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Buspirone-associated Movement Disorder: A Literature Review

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Key words: Buspirone – MJ 9022-1 – Review – Movement disorder – Drug-induced

Abstract: Buspirone (BUS) belongs to the azapirone chemical class. The aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of BUS-associated movement disorders (MD). Relevant reports in six databases were identified and assessed by two reviewers without language restriction. A total of 25 reports containing 65 cases were assessed. The MD associated with BUS were: dyskinesia in 14 cases, 10 of akathisia, 8 of myoclonus, 6 of Parkinsonism, and 6 of dystonia. The cases not clearly defined were 7 tension, 14 incoordination, and the undefined number of dyskinesia, tics, and Parkinsonism. The mean age was 45.23 years (range: 15–74). The male was the predominant sex in 60.86% and the most common BUS-indication was anxiety disorder. The mean BUS-dose was 42.16 mg (range: 5–100). The time from the beginning of BUS administration to the MD onset was one month or less in 76%. The time from BUS withdrawal to complete recovery was within one month in 87.5%. The most common management was BUS withdrawal. In 16 patients the follow-up was reported: 14 had a full recovery, but in two (1 dyskinesia + 1 dystonia) the symptoms continued after the BUS withdrawal. MD associated with BUS were scarcely reported in the literature. Moreover, in the majority of cases, no clear description of the clinical profile, neurological examination, or the time data of the movement disorder onset and recovery were given.

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Introduction

Buspirone (BUS) belongs to the azapirone chemical class. The chemical studies of this compound began in the 1960s, in which Mead Johnson and Company was attempting to develop an antipsychotic drug with a selective interaction to dopamine receptors and a lesser number of side effects (Howland, 2015). In rhesus monkeys during the 1970s, it was noted that the BUS can lead to hypoactivity controlling aggressive behaviour but it was not effective as antipsychotics (Tompins et al., 1980); further animal studies confirmed these results (Loane and Politis, 2012). The approval by the Food and Drug Administration (FDA) in 1986 was done after one large clinical trial with more than nine hundred patients showing the safety and efficacy of the medication when compared to alprazolam, clorazepate, diazepam, and lorazepam to the management of anxiety disorders (Newton et al., 1986). At the end of the 1980s, more than thirty countries had approved BUS for clinical use including the United Kingdom (Taylor, 1988). It is worthy of mentioning that even though clinically BUS may resemble benzodiazepines, it does not have an affinity for benzodiazepine-GABA receptor complex (Loane and Politis, 2012) or has physical dependence (Griffith et al., 1986).

The azapirone medication is approved by the FDA to anxiety disorders, mainly generalized anxiety disorder, or the short-term relief of the symptoms of anxiety. In addition, BUS is used off-label for bruxism, depression (often in combination with other agents), neuropathic pain, posttraumatic stress syndrome, smoking cessation, substance abuse, and tardive dyskinesia (Howland, 2015; Wilson and Tripp, 2019). The main mechanism of action of BUS is the partial agonism to serotonin 5HT1A auto and heteroreceptors decreasing the adenylate cyclase in the raphe nuclei, cortex, and hippocampus (Eison and Temple, 1986). The interaction with this receptor probably explains the majority of the therapeutic benefits of the medication. Also, it has an antagonism to dopamine receptors, which may be involved with the rare side effects of the medication in predisposed individuals (McMillen et al., 1983). The bioavailability is less than five percent, and more than half of the drug is metabolized to the 1-(2-pyrimidinyl) piperazine (1-PP) by the cytochrome P450 3A4. The 1-PP is believed to have a greater affinity to the adrenergic α2A receptors leading to the disinhibition of the central noradrenergic system (Engberg, 1989) (Figure 1) (McMillen et al., 1983; Eison and Temple, 1986; Taylor, 1988; Wilson and Tripp, 2019).

The most common side effect related with the use of BUS is dizziness, other adverse events that occurred in more than one percent of the individuals are nausea, headache, nervousness, blurred vision, confusion, diarrhea, insomnia, myalgia, numbness, paresthesias, rash, tremor, weakness, nonspecific chest pain (Taylor, 1988; Bristol-Myers Squibb Company, 2001). The only absolute contraindication is hypersensitivity to the drug (Bristol-Myers Squibb Company, 2001). During the clinical trials to the approval of the BUS, the most frequently reported movement disorders related to this drug were incoordination and tremor (Newton et al.,
Figure 1 – Skeletal formula and pharmacodynamics of buspirone (BUS). The size of the arrow is inversely proportionally to the Ki (smaller the value stronger is the drug binds to the site). BUS acts as an agonist of the serotonin receptors (5HT1A, 2A, and 2B) and antagonists of adrenergic (α2A) and dopamine receptors (D2, 3, 4).

1986). Other abnormal movements were rarely reported and only registered after the post-marketing experience, these are struggling to diagnosis and when present significantly affect the patients’ quality of life. In this way, the aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of buspirone-associated movement disorders.

**Methods**

**Search strategy**

We searched six databases in an attempt to locate all existing reports on the movement disorders secondary to buspirone treatment published between 1985 and 2019 in electronic form. Excerpta Medica (Embase), Google Scholar, Latin American and Caribbean Health Sciences Literature (Lilacs), Medline, Scientific Electronic Library Online (Scielo), and ScienceDirect were searched. Search terms were “Parkinsonism, dyskinesia, chorea, ballism, akathisia, myoclonus, dystonia,
Table 1 – FreeText and MeSH search terms in the US National Library of Medicine

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<thead>
<tr>
<th>Category</th>
<th>Search terms</th>
<th>Results</th>
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<td>Stuttering</td>
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<td>------------------------------------------------------------------------</td>
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<td>Akathisia</td>
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<td>Tremor</td>
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<td>Chorea</td>
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<td>Ataxia</td>
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</tr>
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<td>Hypokinetic</td>
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<td>Bradykinesia</td>
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</tr>
<tr>
<td>Movement disorder</td>
<td>(((“buspirone”[MeSH Terms] OR “buspirone”[All Fields]) OR “buspiron”[All Fields]) OR “buspirone’s”[All Fields]) AND (((“movement disorders”[MeSH Terms] OR (“movement” [All Fields] AND “disorders”[All Fields])) OR “movement disorders”[All Fields]) OR (“movement”[All Fields]) AND “disorder”[All Fields]) OR “movement disorder”[All Fields])</td>
<td>93</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>604</td>
</tr>
</tbody>
</table>
restless legs syndrome, tremor, tic, restlessness, ataxia, hyperkinetic, hypokinetic, bradykinesia, movement disorder”. These terms were combined with “buspirone, MJ 9022-1” (Table 1).

