which is currently employed causes high rates of death and severe and permanent co-morbidities such as brain damage, epilepsy, stroke, paralysis, hearing loss deafness and loss of sight or blindness (5). TBM remains a major global threat due to the dramatic rise of multi-DRTB chemotherapy, treatment compliance and the vast reservoir of latently infected individuals who may develop active disease after the initial infection.

Cerebral infarction is one of the main complications and predictors for death or permanent disability in TBM (6). An observational retrospective tertiary level hospital based study on TBM cases by Wasay et al., from Pakistan found that 25.8% of patients had cerebral infarcts on brain imaging of which three quarters were acute or subacute (7). Another study on 507 TBM cases reported that total 86 patients (17%) died. Out of these died, 35 patients (40%) died during hospital stay and out of these 35 patients, 45% had stroke identified on neuro imaging (8). The unpredictable course and prognosis seen in TBM, are a result of the heterogeneity of disease, the virulence of Mycobacterium Tuberculosis and host factors such as immune status of the individual and inter-individual variations in a person's inflammatory response.

Apart from antimicrobial treatment, an important focus in the treatment of TBM is prevention of stroke to minimize death and disability. The key challenge in this regard is to reduce the high early risk of stroke as well as other fatal and non-fatal vascular events. Published literature suggests two therapeutic strategies: Treatment with steroids and antiplatelets. Steroids have been suggested as a therapeutic option due to the neuro inflammatory response that accompanies TBM which can lead to vasculitis, vasculopathy, necrosis and even raised intracranial pressure. (9)Corticosteroids have been used for decades for treating TBM (10-11). However, despite the use of steroids, stroke has remained the most common cause of long term neurological disability and some have suggested that steroids have no effect on the incidence of stroke in TBM (10). A recent Cochrane Review found no significant benefit on neurological recovery in TBM from use of corticosteroids (11).

The other option to prevent TBM associated stroke is antiplatelet therapy (12). Aspirin has remained the most commonly prescribed agent for secondary stroke prevention worldwide (13-14). Meta-analyses indicate that aspirin is associated with 13% relative risk reduction for the secondary prevention of stroke (15). It has been shown that TBM patients who are treated with aspirin at a dose of 150 mg once a day have significantly less 3-month mortality, and a trend towards a lower incidence for stroke (16). A further study has shown that Aspirin at a dose of 81mg or 1000mg a day can

significantly reduce the risk of both death and new ischemic events (17). In pediatric populations a small cohort study showed no benefit of aspirin use at both low and high dose (18), but concluded further data collection of bigger cohorts was needed.

In western countries, antiplatelet therapy for stroke prevention includes Aspirin, Clopidogrel, and Dipyridamole, alone or in combination [19]. In Japan Cilostazole, another antiplatelet and vasodilation agent is approved for stroke prevention and its use is recommended in Japanese stroke treatment guideline [20]. It is used as direct and indirect antiplatelet agent through inhibiting platelet activation by various stimuli and by improving overall vascular endothelial function [21]. A meta-analysis of studies concluded that the Cilostazol alone significantly reduces stroke recurrence, post stroke intracranial hemorrhage, and extra cranial bleeding in patients with prior ischemic stroke when compared with other antiplatelet therapies [22]. However, to the best our knowledge, there are no studies evaluating Cilostazol in TBM stroke prevention.

A further issue complicating the management of patients with TBM is the duration of ATT treatment. Guidance from various neurological societies recommend treatment duration between 6 and 12 months [23]. The World Health Organization (WHO) recommends a 12-month treatment regime [24], but this guidance is not evidenced by high level randomized clinical trial data. One literature review concluded that 6-month treatment is sufficient for TBM with fully susceptible mycobacteria [25]. While another literature review found that the existing trials for TBM treatment are limited by low power, poor methodology and varying treatment regimens confounding results [26]. When studies are compared that have similar treatment regimes, and numbers of patients that have completed treatment, 6-months of therapy appears to be sufficient. A recent Cochrane review found no difference in relapse rates when comparing cohorts of patients who received 6 months ATT with those who received longer durations of therapy [27]. When interpreting the results from this review though caution is needed as the authors were not able to include any randomized control trials that directly compared 6 months of ATT with longer durations of treatment. Importantly, this highlights the scarcity of evidence from randomized controlled trials comparing the outcomes of short versus prolonged treatment regimens for TBM patients.

There is an urgent need to identify the most appropriate length of ATT in TBM, as longer ATT regimens are associated with poorer compliance that may contribute to developing drug resistance, complications of drug therapy and increased costs to patients and health care systems. Practice trends appear to be determined by the fear of poor outcomes associated with recurrence of the disease [28], and that available guidelines for TBM treatment are to a large extent based on the principles governing the treatment of pulmonary TB [23, 29-31], which is almost always longer than the regime thought to be needed for TBM treatment. Further confounding factors include that most published studies focus on pediatric populations, and that different guidelines recommend different treatment lengths [23].

Going forward we emphasize the need for conducting well-designed randomized controlled trials to address the challenges of treatment length, and use of antiplatelet agents to prevent TBM associated stroke. Independently evaluating the safety and efficacy of antiplatelets such as aspirin, Clopidogrel and Cilostazol at a standardized dose, directly comparing six months of ATT therapy with longer treatment regimens and long patient follow-up periods would help resolve some of this uncertainty. It is important to scientifically resolve such issues and provide clear treatment guidelines for appropriate management of TBM.

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