Review

Risk of Transverse Myelitis following Dengue Infection: A Systematic Review of the Literature

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Abstract: Introduction: Dengue virus (DENV) is the most common arbovirus disease, with wide spectrum of presentation. Spinal cord involvement in dengue infection (DF) is rare. However, the risk of transverse myelitis (TM) following Dengue has not been systematically assessed. **Methods**: We undertook a systematic review of the English literature published from January 1974 to December 2017 to assess risk of TM and outcomes following DF. Data sources included MEDLINE, EMBASE Cochrane library, and references within identified articles. **Results**: We identified 242 potential studies, 62 were duplicates. A further 136 were excluded on the basis of title and abstract and 19 studies did not meet the eligibility criteria on full text screening. We included 25 publications involving 2672 cases of DF. 10.8% (289/2672) had neurological complications, of which 2.3% (61/2672) was TM. For articles reporting epidemiological data, the neurological complication was twice in males compared to female 67.7% (130/192) vs 32.7% (62/192) and 1.5 fold increase TM for males 59.3% (32/54) vs 40.7% (22/54). The mean age at presentation was 33.1years (Range 0.75 – 61), with onset at 11.7days. The method of diagnosing TM due to DF was mainly IgM seropositivity 92% (n=23/25) and the commonest treatment modality was steroid 78.3% (n=18/23). Only half had full recovery 50.8% (n=31/61). There was no mortality following dengue, however, the crude case fatality rate following TM was 3.3% (n=2/61). **Conclusion**: This review highlights the risk of TM following dengue. Although neurological complications are rare, especially TM, once set in, it is associated with a significant morbidity.

Key words: dengue fever; transverse myelitis; risk; systematic review

Introduction

Dengue is a viral disease transmitted by the *Aedes* mosquito and is endemic in tropical and subtropical areas, in particular the Americas and Asia. This puts an estimated 4 billion people at risk of acquiring the virus; currently it is estimated 100 million cases of symptomatic dengue occur annually (1). Lack of treatment and immunisation therapy as well as inadequate vector control have meant that there are no option in the management of severe disease apart from supportive measures (1,2). In addition, with, population growth and increased inter-continental travel over the past decade, it is more likely, if no other combative measures, the number of cases will continue to increase.

The vast majority of cases are asymptomatic (1), where symptoms do occur, these commonly manifest with a fever, generalised pain and nausea and vomiting (2,3). Severity of infection has been traditionally assessed by cardiovascular compromise but most recently the addition of central nervous system (CNS) involvement as a factor of severity as the number of cases describing dengue neurotropism have come to light (2,3). This may be because factors contributing to neurological manifestations are themselves of increased severity of disease, for example prolonged shock, hepatic failure and hyponatraemia (4–6).

Damage to the spinal cord (myelitis) following infection can occur during infection (para-infectious) via direct invasion or after infection (post-infectious) via a proposed immune-mediated inflammatory process (3,7,8). Transverse-myelitis has been described in a number of case reports where the main manifestations are sensorimotor disturbance of the lower limbs and urinary retention (9–15,7). Currently the mechanisms of spinal cord damage in dengue are poorly defined and the exact burden of these neurological manifestations is yet to be fully assessed. Hence, we summarised the literature on the risks of transverse myelitis following dengue infection as well as the proposed mechanisms behind this.

Methods

2.1 Data Search and Selection

A search strategy was designed to identify case reports and observational studies (cohort study, case-control study, case series) reporting transverse myelitis as a complication of dengue viral infection. It aimed to include all publications that evaluated the current data in use of the risk of transverse myelitis (TM) following dengue virus infection globally. We searched MEDLINE and EMBASE from 1st January 1974 to 26th December 2017. Both free text and the use of medical subheadings (MeSH) terms were used as search items. An initial search was conducted in order to scope all appropriate search terms followed by a more extensive search using 2 similar search criteria. The MeSH terms and free text terms used are included in the Appendix 1.