Inclusion and exclusion criteria
Case reports, case series, original articles, letters to the editor, bulletins, and poster presentations published from 1985 to 2019 were included in this review with no language restriction. The two authors independently screened the titles and abstracts of all papers found from the initial search. Disagreements between the authors were resolved through discussion.

We excluded cases that the abnormal movement was not worsened or related to buspirone. Cases that had more than one factor contributing to the movement disorder were evaluated according to the probability of the event occurrence based on the Naranjo algorithm. Also, cases that were not accessible by electronic methods including direct request to the authors of the study by email were excluded. Reports that the individuals only developed tremor or ataxia after buspirone use were also not included.

Figure 2 – Flow chart of the screening process.
Data extraction
A total of 4,004 papers were found; 3,484 were irrelevant (Figure 2). When provided, we extracted author, department, year of publication, country of occurrence, number of patients affected, buspirone indication including off-label uses, time from first buspirone-dose till movement disorder onset, time from buspirone withdrawal to symptoms improvement, patient’s status at follow-up, and important findings of clinical history and management. A large percentage of the reports did not describe the management and even the onset and recovery times of movement disorder. The data were extracted by two independent authors, double-checked to ensure matching, and organized by whether the movement disorder was a side effect of the buspirone use.

Statistical analysis
Categorical variables were represented as proportions; continuous variables were represented as mean, standard deviations (SD), median, and range.

Definitions
The clinical characteristics and definitions of the movement disorders such as Parkinsonism, dyskinesia, chorea, ballism, akathisia, myoclonus, dystonia, restless legs syndrome, tremor, and tic were obtained from the reference Jankovic and Tolosa (2007). The clinical diagnosis for the psychiatric conditions was obtained from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The Naranjo algorithm was used for determining the likelihood of whether an adverse drug reaction was actually due to the drug rather than the result of other factors (Naranjo et al., 1981).

Results
For the years 1985 and 2019, a total of 25 reports containing 65 cases from eight countries who developed a movement disorder secondary to buspirone were reported (Table 2) (Hammerstad et al., 1986; Ludwig et al., 1986; Newton et al., 1986; Liegghio et al., 1988; Patterson, 1988; Ritchie et al., 1988; Strauss, 1988; Lydiard, 1989; Boylan, 1990; Brody et al., 1990; Metz, 1990; Rock, 1990; Goff et al., 1991; Kleedorfer et al., 1991; Goldberg and Huk, 1992; Naber et al., 1992; LeWitt et al., 1993; Pranzatelli et al., 1993; Bonifati et al., 1994; Coulter and Pillans, 1995; Poyurovsky and Weizman, 1997; Manos, 2000; Clay and Adams, 2003; Mejia and Jankovic, 2005; Scholtissen et al., 2006). Figure 3 shows the number of reports associated with movement disorders and BUS throughout time. The origin was North American in 56, European 6, Asian 2, and 1 Australian. The movement disorders associated with BUS were 14 dyskinesias, 10 akathisia, 8 myoclonus, 6 Parkinsonism, and 6 dystonia. The cases not clearly defined were 7 tension, 14 incoordination, and the undefined number of dyskinesia, tics, and Parkinsonism.
The following data will be only about the clearly defined group, which includes 44 individuals. The mean and median age were respectively 45.23 (SD 16.82) and 52 years (age range: 15–74 years). The male was the predominant sex in 60.86% (14/23). The indications of BUS were in decrescent order anxiety disorders in 39.39% (13/33), Parkinson’s disease (5), schizophrenia (5), myoclonus (4), panic disorders (3), akathisia (2), and dystonia (1). The mean and median BUS-dose were respectively 42.16 (SD 29.23) and 30 mg (dose range: 5–100 mg); 1 at 5 mg, 1 at 10 mg, 5 at 15 mg, 4 at 20 mg, 2 at 25 mg, 3 at 30 mg, 3 at 40 mg, 4 at 60 mg, 1 at 65 mg, 2 at 70 mg, 1 at 90 mg, 3 at 100 mg.

The time from the beginning of BUS administration to the movement disorder onset was defined by 30 individuals, the mean and median onset time were 4.6 (SD 4.6) and 4 weeks (onset range: 1 day–21 weeks). The onset time was within one month in 76% of the cases. The time from BUS withdrawal to complete recovery was defined in 8 individuals and was within one month in 7 cases. A moderate linear correlation (r: 0.4550) between the time from BUS start to movement disorder onset and BUS-dose was found.

In almost all cases that the management was reported, the BUS was withdrawn after the onset of movement disorder. Other options were BUS-dose reduction, maintenance even with the presence of the abnormal movement, and the start of other medications such as benzodiazepines, diphenhydramine, benztropine, trihexyphenidyl, baclofen, and carbidopa/levodopa. In some cases, there was a possible interaction between the medications and other drugs were also withdrawal.
together with BUS. In 16 patients the follow-up was reported; 14 had a full recovery, but in two (1 dyskinesia + 1 dystonia) the symptoms continued after the BUS withdrawal.

**Discussion**

**General**

Movement disorders associated with buspirone (BUS) were scarcely reported in the literature. It is worth mentioning that buspirone hydrochloride was the 80th most used medication with more than ten million prescriptions in 2016 (ClinCalc, 2019). In addition, the majority of the reports occurred due to possible interaction with other medications; the use of BUS and haloperidol is one example of that, which when used together, an increasing number of dyskinesias was shown, that were first thought to be related with BUS alone (Goff et al., 1991). However, clear analyses revealed that the increase in the concentration of haloperidol by BUS may be the best explanation. Another example is the interaction with fluoxetine since both can increase serotonin levels. There is a greater probability of serotoninergic syndrome when they are used together (Coulter and Pillans, 1995).

The cases that only reported ataxia and tremor were excluded from the analysis to limit the number of references and due to different reporting purposes. The incidence of these two abnormal movements with BUS is approximately one percent (Taylor, 1988). The complaints about tremors occurred since the first clinical trials; the ataxia was only post-marketing, but the trials described incoordination in their side effect lists (Newton et al., 1986). The data of Newton et al. (1986) in Table 2 were included because some reports like Boylan (1990) described that they represent dystonic cases.

