Acute Transverse Myelitis and Dengue: A Systematic Review

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Abstract

Introduction: Dengue is the most common arboviral infection in humans, being a serious public health problem in tropical and subtropical countries. Neurological manifestations of this condition include acute infectious processes by direct action of the virus or post-infectious immune-mediated inflammatory processes. Despite its epidemiological characteristics and its main clinical signs and symptoms being widely known, there are few studies on the neurological manifestations of the disease, a number that is even lower when its association with transverse myelitis is investigated.

Objectives: To identify the association between dengue and transverse myelitis described in the literature through a systematic review, and compare the reported clinical, laboratory and epidemiological data.

Methods: It was performed a systematic review of the literature using the Pubmed, Lilacs and SciELO databases by the keywords: "transverse myelitis", dengue and "dengue hemorrhagic fever", including articles published up to October 2014. After applying the inclusion and exclusion criteria, two researchers worked independently and then had a consensus meeting to resolve any differences of opinion. Seven articles were selected for analysis.

Results: From the seven selected articles we could observe that the transverse myelitis related to dengue was mostly post-infectious, being that the most affected medullary segment was the thoracic and the majority of the clinical outcomes were favorable either spontaneously or after the use of methylprednisolone for the more severe cases.

Conclusion: Transverse myelitis and dengue fever are a rare combination; however, the dengue virus should be part of the differential diagnosis for infectious and post-infectious myelitis.

Keywords: Transverse myelitis; Dengue; Dengue hemorrhagic fever

Introduction

Dengue is a viral infection, whose etiologic agent is an arbovirus of the genus Flavivirus and Flaviviridae family. This is the arbovirus that most affects the human being, affecting approximately 100 million people per year in the world. Epidemics occur frequently in tropical and subtropical countries, making it a serious public health problem [1,2].

Transverse Myelitis (TM), in turn, is a neurological syndrome that reaches from one to four people in 1 million inhabitants and its clinical diagnosis is defined by varying degrees of motor, sensory and autonomic dysfunction. The TM can be associated with different types of diseases, among which stand out systemic diseases, infections, vaccinations, radiation and vascular accidents. The idiopathic inflammatory demyelinating diseases (IIDD) of the central nervous system (CNS), may monophasically or recurrently evolve or be the initial manifestation of other conditions such as neuromyelitis optica (NMO) multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) [3].

The neurological manifestations related to dengue are exceptional occurrences and little described by literature. They may be justified by metabolic, hematological and hemodynamic changes that have occurred in the acute phase of the disease, by direct aggression of the virus to the CNS or by immunomeditated processes [4-6]. Considering the epidemiological importance of dengue and its possible complications in tropical and subtropical countries, we seek to identify, by means of a systematic review, the associations between dengue and transverse myelitis described in literature, as well as to compare the clinical data, laboratory and epidemiological reported by these publications.

Methods

A systematic review of the literature was performed, without meta-analysis, in Pubmed, Scielo and Lilacs, using the key words "transverse myelitis", "dengue" and "dengue hemorrhagic fever". The employed search strategies were: 1) In Lilacs: transverse myelitis (words) and dengue (words); 2) In Scielo: Dengue (All indices) and transverse myelitis (All indices); 3) In Pubmed: "Transverse, Myelites"[MeSH] AND (Dengue[MeSH] OR "Dengue Hemorrhagic Fever"[MeSH]), sensitized with the use of its "entry terms" "entry terms" - ("Transverse Myelopathy Syndrome" OR "Transverse Myelopathy Syndromes" OR "Transverse Myelitis" OR "Myelitis, Acute Transverse" OR "Acute Transverse Myelitis" OR "Transverse Myelitis, Acute" OR "Myelitis, Subacute Transverse" OR "Myelitides, Subacute Transverse" OR "Subacute Transverse Myelitis" OR "Transverse Myelitis, Subacute" OR "Myelitis, Paraneoplastic" OR "Paraneoplastic Myelitis" OR "Myelitis, Postinfectious" OR "Postinfectious Myelitis" OR "Myelitis, Postvaccinal"

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OR "Postvaccinal Myelitis" OR "Demyelinating Myelitis" OR "Myelitis, Demyelinative" OR "Myelitis, Necrotizing" OR "Necrotizing Myelitis") AND ("Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical" OR "Dengue Fever" OR 'Fever, Dengue' OR 'Classic Dengue' OR "Dengue, Classical"

The articles identified by the search strategy were evaluated independently and blinded by two researchers (authors), strictly obeying the inclusion criteria: full text, search time (by October 2014), the target population (children, adolescent, adult and elderly), intervention (without delimitation), study type (without delimitation) and languages (Portuguese, English and Spanish). Studies were excluded if they did not comply with the inclusion criteria described above, if they were duplicated or if they were not directly related to the proposed goal of this study (association between transverse myelitis and dengue).