Studies were excluded if they were individual opinion or non-availability of full text, laboratory or experimental studies, or not original research. We only included studies published in English language in our review. After the initial screening process, all publications were assessed for eligibility based on their titles followed by abstracts and full text.

2.2 Study Selection

Studies were eligible for inclusion if they reported neurological complications following dengue infection which were relevant to our study focus; to review the risk of TM following dengue infection.

Articles irrelevant to the study were excluded or if they didn't mention the risk of TM in relation to dengue infection.

Two independent reviewers (G.O. and N.B.) screened the title and abstract of papers identified by the electronic searches, evaluating inclusion and exclusion criteria for all papers. We retrieved full articles of included publications and each publication was then independently reviewed for eligibility.

2.3 Quality Assessment and Data Extraction

Two reviewers (G.O. and N.B.) independently reviewed the methodological quality of included studies, comparability of case and controls, and outcomes. The explanatory variables extracted included: study design, country, description of study subjects, underlying co-morbidity, clinical presentation, management, and outcome of the patient with TM. The study quality assessment was undertaken according to the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct and reporting of systematic reviews (16).

2.4 Data Analysis

Included studies were summarised using descriptive analyses to provide an overview of the information on populations studied, clinical presentations, underlying co-morbidity, and patient mortality outcomes. We calculated the age and sex distribution of TM generalized from the extracted data. We also calculated the risk of TM following dengue infection in children following dengue infection and compare this with that obtained in the adults for the outcome of interest where data were available. We calculated the crude fatality rate as the total number of mortality following TM divided by total number of reported TM cases over the same period. Eligible studies were then analysed qualitatively and summarised.

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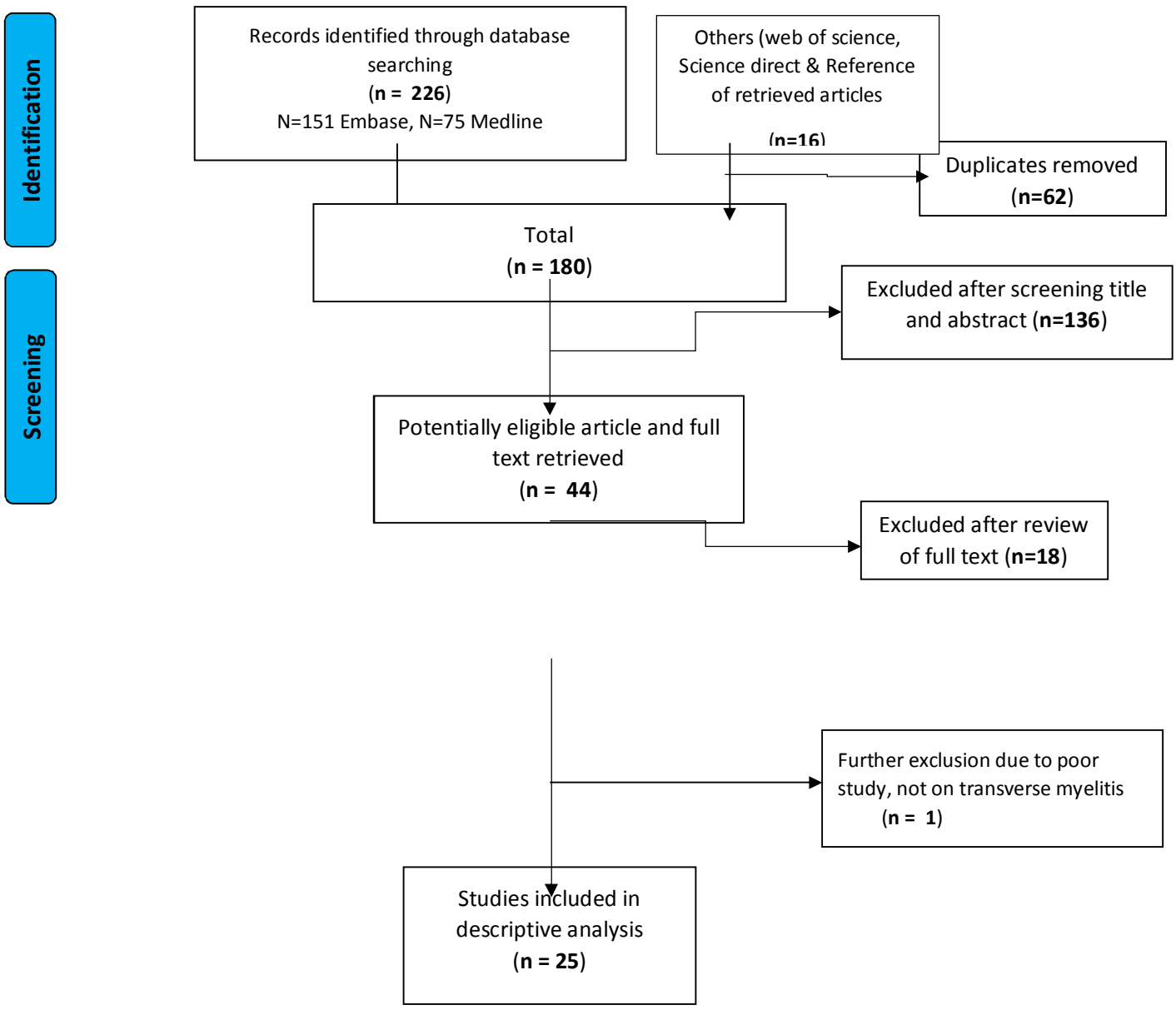