Based on the cases reported in Table 2, we can describe a hypothetical case report. A North American middle-aged male presented to his psychiatrist due to the worsening of anxiety. The physician started BUS treatment with progressive increase till 10–15 mg tid. One month after in the follow-up, the individual complained of abnormal movements, and he was diagnosed with dyskinesia. BUS was withdrawn, and within one month the individual had a full recovery of the motor symptoms.

Figure 4 shows a resume of the mechanisms to explain the BUS-use for neuropathic pain (dorsal horn) and dyskinesia (dorsal raphe) (Shireen, 2016; Haleem et al., 2018). We believe that some of the movement disorders can be explained by the same process as represented by the treatment of these two pathologies. Herein, we would like to discuss some of the movement disorders in subtopics to give a better comprehension of the data.

**Dyskinesias (DKN)**

This was the most common reported movement disorder secondary to BUS, but the description of the cases was poor with all reports missing at least one important information. The age of the affected individuals was higher when compared to the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country/year</th>
<th>No. cases</th>
<th>Age/sex</th>
<th>indication</th>
<th>dose (mg)</th>
<th>start to MD</th>
<th>withdrawal to recovery</th>
<th>Follow-up</th>
<th>Important clinical history and clinical management</th>
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<td><strong>PARKINSONISM</strong></td>
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<td>Hammerstad et al.</td>
<td>USA/1986</td>
<td>2</td>
<td>54/F</td>
<td>PD</td>
<td>90</td>
<td>21 weeks</td>
<td>NR</td>
<td>NA</td>
<td>CH: BUS worsened PD. CM: BUS withdrawal</td>
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<td></td>
<td></td>
<td></td>
<td>44/F</td>
<td>PD</td>
<td>65</td>
<td>17 weeks</td>
<td>NR</td>
<td>NA</td>
<td>CH: BUS worsened PD. CM: BUS withdrawal</td>
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<td>56 (mean)/M</td>
<td>PD</td>
<td>60</td>
<td>weeks</td>
<td>weeks</td>
<td>NA</td>
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<td>Clay and Adams</td>
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<td>anxiety</td>
<td>70</td>
<td>6 weeks</td>
<td>2 weeks</td>
<td>CR</td>
<td>CH: HIV positive, possible interaction with ritonavir. CM: BUS-dose reduction with ritonavir withdrawal and amprenavir start</td>
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<td><strong>DYSKINESIA</strong></td>
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<td>PD</td>
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<td>NR</td>
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<td>No</td>
<td>CH: orofacial DKN. CM: BUS withdrawal with symptoms maintenance</td>
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<td>3 weeks</td>
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<td>CR</td>
<td>CM: BUS withdrawal</td>
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<td>CH: associated AKT to the DKN. CM: BUS withdrawal</td>
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<td>CR</td>
<td>CH: associated AKT to the DKN. CM: BUS withdrawal</td>
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<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Duration</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Notes</td>
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<td>Patterson</td>
<td>USA</td>
<td>1988</td>
<td>54</td>
<td>M</td>
<td>anxiety</td>
<td>15 days</td>
<td>CR</td>
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<tr>
<td>Brody et al.</td>
<td>USA</td>
<td>1990</td>
<td>2</td>
<td>NR</td>
<td>schizophrenia</td>
<td>30 days</td>
<td>CR</td>
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<td>Rock</td>
<td>Israel  and USA</td>
<td>1990</td>
<td>33</td>
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<td>anxiety</td>
<td>70 weeks</td>
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<td>Poyurovsky and Weizman</td>
<td>Israel</td>
<td>1997</td>
<td>19</td>
<td>M</td>
<td>AKT</td>
<td>20 days</td>
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<td>Ritchie et al.</td>
<td>USA</td>
<td>1998</td>
<td>62</td>
<td>F</td>
<td>anxiety</td>
<td>15 single-dose</td>
<td>CR</td>
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</table>

CH: BUS worsened the levodopa-induced DKN
CM: BUS withdrawal
AKATHISIA: possible interaction with alprazolam. CM: BUS withdrawal with symptoms improvement
CH: BUS withdrawal. After 7 days, BUS rechallenge caused the reappearance of AKT; BUS withdrawal with symptoms recovery
CH: BUS withdrawal and benzodiazepines started. BUS rechallenge with the reappearance of the symptoms; BUS withdrawal
CH: She developed MCL, DTN, and AKT after a single-dose. CM: BUS withdrawal; clonazepam, diphenhydramine, and benztropine start with symptoms recovery
<table>
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<th>Country/Year</th>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Duration</th>
<th>Onset</th>
<th>CH: Multifocal</th>
<th>CM:</th>
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<td>Goldberg and Huk</td>
<td>USA/1992</td>
<td>1</td>
<td>74/M</td>
<td>anxiety</td>
<td>15</td>
<td>10 days</td>
<td>1 day</td>
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<td>Pranzatelli et al.</td>
<td>USA/1993</td>
<td>4</td>
<td>15/M</td>
<td>MCL</td>
<td>15</td>
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<td>CH: BUS worsened epileptic myoclonus; apparently dose-dependent</td>
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<tr>
<td></td>
<td></td>
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<td>18/M</td>
<td>MCL</td>
<td>25</td>
<td>18 days</td>
<td>NA</td>
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</tr>
<tr>
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<td>19/F</td>
<td>MCL</td>
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<td>3 days</td>
<td>NA</td>
<td>CH: BUS worsened epileptic myoclonus</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>22/F</td>
<td>MCL</td>
<td>5</td>
<td>13 days</td>
<td>NA</td>
<td>CH: BUS worsened epileptic myoclonus</td>
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<td>Coulter and Pillans</td>
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<td>1</td>
<td>49/M</td>
<td>anxiety</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>CH: Possible interaction with fluoxetine</td>
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<td>Manos</td>
<td>USA/2000</td>
<td>1</td>
<td>37/M</td>
<td>anxiety</td>
<td>60</td>
<td>4 weeks</td>
<td>2 days</td>
<td>CH: Multifocal MCL; possible interaction with fluoxetine. CM: BUS withdrawal</td>
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<tr>
<td>Boylan</td>
<td>USA/1990</td>
<td>1</td>
<td>64/F</td>
<td>anxiety</td>
<td>40</td>
<td>4 weeks</td>
<td>months</td>
<td>CH: unilateral upper limb dystonia, later she developed athetosis in the contralateral limb. CM: BUS withdrawal. Trials with trihexyphenidyl, baclofen, and diazepam were ineffective; carbidopa/levodopa worsened the symptoms</td>
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<td>Author(s)</td>
<td>Country</td>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Duration</td>
<td>Management</td>
<td>Outcome</td>
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<tr>
<td>----------------</td>
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<td>-----------</td>
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<tr>
<td>Metz et al.</td>
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<td>1990</td>
<td>36</td>
<td>F</td>
<td>anxiety</td>
<td>20 years</td>
<td></td>
<td>CR</td>
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<tr>
<td>Naber et al.</td>
<td>Germany</td>
<td>1992</td>
<td>52</td>
<td>F</td>
<td>cervical DTN</td>
<td>100 weeks</td>
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<td>LeWitt et al.</td>
<td>USA</td>
<td>1993</td>
<td>45</td>
<td>M</td>
<td>anxiety</td>
<td>40 weeks</td>
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<td></td>
<td></td>
<td></td>
<td>54</td>
<td>M</td>
<td></td>
<td>30 6 weeks</td>
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</table>