With the aim to preserve the relevance of the study in question, we applied the Kappa statistical test to evaluate the concordance between the researchers. In addition, we scheduled a consensus meeting for discussions about the possible discordances.

Results and Discussion

By the strategy of the initial search, conducted in the month of October 2014, 11 articles were identified. After applying the exclusion criteria, the remaining 9 articles were independently assessed by two authors. The Kappa statistical test showed total concordance between the authors, even so, a consensus meeting was held, not changing the result of the exclusion of two articles that had already been previously excluded. The characteristics of selected and excluded studies are arranged in Table 1. Thus, as detailed in Figure 1, were included only seven studies in the final selection, which contemplated the methodological criteria, stipulated for the proposed objective of this review. The comparison between the studies is summarized in Table 2.

From the selected studies five were case reports, one was characterized as a series of 10 cases, in which three were related with the proposed subject, and other was a survey of medical records with 26 cases, which amounts to the publication thirty-four cases regarding the proposed subject, and other was a survey of medical records with 26 cases, which amounts to the publication thirty-four cases regarding the association between transverse myelitis and dengue until October 2014. Regarding the origin of articles, 57% are from Brazil, 28% in Singapore and 14% in Thailand. With respect to the year of publication, they were found in the range of 2002 to 2014. The reports showed a slight predominance of the classification in females (1.43:1) and the age ranged from 11 to 71 years, with an average age of 36 to 24 years.

The quantity of studies found reveals the scarcity of scientific literature on the topic, which indicates the rare relationship between the dengue virus and the transverse myelitis, should not ignore the fact that the late post-infectious myelitis may lead to possible underreporting. The geographical origin of the articles confirmed the predominance of dengue in tropical regions. The small number of cases considerably impaired the association between age and genre for the classification in the study, with emphasis on the case of neuromyelitis optica reported by Miranda de Sousa et al. [7] to be the sole pediatric report.

Despite of the apparent controversy in the literature regarding the classical form of dengue and neurological manifestations [8,9], the clinical classification of classical dengue was clearly defined by articles, not being described hemorrhagic complications. The myelitis was characterized by varying degrees of motor, sensory and sphincteric dysfunction, according to the clinical criteria proposed by "Transverse Myelitis Consortium Working Group" [3]. With respect to the installation of myelitis, they were in their majority (94.1% of cases) post infectious, arriving to manifest itself until 30 days after the onset of infection by dengue [10].

These manifestations reinforce the hypothesis of immune mediated mechanism where the virus could act as a trigger of the inflammatory process that has as its target forming cells of the myelin sheath. The cluster of post-dengue transverse myelitis with favorable clinical outcome corroborate this mechanism [7,11].

The titration of IgM antibodies against the dengue virus using the ELISA method is highly sensitive, confirming the laboratory diagnosis of dengue infection in all cases. The polymerase chain reaction (PCR) technique for detection of the viral genome was performed only by Leao et al. [12], however, this technique is not used routinely for epidemiological purposes [1,2].

The resonance examination of the spinal cord has confirmed the abnormalities of the neurological exam in 41.1% of the cases. The normal MRI was found in two thirds of the patients surveyed by Miranda de Sousa et al. [11], in one case described by Leao et al. [12], in one by Seet et al. [13] and in other by Puccioni Sohler et al. [10], a normal MRI does not invalidate the clinical diagnosis of transverse myelitis. The thoracic spinal cord was the most affected and T9 segment was slightly more associated with the disease compared to other spinal

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>ArticleTitle</th>
<th>Periodical</th>
<th>Type of Study</th>
<th>Inclusion/Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seet RC et al. [13]</td>
<td>2006</td>
<td>Acute transverse myelitis following dengue virus infection.</td>
<td>Journal of Clinical Virology</td>
<td>Case Report</td>
<td>Included</td>
</tr>
<tr>
<td>Larik A et al. [14]</td>
<td>2012</td>
<td>Longitudinally extensive transverse myelitis associated with dengue fever.</td>
<td>BMJ Case Rep</td>
<td>Case Report</td>
<td>Included</td>
</tr>
<tr>
<td>Shinvantan MC et al.</td>
<td>2012</td>
<td>Paralytic squint due to abducens nerve palsy: a rare consequence of dengue fever</td>
<td>BMC Infect Dis</td>
<td>Case Report</td>
<td>Excluded</td>
</tr>
<tr>
<td>Miranda de Sousa A et al. [7,11]</td>
<td>2014</td>
<td>A cluster of transverse myelitis following dengue virus infection in the brazilian amazon region</td>
<td>Tropical Medicine and Health</td>
<td>Retrospective Study</td>
<td>Included</td>
</tr>
</tbody>
</table>

Table 1: References included in the systematic review of agreement with authors, year, title of Article, periodical and data base.
### Authors 1, 2 and 3: Methodological Planning

Definition of search strategy; keywords, database, inclusion and exclusion criteria.