Fig. 1. Identification and selection of eligible studies in the systematic review

Results

We identified 242 potential studies, 62 were duplicates. A further 136 were excluded on the basis of title and abstract and 19 studies did not meet the eligibility criteria on full text screening (**Fig. 1**). The remaining 25 studies were eligible and the full text was assessed for inclusion in the final review (7, 9-10, 12-15, 17-34). Most of the studies were from Asia (76%; 19/25) and the rest from South America (24%; 6/25). Majority of the studies were case reports (64%; 16/25), case series (8%; 2/25), cohort study (16%,4/25), cross sectional studies (8% 2/25) and prospective study (4%; 1/25). Only 5 studies reported dengue serotype; 3 studies had serotype 1 only, serotype 2 only, and serotype 3 only. The other two

studies displayed had either dengue serotypes 1-3, or all 4 serotypes. A summary of the study design, data collection method, study subjects, and treatment is presented in Tables 1 and 2. The majority of studies did not report the ethnicity.

A total 2672 cases of Dengue fever in all ages involving 289 (10.8%; (289/2672)) with neurological complications in 25 studies were included in the final analysis (**Table 2**).

Overall 2.3% (61/2672) had TM, and children (<18 years old) constitute 13% (8/61) of TM cases reported by 6 studies. 22 studies reported epidemiological data, the neurological complication was twice in males compared to female 67.7% (130/192) vs 32.7% (62/192) and 1.5 fold increase TM for males 59.3% (32/54) vs 40.7% (22/54). The mean age at presentation was 33.1years (Range 0.75 – 61). Of the 19 papers reporting the onset of DF to the time it was complicated by TM, the average was 11.7days (Range 5-42).

All the studies reported method of diagnosing TM, and apart from the use of radiological investigation by all the studies, the method of diagnosing TM due to DF was mainly IgM seropositivity (92% (n=23/25). In addition, 12 papers mentioned, additional methods were also used in diagnosing cases of TM; cerebrospinal fluid analysis (CSF) analysis (9 studies), IgG antibodies (2 studies), clinical features and non-structural protein 1 (NS1) antigen assay (2 studies), with one other study who used an antibody index ratio of IgM to IgG.

Out of the 25 studies, 92% (n=23/25) specified their management plans. High dose methylprednisolone was used in 78 (n=18/23) of studies with additional antibiotic cover. 22% (n=5/23) studies required in addition, intravenous immunoglobulins, of which 2 had assisted ventilation and one had blood/platelet transfusions. In one of those studies, the management was conservative and 2 studies employed a symptomatic management plan. Only one study treated with antibiotics only and a laminectomy was a modality of management in one of the studies.