LITERATURE REVIEWS AND CASES NOT CLEARLY DEFINED

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Country</th>
<th>Year</th>
<th>Condition</th>
<th>Details</th>
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</thead>
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<td>Ludwig et al.</td>
<td>USA</td>
<td>1986</td>
<td>tension</td>
<td>Assessment of BUS for the management of idiopathic PD in 16 individuals.</td>
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<tr>
<td>Newton et al.</td>
<td>USA</td>
<td>1986</td>
<td>incoordination</td>
<td>Assessment of BUS for the management of generalized anxiety disorder in 984 individuals. We included these “incoordination” patients because in the literature some authors classified them as being DTN.</td>
</tr>
<tr>
<td>Goff et al.</td>
<td>Canada</td>
<td>1991</td>
<td>DKN</td>
<td>Assessment of BUS for the management of anxiety in schizophrenic patients. It was observed that when administered with haloperidol, the haloperidol concentration increases leading to an increased number of DKN.</td>
</tr>
<tr>
<td>Mejia and Jankovic</td>
<td>USA</td>
<td>2005</td>
<td>tics</td>
<td>Assessment of tics in 155 individuals. The tics were associated with BUS in one patient treated for a psychiatric condition.</td>
</tr>
<tr>
<td>Scholtissen et al.</td>
<td>Netherlands</td>
<td>2006</td>
<td>PKN</td>
<td>Assessment of BUS on cognition, mood, and motor performance in 21 individuals with PD.</td>
</tr>
</tbody>
</table>

AKT – akathisia; BUS – buspirone; CH – clinical history; CM – clinical management; CR – complete recovery; DKN – dyskinesia; DTN – dystonia; F – female; M – male; MCL – myoclonus; MD – movement disorder; NA – not applicable/not available; NR – not reported; PD – Parkinson’s disease; PKN – Parkinsonism
Figure 4 – Schematic diagram of buspirone (BUS) metabolism. After ingestion, BUS goes to the liver and is metabolized by CYP 3A4 to the 1-(2-pyrimidinyl) piperazine (1-PP), which is the major BUS metabolite. The locus coeruleus, dorsal raphe, and dorsal horn of the spinal cord are some of the sites of BUS action in the central nervous system. The arrows show a resume of the mechanisms to explain the BUS-use for neuropathic pain (dorsal horn) and dyskinesia (dorsal raphe).

general data, which could represent an important factor for the development of this abnormal movement (Smith and Baldessarini, 1980). By the way, one of the cases that did not have a full recovery was reported with DKN; to be more specific, the only among the DKN that had orofacial involvement (Strauss, 1988). Some individuals had a previous diagnosis of DKN, and when BUS was used, they had a worsening of DKN (Bonifati et al., 1994).

One of the hypotheses to explain the development of DKN involves the relationship of the serotonin, dopamine, and glutamate neurotransmitters in the striatum (Figure 5) (Floresco and Magyar, 2006; Shireen, 2016; Sokoloff and Le Foll, 2017; Atoji and Sarkar, 2019). Especially antipsychotics with dopamine D2 blockage can provoke an inflammatory process and release reactive oxygen species causing an abnormal adaptation of the striatal organization, and ultimately leading to
overactivation of the direct pathway (Lepping et al., 2011). With this background, the benefit of BUS for the management of DKN is due to the agonism of 5HT1A (coupled to the Gi protein and mediates inhibitory neurotransmission) that decrease the release and synthesis of serotonin; the serotonin concentration decrease causes a reduction of 5HT2C (coupled to the Gq protein and mediates excitatory neurotransmission) activity, which reduces the release of dopamine (Shireen, 2016). We believe that in some older individuals BUS may cause a selective block of D2 more than the agonism in 5HT2A can hold. This assumption is plausible in the cases

Figure 5 – Schematic diagram of the pathophysiological mechanism of antipsychotic-induced extrapyramidal symptoms (EPS) with serotoninergic modulation. Current antipsychotics act at D2/3 receptors, in which the D2 blockage may cause EPS and disbalance glutamate/GABA in the cortex leading to interference in task-dependent neuronal activities such as decision-making. D3 receptor antagonists (F17464) regulate dopamine (DA) neurotransmission in the ventral tegmental area (VTA) contributing to the normalization of DA release in the prefrontal cortex. 5HT1A receptor agonists (buspirone and 8OHDPAT) inhibit the release and synthesis of 5HT at 5HT2C receptors decreasing the dopaminergic activity. 5HT2A/2C receptor antagonists (mianserin) free DA from the 5HT modulation influence. Dopamine (D1, 2, 3), GABA (GABA), glutamate (NMDA), and serotonin (5HT1A, 2C) receptors. Dopaminergic (DP), GABAergic (GB), glutamatergic (GL), and serotoninergic (SR) neurons. DRN – dorsal raphe nucleus.
reported and is supported by the relative longer movement disorder onset time when compared to general data.