### Authors 2 and 3: Strategy of initial search made in October 2014.

- **Database:** PubMed
  - Keywords: “Transverse Myelites” [MeSH] AND (Dengue [MeSH] OR Dengue Hemorrhagic Fever”[MeSH] sensitized with the use of its “entry terms”. N = 09

- **Database:** ScienceDirect
  - Keywords: Dengue [All indices] and transverse myelitis [All indices] N = 01

- **Database:** Ulacs
  - Keywords: transverse myelites [Words] and Dengue [Words] N = 1

**RESULTS FROM SEARCHES (N = 11)**

- **Excluded articles (N=2)**
  - **Reason:** duplication

**SELECTED ARTICLES (N = 9)**

- **Author 2:** Reading the abstracts and application of inclusion / exclusion (2 articles excluded)
- **Author 3:** Reading the abstracts and application of inclusion / exclusion (2 articles excluded)

**Authors 2 and 3 (Consensus Meeting):** 2 articles excluded (because they are not directly related to the subject); 7 articles included for reading and systematization. N=7.

- **Case Report (N = 5)**
- **Series of Cases (N = 2)**

**Critical analysis and evaluation of the studies included in the review.**

**Figure 1:** Flowchart used for systematization of studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Patients (Gender/age)</th>
<th>Diagnosis of Dengue</th>
<th>Diagnosis of Transverse Myelitis</th>
<th>Stage of the infection</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leao et al. (2002)</td>
<td>Case Report</td>
<td>M / 58 years old</td>
<td>Fever, weakness, malaise, headache, diarrhea, ileus</td>
<td>Acute urinary Retention, drowsiness and confusion in response verbally, locomotion difficulties, flaccid paraparesis. Neurological Examination: Flaccid paralysis, muscle strength, decreased reflexes bilaterally.</td>
<td>Without changes.</td>
<td>Cerebrospinal Fluid: 21 Cells/mm³ (100% mononuclear cells); Protein: 89mg/dl; Glucose: normal</td>
<td>Negative for HIV, HTLV-I, CMV, HSV, HBV, HCV and other bloodstream pathogens; RT-PCR-negative for DEN-2 (after 12 days).</td>
</tr>
<tr>
<td>Seet et al. (2006)</td>
<td>Case Report</td>
<td>F / 44 years old</td>
<td>Fever, joint pain and rash.</td>
<td>Dengue IgM and IgG 3.40/1.64</td>
<td>Weakness of the lower limbs, urinary retention and numbness of lower limbs that arose in days of the foot climbed up to the waist in a period of 12 hours. Neurological Examination: Spastic paralysis of the lower limbs, bilateral Babinski sign, sensorial deficit (pain, proprioception and position sense articulate) below T5.</td>
<td>Without changes. (transcranial magnetic stimulation revealed central motor conduction delay level mid-thoracic).</td>
<td>Leukocytes:20 cells µl⁻¹; lymphocytes (90 %). Erythrocytes 5 cells µl⁻¹; Protein 0.78 g L⁻¹; Glucose: 2.3 MmL⁻¹. Dengue IgM/IgG: - / -; PCR-negative; HSV negative; negative for other pathogens.</td>
</tr>
<tr>
<td>Miranda de Sousa et al. (2001)</td>
<td>Case Report</td>
<td>F / 11 years old</td>
<td>Fever, myalgia, orbital pain and arthralgia.</td>
<td>Dengue IgM / IgG: -.</td>
<td>Acute Loss of vision in the right eye and weakness of the lower limbs, without sphincter dysfunction. Neurological Examination: Severe reduction of visual acuity in the right eye with papilledema, paraparesis (stage 4), hyperesthesia and signs of bilateral Babinski.</td>
<td>Hypointensia lesion in the T1 sequence and a hyperintense signal in T2 sequence between T7-T9.</td>
<td>Dengue IgM/IgG: + / -. Negative for HIV, CMV, HSV, HTLV-I IgG oligodendral band.</td>
</tr>
</tbody>
</table>

**Keywords:** Transverse Myelitis AND (Dengue [MeSH] OR Dengue Hemorrhagic Fever)”[MeSH] sensitized with the use of its “entry terms.”