The commonest treatment modality was steroid 78.3% (n=18/23). In terms of recovery after, only half had full recovery 50.8% (n=31/61) from TM. There was no mortality following dengue infection reported, however, the crude case fatality rate following TM was 3.3% (n=2/61), involving a 45-year-old male and a 9-month-old male infant.

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1 **Table 1: Description of study design and reported outcome**

Study	Year of Study	Country	Study Design	Number of Dengue Cases	Diagnosis Method	Outcome
Singh et al (17)	2013	India	Case Report	1	Dengue IgM seropositivity	died
Ghosh et al (18)	2011	India	Case Report	1	Dengue IgM seropositivity CSF analysis	full recovery
Seet et al (7)	2006	Singapore	Case Report	1	Antibody index ratio of dengue IgM to IgG	full recovery
Kunishige et al (13)	2004	Singapore	Case Report	1	Dengue IgM seropositivity CSF	partial recovery
Fong CY et al (19)	2016	Malaysia	Case Report	1	Dengue IgM seropositivity	full recovery
Gupta et al (20)	2013	India	Case report	1	History, NS1 ag assay, Dengue IgM seropositivity (ELISA)	full recovery
Wasay et al (21)	2008	Pakistan	Case Series	6	Dengue IgM seropositivity according to	4 patients made a full recovery

					WHO criteria	
Samanta et al (22)	2012	India	Case Series	3	Dengue IgM seropositivity serum/viral/blood	1 patient made a full recovery
Misra et al (23)	2015	India	Case Study	116	History, Exam, NS1 ag/Dengue IgM seropositivity	101 patients recovered.
Sahu et al (24)	2014	India	Cohort	484	Dengue IgM seropositivity according to WHO criteria	5 patients died
Soars et al (25)	2006	Brazil	Cross sectional study	13	Dengue IgM seropositivity blood/CSF (ELISA) according to WHO criteria	1 patient with encephalitis died
Weeratunga et al (26)	2014	Sri Lanka	Cross Sectional Study	7	Dengue IgM seropositivity in blood/CSF according to WHO criteria.	Patients recovered after infection
Puccioni-Sohler et al (Brazil) (12)	2009	Brazil	Retrospective study	27	Dengue IgM seropositivity according to WHO criteria	Partial recovery
Larik et al (10)	2012	Singapore	Case Report	1	IgM seropositivity and Dengue RNA	Full recovery
Lim et al (27)	2012	Singapore	Case Report	1	IgM seropositivity	Partial recovery

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Tomar et al (28)	2015	India	Case Report	1	IgM seropositivity	Full recovery
Mo et al (29)	2016	China	Case Report	1	IgM seropositivity and in CSF (and IgG)	Partial recovery
Mota et al (30)	2017	Brazil	Case Report	1	IgM seropositivity	Partial recovery
Leão et al (14)	2000	Brazil	Case Report	1	IgM seropositivity and in CSF	Full recovery
Miranda de Sousa A et al (31)	2014	Brazil	Case Report	1	IgM seropositivity and in CSF	Full recovery
Renganathan et al. (32)	1996	Malaysia	Case Report	1	IgM seropositivity	Full recovery
Chanthamat et al (15)	2010	Thailand	Case Report	1	NA	Full recovery
Solomon et al (33)	2000	Vietnam	Prospective Study	1675	IgM seropositivity and in CSF, and IgG	Partial recovery
Sousa et al (9)	2004	Brazil	Retrospective Study	51	Dengue IgM seropositivity and in CSF	25 patients made a full recovery
Verma et al (34)	2011	India	Retrospective Study	26	IgM seropositivity	Partial recovery

Abbreviations: IV: intravenous; IgM: immunoglobulin M; IgG: immunoglobulin G; NA: not available; CSF: cerebrospinal fluid; ELISA: enzyme-linked immunosorbent assay; RNA: ribonucleic acid electroencephalogram; NS1: nonstructural protein 1; WHO: world health organisation.