**Akathisia (AKT)**
The AKT patients were younger than the mean data and all the subjects were males. The most frequently management was BUS withdrawal; in some reports, benzodiazepines were started (Rock, 1990). The BUS re-challenge was attempted in two cases, but in both the AKT reappeared earlier than in the first episode (Patterson, 1988; Rock, 1990). In the majority of the reports, the patients had previously used antipsychotics, so it may be a predisposition factor for the development of AKT (Jann et al., 1990). Poyurovsky and Weizman (1997) did an open-label study to investigate BUS for the treatment of acute-neuroleptic induced akathisia in 10 individuals; the therapeutic response was an improvement in 2, worsening 2, unchanged 6.

We hypothesized that the BUS-induced AKT is probably related to the noradrenergic neurotransmission. The 1-PP metabolite strongly interacts with the adrenergic α2A receptors leading to the disinhibition of the central noradrenergic system (Engberg, 1989). This can be supported by studies with animal models, which showed that noradrenaline causes the release of dopamine in the orbitofrontal cortex leading to the dopamine receptor D1 (coupled to the Gs protein and mediates excitatory neurotransmission) hyperactivation inducing AKT symptoms (Hurd et al., 2001; Dalley et al., 2008).

**Myoclonus (MCL)**
The individuals were younger, the BUS-dose were lower, and the time of movement disorder onset was shorter than the in general population. The management was drug withdrawal; benzodiazepines were also started (Ritchie et al., 1988). The presentation was apparently multifocal. The source cannot be characterized due to insufficient clinical features and the absence of electrodiagnostic studies, but we believe that was cortical origin because the use of BUS worsened MCL epileptic patients (Pranzatelli et al., 1993; Caviness and Brown, 2004). This abnormal movement was found in association with other drugs such as fluoxetine and trazodone, as a result, maybe the MCL was part of serotonin syndrome (Ables and Nagubilli, 2010).

MCL has been already associated with the deficiency and increase of serotonin (Jiménez-Jiménez et al., 2004). This is presupposed because in some individuals the use of drugs that increase the serotonin concentration like selective serotonin reuptake inhibitors showed a reduced frequency of jerks, but in other cases, the enhanced serotonin syndrome caused the increase of the frequency (Giménez-Roldán et al., 1988). An important fact is that the interaction between serotonin 5-HT1A and 5-HT2 receptors is necessary to induce MCL (Klawans et al., 1973); both receptors are involved with BUS (Taylor, 1988).
Parkinsonism (PKN)
In almost all the PKN cases, the patients had a previous diagnosis of Parkinson’s disease (PD), and when BUS was tried the bradykinesia significantly worsened (Hammerstad et al., 1986; Kleedorfer et al., 1991). The management was BUS withdrawal. In only one patient without a movement disorder, the BUS caused the occurrence of PKN (Clay and Adams, 2003). The most interesting finding was that the BUS-doses related to this abnormal movement were about twice the average. One possible explanation for the BUS-induced PKN is the blockage of dopaminergic receptors, but the agonism to the serotoninergic neurotransmission leading to a decrease of dopamine also can contribute (López-Sendón et al., 2013). Therefore, we believe that in the patients with the previous diagnosis of PD probably predominated the dopamine block, and in the patients without a movement disorder the serotoninergic pathway. This can be supported by the BUS Ki values, time of movement disorder onset, and alteration in the dopaminergic striatum throughout the time in PD (Taylor, 1988; Zhai et al., 2018).

Dystonia (DTN)
The presentation was usually focal, such as a cervical and unilateral upper limb. It manifested more frequently in females (1:2), and this feature is similar to the studies of drug-induced DTN (Swett, 1975; Jiménez-Jiménez et al., 1997). The BUS-dose was slightly higher than in the general data. A characteristic feature that differs from the literature data is the time from BUS start to the DTN onset which was the highest among the BUS-associated movement disorders, while in the majority of the drug-induced DTN the time was relatively short (Jiménez-Jiménez et al., 1997).

Boylan (1990) reported the first case of DTN and three hypotheses were proposed to the development of this abnormal movement. First, Boylan (1990) suggested that the DTN occurred due to the antagonism of dopamine receptors, which is a possible explanation for all the extrapyramidal symptoms (EPS) associated with this drug if we believe that all of them were predisposed due to a higher affinity to dopaminergic instead of serotoninergic receptors by BUS (McMillen et al., 1983). Second, Jansen (1991) proposed that the BUS-induced DTN was due to the interaction of BUS with sigma (σ) receptors; one important drawback to this assumption is that in animal studies the interaction with this receptor did not cause any abnormal movement, instead the serotonin receptors showed some influence (Paquette et al., 2009; Mohajel Nayebi and Sheidaei, 2010). Third, Jiménez-Jiménez (1991) assumed that due to the higher affinity to serotonin receptors the cause was related to the increase of serotonin. We believe that the third mechanism is the most probable in the individuals reported and some facts in rat and monkey models can support this hypothesis: serotonin reuptake inhibitors can themselves induce EPS (Korsgaard et al., 1985); antipsychotic-induced EPS is worsened by the increase of serotonin concentration (Carter and Pycock, 1977); the antagonism of serotonin receptors can alleviate DTN (Richter and Löscher, 1995).
Conclusion
In summary, movement disorders (MD) associated with BUS (buspirone) administration were encountered in descending order of frequency: dyskinesia, akathisia, myoclonus, Parkinsonism, tics, and dystonia. The Ki values of BUS may explain the mechanistic receptor preference for the occurrence of these disorders. In this context, BUS-induced akathisia is probably related to norepinephrine; myoclonus and dystonia are related to serotonin; dyskinesia and Parkinsonism to the dopamine-serotonergic hypothesis. The best management is probably the discontinuation of the offending agent in all cases of BUS-induced MD. It is worth mentioning that most of the reports not clearly describe the neurological examination, or the onset and recovery times of movement disorder.

References
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Rissardo J. P.; Caprara A. L. F.