**Case Report:**
- M / 58 years old
- F / 44 years old
- F / 11 years old

**Diagnosis of Dengue**
- Fever
- Malaise
- Headache
- Diarrhea
- Ileus

**Diagnosis of Transverse Myelitis**
- Acute urinary retention
- Drowsiness and confusion
- Locomotion difficulties
- Flaccid paraparesis

**Stage of the infection**
- Without changes
- Post-infection

**Intervention**
- Methylprednisolone 1g/day

**Outcome**
- Full recovery from paralysis
- Full recovery of sensory and motor functions

**Database:** PubMed
- Keywords: “Transverse Myelites” [MeSH] AND Dengue [MeSH] OR Dengue Hemorrhagic Fever”[MeSH]
- Sensitized with the use of its “entry terms.”

**Reference:**
<table>
<thead>
<tr>
<th>Case Report</th>
<th>F / 43 years old</th>
<th>Fever, rash, generalized myalgia.</th>
<th>Dengue IgM and IgG +</th>
<th><strong>Weakness in the lower limbs, paraplegia and urinary incontinence.</strong> Neurological Examination: spastic paraparesis, Babinski sign bilateral, hyperreflexia and aquilliana, sensorial level T4.</th>
<th>Hyperintense Signal on T2 sequence between T2-T10. Dengue IgM and IgG +; abnormal Protein.</th>
<th>For-infection (7 Days)</th>
<th>Methylprednisolone 1g/day for 5 days</th>
<th>After 1 year: persistence of spastic paraparesis with abnormalities of protein in cerebrospinal fluid.</th>
<th>After 5 days, the patient had significant improvement, but the urinary retention remained.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrospective study</td>
<td>11 Male patients</td>
<td>Acute febrile syndrome, severe headache, retroorbital pain, myalgia and arthalgia.</td>
<td>Dengue IgM+</td>
<td>&quot;at Nadir&quot;: plegia in the lower limbs (30.8%), associated with a moderate decrease in sensitivity in the lower limbs (65.4%) and bladder or bowel incontinence (61.5%).</td>
<td>After three months: mild weakness in the lower limbs (60.8%) associated with pyramidal signs; 61.5% had decreased in sensitivity in the lower limbs and abdomen with a higher level in the thoracic region and 7.7% had a lack of sphincter control.</td>
<td>Inflammatory spinal cord MRI lesions identified in one-third of the patients. CSF did not show any significant changes in cellularity or chemistry. Dengue IgM and IgG +.</td>
<td>Post-infection (1 to 17 days****) Five patients received methylprednisolone 1g/day for 5 days</td>
<td>Only one patient had objective neurological deficit characterized by moderate weakness in the lower limbs.</td>
<td></td>
</tr>
<tr>
<td>Case Report</td>
<td>M / 71 years old</td>
<td>Fever, orbital and articular pain, headache and vomiting.</td>
<td>Dengue IgM and IgG +</td>
<td><strong>Weakness in the lower limbs, paraplegia and urinary incontinence.</strong> Neurological Examination: spastic paraparesis, Babinski sign bilateral, hyperreflexia and aquilliana, sensorial level T4.</td>
<td>Hyperintense Signal on T2 sequence between T2-T10. Dengue IgM and IgG +; abnormal Protein.</td>
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<td>After 5 days, the patient had significant improvement, but the urinary retention remained.</td>
</tr>
<tr>
<td>Series of Cases *</td>
<td>F / 40 years old</td>
<td>Headache, skin rash, fever and myalgia.</td>
<td>Dengue IgM and IgG +</td>
<td><strong>Paraparesis and urinary incontinence.</strong> Neurological Examination: spastic paraparesis, Babinski sign bilateral, hyperreflexia, hypoesthesia of lower limbs (up to the level of the thigh).</td>
<td>Without changes. Dengue IgM and IgG +.</td>
<td>Post-infection (10 days / no report)</td>
<td>Methylprednisolone 1g/day for 5 days</td>
<td>After 10 days of the onset of symptoms: weakness of lower limbs grade 3/5, spastic function normal motor function, with signs of improvement. After 1 year: complete neurological recovery.</td>
<td>Motor Function with significant improvement in a few days.</td>
</tr>
<tr>
<td>Case Report</td>
<td>F / 26 years old</td>
<td>Myalgia, headache and fever.</td>
<td>Dengue IgM and IgG +</td>
<td>Acute lumbar PAIN, sphincter dysfunction, parasthesias and weakness in the lower limbs. Neurological Examination: spastic paraparesis, Babinski sign bilateral patalett, hyperreflexia and aquilliana, sensorial level T8.</td>
<td>Hyperintense Signal on T2 sequence between T3-T5 and T11-T12, with same results in C5-C6. Dengue IgM and IgG +.</td>
<td>Post-infection (30 days / no report)</td>
<td>Methylprednisolone 1g/day for 5 days</td>
<td>After 10 days of the onset of symptoms: weakness of lower limbs grade 3/5, spastic function normal motor function, with signs of improvement. After 1 year: complete neurological recovery.</td>
<td>Motor Function with significant improvement in a few days.</td>
</tr>
</tbody>
</table>