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7 **Table 2: Characteracteristics of studies included in the systematic review**

Study	Age	Sex	Number of TM cases	Serotype	Treatment
Singh et al (17)	45	Male	1	-	T9-11 laminectomy and evacuation of epidural haematoma. Multiple blood and platelet transfusions. Conservative management also.
Ghosh et al (18)	4		1	-	High dose methylprednisolone. Packed red cell and platelet transfusion and supportive therapy for hepatitis and glomerulonephritis
Seet et al (7)	44	Female	1	-	Spinal MRI, catheterisation for urinary retention, IV methylprednisolone 1g for 5 days, intensive physiotherapy
Kunishige et al (13)	42	Male	1	1	IV methylprednisolone and antibiotics
Fong CY et al (19)	12	Female	1	-	Intubated, IV methylprednisolone 30 mg/kg/day for 3 days followed by oral prednisolone and IV Immunoglobulin (IVIG) 1 g/kg/day for 2 days. Cervical epidural haematoma was managed conservatively in addition to 6 cycles of plasma exchange.
Gupta et al (20)	26	Female	1	-	Methylprednsolone 1.0mg/5days and additional mechanical ventilation for 2 weeks
Wasay et al (21)	18-35	5 females, 1 male	1	-	MRI/CT +/- EEG observations

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Samanta et al (22)		Male	1	primary/ secondary infection	Conservative therapy
Misra et al (23)	5-70.	26 females/ 90 males	1	1, 2 and 3	-
Sahu et al (24)	25+/- 18.3	Male:Female ratio 3:1	7	-	Symptomatic and supportive treatment
Soars et al (25)	11-79.	10 female, 3 male	2	1, 2 and 3	Corticosteroids and IVIG
Weeratunga et al (26)	Mean: 35	1 female, 6 male	2	-	Methylprednisolone pulsed 1g/3days
Puccioni-Sohler et al (Brazil) (12)	22-74	Years	3	-	Methylprednisolone 1.0mg/5days and additional human IVIG 400mg/kg/5days for 1 patient
Larik et al (10)	43	Male	1	-	IVIG
Lim et al (27)	43	Male	1	-	IVIG
Tomar et al (28)	42	Male	1	-	IV Methylprednisolone
Mo et al (29)	65	Male	1	-	IV Methylprednisolone, IVIG, Plasma Exchange
Mota et al (30)	21	Male	1	-	IV Methylprednisolone
Leão et al (14)	58	Male	1	-	Ceftriaxone
Miranda de Sousa A et al (31)	11	Female	1	-	IV Methylprednisolone 1g/day followed by prednisolone

Renganathan et al. (32)	14	Female	1	-	Symptomatic treatment
Chanthamat et al (15)	61	Female	1	-	IV Methylprednisolone
Solomon et al (33)			2	-	Symptomatic treatment
Sousa et al (9)	Mean:34		26	3	IV methylprednisolone for 5 days
Verma et al (34)		8 female,18 male	1	-	IV Methylprednisolone

Abbreviations: IV: intravenous; IVIG: intravenous immunoglobulin; TM: transverse myelitis; MRI: magnetic resonance imaging; CT: computed tomography; EEG: electroencephalogram; T9-11: thoracic vertebra 9 to 11; kg: kilogram.

Discussion

A thorough systematic review of the literature identified all reported cases of TM following DF in endemic countries irrespective of the mode of presentation. Overall there were 61 cases in the literature, accounting for 2.3% of DF and the crude case-fatality rate among TM cases was very low at 3.3%. These findings, contrary to previously reported rare occurrence, confirm the prevalence of TM following Dengue. Moreover, Dengue is the most common arboviral disease (35), and occurs in Southeast Asia, East and West Africa, the Caribbean, and the Americas (36). Interestingly, the majority of TM cases were in the Asia and few reported cases in North America, the non-prevalence of TM following TM in West Africa and the Caribbean shows that the Asian population appears to be prone to autoimmune injury of the spinal cord and some genetic make-up, including the type of Dengue that causes TM might be different and contributing factor. Although neurological complications in dengue fever have been documented with all serotypes, we also observed that it is more common in serotypes 2 and 3 (33).