BUS-associated Movement Disorder


Colonoscopic Finding of Patients with Lower Gastrointestinal Bleeding at Different Age Group in Eastern Part of India – An Observational Study

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Key words: Lower GI bleeding – Eastern part of India – Etiologies – Hemorrhoids – Colon carcinoma – Anal fissure – Isolated rectal ulcer – Pancolitis – Colonoscopic findings

Abstract: Incidence of lower gastrointestinal (GI) bleeding (LGIB) is increasing over time. It can be seen in all age group patients, commonly associated with pre-existing comorbidities and is one of the common indications of colonoscopy. This study was done to identify common causes of LGIB in eastern part of India, because there is no previous study from Eastern India to identify the common causes of lower GI bleeding diagnosed by colonoscopy in different age group patients. Consecutive 64 patients with LGIB were included in this study from June 2018 to March 2019. We divided our study population into three groups, such as group A (20 years to 40 years), group B (41 years to 60 years), and group C (more than 60 years). Data were entered into Excel and then transferred into SPSS version 22 for statistical analysis. Mean age of study population was 49.83 ± 19.06 years. Normal colonoscopic finding was seen in 7 patients (10.9%). Most common colonoscopic findings of our study population were hemorrhoids (n=32; 50%), anal fissure (n=11; 17.2%) and isolated rectal ulcer (n=9; 14.1%). Colorectal growth was seen in 6 patients (9.4%), among them female patients were more commonly affected than male patients. Therefore, most common causes of LGIB in eastern part of India are hemorrhoids, anal fissure and isolated rectal ulcer. Male individuals are more commonly affected by LGIB.

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Introduction

Lower gastrointestinal bleeding (LGIB) is gastrointestinal (GI) bleeding originated from a source distal to the ligament of Treitz and is commonly presented with hematochezia which is different from the clinical presentation of upper GI bleeding, which includes hematemesis and/or melena depending on the volume of bleeding and the speed of colonic transit. Approximately 85% of LGIB is from colon, 10% from bleeds are actually from upper gastrointestinal tract and present as hematochezia and 3–5% from small intestines (Dutta and Panda, 2008). Acute LGIB is arbitrarily defined as bleeding of less than three days duration leading to instability of vital signs, anemia, and/or need for blood transfusion, and chronic LGIB is defined as slow blood loss over a period of several days. Incidence of LGIB in the western countries ranges from 20.5 to 27 cases/100,000 adults. In comparison with the western countries, in India, LGIB patients are younger, mortality rate is lower and re-bleed rate is 4% (Farrell and Friedman, 2005). Lower GI bleeding has an annual incidence of hospitalization of approximately 36/100,000 population (Ghassemi and Jensen, 2013) and the colonoscopy is a primary method of investigation in presence of bleeding from lower GI tract (Dar et al., 2015; Oakland et al., 2019).

The etiology and the epidemiology of LGIB depend on the life style, dietary habits, smoking, history of drug intake, age, longevity of the population, etc. The most common cause of LGIB in UK is diverticular bleeding and the second most frequent diagnoses are hemorrhoids, fissures and rectal ulcers (Oakland et al., 2019). Diverticular disease is the most common cause of LGIB in Brazil, followed by polyps, malignancy, inflammatory bowel disease and angiodysplasia (de Souza e Benevides and dos Santos, 2016).

In Asia, however, colon diverticulosis is not common and is a much less common cause of LGIB. In the Indian experience, the etiology differs significantly. Growth/polyp are the most common colonoscopic finding in Jammu and Kashmir, India followed by inflammatory bowel lesions (Dar et al., 2015). An internal hemorrhoid is the most common cause of LGIB followed by ulcerative colitis in South India (Badiger et al., 2017). A study from USA showed that diverticular bleeding (37%) was the most common cause of severe LGIB followed by ischemic colitis (13.2%), delayed post polypectomy induced bleeding (11.1%), rectal ulcer (8.9%), internal hemorrhoids (6.4%) and colon angiomas (6.4%) (Camus et al., 2017). Another study from western country discovered that the most common causes of LGIB were diverticulosis and ischemic colitis (Diamantopoulou et al., 2017). Study from Middle East indicated that the most common colonoscopic findings of LGIB were hemorrhoids followed by diverticulosis, neoplasm, rectal ulcer, colitis and polyps respectively, and colon was normal in 14.6% patients (Alruzug et al., 2016).

There is no previous study from Eastern India to find out the common causes of lower GI bleeding in different age group patients diagnosed by colonoscopy. Aim of this study is to fill up this gap.
Material and Methods
Colonoscopies in patients with lower gastrointestinal bleeding were prospectively evaluated from June 2018 to March 2019 in the endoscopy unit of Divine Nursing Home, Kolkata, India. This study included 64 patients aged 18 years or over, who presented with hematochezia, melena with normal upper GI endoscopy. Patients with poor bowel preparation and incomplete examination were excluded. All patients were advised to take liquid diet at dinner along with two 10 mg of bisacodyl tablets on the day before procedure, while fasting over midnight. The medication used for bowel preparation in this study was two bottles of coloprep solution (each bottle contains magnesium sulphate 3.13 g + potassium 1.6 g + sodium chloride 17.5 g in 177 ml of solution). 177 ml of each bottle of coloprep solution was mixed with 573 ml of drinking water to make it 750 ml. The Boston bowel preparation scale (BBPS) was used as bowel cleanliness rating scale. When required, tissue from the colonic lesion was sent for histopathological diagnosis. The following variables were studied: gender, age, coloscopic diagnosis, histopathologic diagnosis, site of the lesion. All colonoscopies were performed by using Olympus colonoscope. We divided our study population into three groups, such as group A (20 years to 40 years), group B (41 years to 60 years), group C (more than 60 years). Data were entered into Excel and then transferred into SPSS version 22 for statistical analysis. Continuous value is expressed in the form of means ± SD, while categorical data is expressed in the form of count and percent.

Results
Out of 64 patients with LGIB, 42 (65.6%) were male and 22 (34.4%) were female. Mean age of this study population was 49.83 ± 19.06 years. Normal colonoscopic finding was seen in 7 patients (10.9%). Most common findings of our study population were hemorrhoids (n=32; 50%) (Figure 1), anal fissure (n=11; 17.2%) (Figure 2) and isolated rectal ulcer (n=9; 14.1%) (Figure 3). Anal fissure (18.2% vs. 11.9%) and rectal ulcer (9.1% vs. 4.8%) were more commonly seen in female patients than male patients. Colorectal growth (Figure 4) was seen in 6 patients (9.4%), among them female patients were more commonly affected than male patients (9% vs. 4.8%) (Table 1, Figure 5).

In our study, maximum number of patients (n=23) were in group C (more than 60 years) and group A (20 to 40 years). In group C, common causes of LGIB were hemorrhoid (n=13; 56.5%), rectal ulcer (n=5; 21.7%), telangiectasia (n=3; 13%) (Figure 6), diverticulae (n=2; 8.7%), anal fissure (n=2; 8.7%), colorectal growth (n=1; 4.3%) and pancolitis (n=1; 4.3%) (Figure 7).