| Legend: (*) We studied 10 patients in this study, of these, only three had transverse myelitis associated with dengue / (**) days after the onset of dengue infection, from the first day prodrome / (***) Days after the discharge when post-infectious / (****) Days after the end of the fever; mean 4.2 days. |

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<tr>
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</table>

| Case Report | F / 61 years old | Fever, headache and generalized petechiae in lower limbs. | Hemagglutinin inhibition Test 1:10240, Hematocrit 40%, normal leukocytes, platelet count of 20mlil/mm3. | Acute urinary Retention, paraplegia, hypoesthesia. Neurological Examination: weakness of lower limbs grade 2/5 and hypotonia; Babinski sign bilateral hyperreflexia, paterlet, and aquilliana; sensory deficit at the level of T10; sensation of articular position lower limbs impaired; absence of anal sphincter tone. | Hyperintense Signal in the sequence T2, the dorsal part of the thoracic spinal cord at the level of T9-T10. Clear with opening pressure of 13 cm H2O, without cells; Glucose: 61MG/dL; Protein: 61.4MG/dL; Negative for bacteria and fungi. | For-infection (13 Days) | Methylprednisolone 1g/day - 3 consecutive days | After 10 days of the onset of symptoms: weakness of lower limbs grade 3/5, spastic function normal motor function, with signs of improvement. After 1 year: complete neurological recovery. | After 6 weeks: mobilization possible, independent, normal sensory deficits and recovery of strength in lower limbs significant; (little improvement) in relation to the function of the bladder; he was discharged with urinary catheter. |

| Case Report | M / 43 years old | Fever, rash, generalized myalgia. | Dengue IgM and RNA + / -. | Urinary retention, weakness of the lower limbs, bilateral sphincteric functions preserved. Neurological Examination: facocius paraparesis, deep tendon reflex absent in legs and reflection of Babinski changed bilaterally, sensorial level in T4. | Irregular Areas of extension T2 sequence between C2-C7; hyperintense Signal on T2 sequence diffusely spread inside the spinal cord up to T9. | For-infection (27 Days / 01 report) | Immunoglobulin B-4g/kg - 5 days; penicillin IV, azithromycin and azytlovir - 2 weeks | After 6 weeks: mobilization possible, independent, normal sensory deficits and recovery of strength in lower limbs significant; (little improvement) in relation to the function of the bladder; he was discharged with urinary catheter. | After 6 weeks: mobilization possible, independent, normal sensory deficits and recovery of strength in lower limbs significant; (little improvement) in relation to the function of the bladder; he was discharged with urinary catheter. |

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**Table 2:** Analysis of the studies included in the review, country, type of study, patients, diagnosis of dengue, diagnosis of transverse myelitis, stage of the infection, intervention and outcome.

Segments. Lesions in the cervical region were also described [10,14], with predominance in the lower cervical region.

Examination of the cerebrospinal fluid in the reviewed studies detected a breaking of the cerebrospinal fluid barrier characterized by increased proteins or by the presence of antibodies against the dengue virus. The study of oligoclonal bands when conducted was normal [7,14].

The outcome of myelitis was favorable with total recovery of vasomotor symptoms in 97% of cases, with the exception of one patient, 71 years old who developed spastic paraparesis [10], which was present even after one year of follow-up. There was a single case of permanent paraparesis of the lower limbs after six months [10] and one case of moderate weakness in the lower limbs after six months [11]. In two cases was reported the persistence of neurogenic bladder [10,14], however, in one of them, the follow-up time was very short (only five days), which weakens the verdict of this outcome; it should have been monitored for a longer period for further evaluation. The intravenous methylprednisolone in the form of pulse therapy was the drug of choice in the clinical intervention in eleven patients; however, human immunoglobulin was also used [14].

**Final Considerations**

Transverse myelitis related to infection by dengue virus are rare, the vast majority are post-infectious with a favorable clinical outcome either
spontaneously or after methylprednisolone pulse therapy. Whereas dengue epidemics are frequent in tropical and subtropical countries, the dengue virus should always be part of the differential diagnosis for infectious and post-infectious myelitis.

References