For example, of the 4 strains of dengue virus implicated in the disease, DEN1, DEN2, and DEN3 are the prominent serotypes in India. DEN2 has been reported in more than 75% of the cases in breakouts since 2010 (37, 38). A similar finding was observed in the review with serotype 2 been the commonly isolated, however, this was only reported in 5 of the studies.

The mechanisms of viral transmission and spinal cord injury induced by dengue virus are unclear. 2 mechanisms have been postulated. by direct invasion of the cord or by active replication within the spinal cord (13), which is common during the early phase or post-infectious immune injury (39). Since only 5 studies were able to isolate dengue IgM/IgG or antigen in the CSF, it is therefore, most likely that both mechanism have been implicated in the cases in this review.

One important finding is the 5 fold increase in neurological complication, and a 1.5 fold increase in those that had TM in females compared to males. In addition, the 2 mortalities were in males. This support the earlier studies indicating that other factors including biology, environment and experience are contributors to human health (40) but contrary to the reports that most autoimmune diseases are more frequent in women than in men (41).

There is currently no agreed consensus on the management of TM. Our findings showed that almost 80% cases were treated with high dose of methyl prednisolone despite insufficient evidence regarding the utility of steroids in treating transverse myelitis (42). It is therefore advisable that until a more robust evidence is available, administration of high-dose IV methylprednisolone will be the first treatment of choice in TM to enhance neurological functions. Few cases required immunoglobulins but this was introduced at a later stage and to those that are presumed to be very sick, assessing the efficacy at this stage becomes difficult. This have been considered mainly has second line therapy in patient who have not or poorly recovering from TM (42).

Due to the supposedly rarity of TM associated DF, there has been controversy as to the actual prevalence of TM following DF. de Sousa AM (9) and colleague in a retrospective study conducted in Brazilian Amazon region almost half of all DF cases had TM following DF (44%, 26/59), this was adduced to an epidemic of DF at the time of the study compared to the study in a tertiary centre in India where of the 116 patients with DF only 1% had TM. Our review of 2.3% of TM-associated DF, may have been underestimated and should therefore be interpreted with caution, since some post infectious TM have been known to present even months after the primary DF infection (23, 31). More importantly, is the significant morbidity associated with TM following DF, only half had a full recovery from TM before discharge with 19.7% with no reported recovery. This highlight the need for a careful evaluation of patient with DF for TM and other possible neurological complication and prompt management as high

dose steroid has shown to be effective, especially if instituted early in the management of suspected cases of TM following Dengue.

However, our results demonstrate the potential strengths of combining outcomes of rare events through a systematic review of the literature. However, the large number of case reports and lack of observational studies was a significant limitation; consequently, we were unable to conduct any meta-analyses to compare differences in other TM-associated neurological complications or calculate risks associated with clinical outcomes. In addition, as would be expected from case report several of the population denominator was not available to identify cases, this could potentially lead to double counting of the same cases. It therefore important that future studies report the number of cases of DF during the time period so that TM rate can be calculated and compared in different population.

Conclusions

This review highlights the risk of TM following dengue. Although neurological complications are rare – especially TM, once set in, it is associated with a significant morbidity. A high index of suspicion is therefore required with careful evaluation and follow-up of patients, and prompt management to enhance recovery.

Ethics approval and consent to participate

Not applicable since published articles were reviewed.

Consent for publication

Not applicable

Conflicts of interest

The author declares that they have no competing interest

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No external funding was received for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

NB reviewed the literature, analysed the data, was involved in the interpretation of the data and writing the report (including the first draft), co-ordinated the production of the manuscript, had full access to all

the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final manuscript as submitted. DA and OO carried out the initial analyses, was involved in the interpretation of the data and writing the report, and approved the final manuscript as submitted. GO conceptualised and designed the study, was involved in the interpretation of the data and writing the report, co-ordinated the production of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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