In group B (41 to 60 years), among 18 patients, 12 (66.7%) and 6 (33.3%) were male and female respectively. Most common cause of LGIB in group B was hemorrhoids (n=9; 50%) and other causes were anal fissure (n=4; 22.2%), colorectal growth (n=3; 16.7%), rectal ulcer (n=1; 5.6%), pancolitis (n=1; 5.6%). Normal colonoscopic finding was in 4 patients (22.2%) in group B (Figure 8).

Common Causes of LGIB in Eastern Part of India
Figure 1 – Hemorrhoids.

Figure 2 – Anal fissure.

Figure 3 – Isolated rectal ulcer.

Figure 4 – Rectal growth.
Table 1 – Colonoscopic findings of patients with lower gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Group (A + B + C)</th>
<th>Number</th>
<th>Male</th>
<th>Female</th>
<th>Hemorrhoids</th>
<th>Anal fissure</th>
<th>Isolated rectal ulcer</th>
<th>Colorectal carcinoma</th>
<th>Pancolitis</th>
<th>Diverticulosis</th>
<th>Telangiectasia</th>
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<td>22</td>
<td>32</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(65.6%)</td>
<td>(34.4%)</td>
<td>(50%)</td>
<td>(17.2%)</td>
<td>(14.1%)</td>
<td>(9.4%)</td>
<td>(6.25%)</td>
<td>(4.68%)</td>
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<td>7</td>
<td>13</td>
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<td></td>
<td></td>
<td>(69.9%)</td>
<td>(30.4%)</td>
<td>(56.5%)</td>
<td>(21.7%)</td>
<td>(13%)</td>
<td>(8.7%)</td>
<td>(8.7%)</td>
<td>(4.3%)</td>
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</tr>
<tr>
<td>Group B (41 to 60 years)</td>
<td>n=18</td>
<td>12</td>
<td>6</td>
<td>9</td>
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<td>3</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td>(66.7%)</td>
<td>(33.3%)</td>
<td>(50%)</td>
<td>(22.2%)</td>
<td>(5.6%)</td>
<td>(16.7%)</td>
<td>(5.6%)</td>
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<tr>
<td>Group C (&gt;60 years)</td>
<td>n=23</td>
<td>14</td>
<td>9</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(60.7%)</td>
<td>(39.2%)</td>
<td>(56.5%)</td>
<td>(8.7%)</td>
<td>(21.7%)</td>
<td>(4.3%)</td>
<td>(4.3%)</td>
<td>(8.7%)</td>
<td>(13%)</td>
</tr>
</tbody>
</table>
Figure 5 – Comparison of causes of lower gastrointestinal bleeding among different groups (series 1: group A, series 2: group B, series 3: group C).

Figure 6 – Telangiectasia.

Figure 7 – Causes of lower gastrointestinal bleeding in group C (more than 60 years) patients.
Figure 8 – Causes of lower gastrointestinal bleeding in group B (41 years to 60 years) patients.

Figure 9 – Colon polyp.

Figure 10 – Causes of lower gastrointestinal bleeding in group A (20 years to 40 years) patients.

Common Causes of LGIB in Eastern Part of India
In group A (20 to 40 years), out of 23 patients, male and female patients were 16 (69.9%) and 7 (30.4%), respectively. Hemorrhoids was most common cause of LGIB (n=13; 56.5%) in this group. Other causes of LGIB were anal fissure (n=5; 21.7%), rectal ulcer (n=3; 13%), colorectal growth (n=2; 8.7%), colon polyp (n=1; 4.3%) (Figure 9), pancolitis (n=2; 8.7%), diverticulae (n=1; 4.3%) (Figure 10).

Discussion
The clinical course of LGIB can vary widely from occult bleeding to massive life-threatening hemorrhage and even death but most patients who are having LGIB have favorable outcome, self-limited course and usually stopped spontaneously. Most of the LGIB patients think that the bleeding is from hemorrhoids and take some conservative measures, and some patients are worried and anxious about the malignancy until a diagnosis is reached. Causes of LGIB show marked geographic variation. Though studies from different parts of India (Dar et al., 2015; Camus et al., 2017) showed different common causes of LGIB, our study is supported by one study from South India (Badiger et al., 2017). Hajare and Kantamaneni (2018) in their study identified that hemorrhoids (48%) followed by ulcerative colitis (24%) were the most common colonoscopic findings in patients with LGIB. Another study from South India revealed that the most common causes of LGIB in patients older than 60 years (group C) were colorectal carcinoma, followed by colitis, hemorrhoids (Morkar and Hazare, 2017), but in our study, patients older than 60 years had hemorrhoids as most common cause of LGIB followed by rectal ulcer and telangiectasia, and colorectal carcinoma was more common in group B patients. One study from Europe (Fernández et al., 1996) indicated that more frequent colonoscopic findings were polyps and diverticulae in LGIB patients. In our study, in all age group hemorrhoids followed by anal fissure were the most common causes of LGIB.

One study from Iran (Khodadoostan et al., 2018) showed that most common causes of LGIB in patients younger than 50 years were hemorrhoids followed by adenoma and diverticulae but in our study, hemorrhoids followed by anal fissure and isolated rectal ulcer were the most common findings in colonoscopy.

Colorectal growth was more common in group B than group A and C in our study and mean age of patient suffering from colorectal growth was 47 ± 12.56 years as seen in other study from India which showed mean age of 43 years (Sudarshan et al., 2013). Pancolitis was seen most commonly in group B as seen in other study (Quezada and Cross, 2012). Solitary rectal ulcerations were more common in group C followed by group A and B, and most of them have one or more of the following predisposing factors: constipation, straining during defecation and digital evacuation.

In our study, telangiectasia was seen in 4.68% of 64 patients and commonly seen in age more than 60 years (13% of group C). Zia et al. (2008) supported our study by showing 1% colonoscopic finding of telangiectasia in their research.
Main limitation of our study was small number of patients in study population; therefore large-scale study is required to validate the findings of this study.

**Conclusion**
Most common causes of LGIB in eastern part of India are hemorrhoids, anal fissure and isolated rectal ulcer. Male individuals are more commonly affected by LGIB. Colonic growth was seen more commonly in female patients. Any LGIB patient requires colonoscopy to identify the underlying cause of bleeding.

**References**


The Prevalence of Absolute and Functional Iron Deficiency Anemia in New Cases of Smear-positive Pulmonary Tuberculosis and Their Sputum Conversion Rate at the End of Intensive Tuberculosis Treatment Phase

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Key words: Tuberculosis – Smear-positive – Absolute iron deficiency anemia – Functional iron deficiency anemia – Sputum conversion

Abstract: About one third of the population is infected with tuberculosis (TB). On the other hand, iron deficiency is the most common micronutrient deficiency in the world. A number of studies have documented anemia in patients with TB, however, this study aimed to assess the prevalence of iron deficiency anemia (IDA) in patients with acid-fast bacilli (AFB) sputum smear-positive, and sputum conversion in these two groups of patients with absolute and functional IDA at the end of the second month of anti-TB therapy in Zahedan, Iran. The results of this study revealed that 91 out of 198 (45.9%) sputum positive pulmonary TB patients were anemic, and among those 72 (79.1%) had iron deficiency anemia. The overall prevalence of IDA in this study was 36.3%. In 72 patients with IDA, 54 (75%) had functional while the
remainder had absolute IDA 18 (25%). Twenty-one out of 72 (29.2%) of patients with IDA remained sputum positive and among 126 non IDA patients 47 (37.3%) had positive sputum smear at the end of intensive TB treatment phase (p=0.278). Approximately, less than half of patients with tuberculosis had anemia among them 79% had iron deficiency anemia. The frequency of functional IDA was three times more than absolute IDA. There was no statistically significant difference in sputum conversion between two groups of IDA and non-IDA patients after intensive phase of anti-TB therapy.

**Introduction**

Tuberculosis (TB) is still an important global health problem and kills about two million people annually. About a quarter of the world population is infected with TB (Moscow Declaration to End TB, 2017). Tuberculosis can present with a variety of hematological manifestations. A variety of factors have been suggested for TB-associated anemia, but the main causes attributed to it include suppression of erythropoiesis by inflammatory mediators, nutritional deficiency failure of iron utilization, and bone marrow suppression (Olaniyi and Aken’Ova, 2003; Lee et al., 2006; Zadeh et al., 2013).

Globally, iron deficiency is considered the most important contributor to the development of anemia, but other causes often coexist. Anemia has been reported in 16% to 94% of patients with pulmonary TB (Roberts et al., 1966; Cameron and Horne, 1971; Lee et al., 2006). In addition, it should be considered that iron deficiency has been associated with impaired immune function and reduced capacity to control infection (Dallman, 1987; Oppenheimer, 2001).

Functional iron deficiency is a state in which there is insufficient iron incorporation into erythroid precursors with adequate body iron stores which is detected by the presence of stainable iron in the bone marrow as well as a serum ferritin value within normal limits (Wish, 2006).

However, absolute iron deficiency anemia is characterized by low or absent bone marrow staining for iron and is distinguished from functional or relative iron deficiency, which is defined as a response to intravenous iron with an increase in hemoglobin (Hb) or a decrease in erythropoiesis-stimulating agent (ESA) requirement (Wish, 2006; Thomas et al., 2013).

If iron deficiency is an important factor related to TB-associated anemia, providing supplemental iron may be useful to increase blood hemoglobin concentrations and improve clinical outcomes in TB patients. Iron deficiency anemia was associated with a nearly 2-fold independent increase in the risk of death in a randomized clinical trial in patients with pulmonary TB in Tanzania, also showed that anemia at the initiation of tuberculosis therapy is responsible for delayed sputum conversion among pulmonary tuberculosis patients (Nagu et al., 2014).

Several studies have been conducted in this context to study the status of iron deficiency anemia in patients who had TB (Roberts et al., 1966; Cameron and
Horne, 1971; Oppenheimer, 2001). However, limited studies were carried out to demonstrate the type of IDA (functional and absolute) in TB patients and conversion rate after anti-TB treatment in these patients.

Therefore, this study aimed to investigate the prevalence of absolute and functional IDA in sputum smear-positive pulmonary TB patients and to demonstrate response to TB chemotherapy at the end of second month of treatment.

**Material and Methods**

This cross-sectional descriptive study was conducted between March 2016 and March 2017 in Zahedan, south-eastern Iran. After approving the project and getting approval from the Ethics Committee of Zahedan University of Medical Sciences, informed consent were obtained from all patients with the diagnosis of sputum smear-positive pulmonary tuberculosis and all of them were recruited into the study.

The inclusion criteria were as follow: smear-positive pulmonary tuberculosis patients over 14 years old with hemoglobin (Hb) less than 13 g/dl for male and less than 12 g/dl for female; and exclusion criteria were history of blood transfusion or blood donation in the last 3 months, history of recent iron supplementation, history of previous TB and anti-tuberculous treatment, known chronic diseases such as hepatitis, AIDS, diabetes, cancer, or other inflammatory diseases, major and bilateral cavitary lesions in lungs, history of addiction, and Hb less than 9 g/dl. Functional iron deficiency anemia is defined as transferrin saturation (TSAT) less than 20% with ferritin levels above 40 micrograms per liter and absolute iron deficiency anemia is described as TSAT less than 20% with ferritin levels below 40 micrograms per liter (Hashemi et al., 2017).

For each patient, at the beginning of study and before standard anti-TB treatment (rifampin, pyrazinamide, isoniazid, and ethambutol), serum iron (SI), total iron binding capacity (TIBC), complete blood count (CBC), and ferritin, were requested. Patients who faced the criteria of IDA were divided into two groups of absolute or functional iron deficiency anemia according to Table 1. After two months of anti-TB treatment, three sputum smears were collected in three consecutive days, and the positive and negative cases were recorded using direct smear test and acid-fast staining. Finally, data obtained from the patients were analysed using descriptive statistics, chi-square and t-test in SPSS software (version 19, SPSS Inc., Chicago, IL, USA). P<0.05 was considered significant.

**Table 1 – Criteria for functional and absolute iron deficiency anemia**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Functional IDA</th>
<th>Absolute IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>TSAT</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Ferritin</td>
<td>normal-high</td>
<td>low</td>
</tr>
</tbody>
</table>

IDA – iron deficiency anemia; Hb – hemoglobin; TSAT – transferring saturation

Iron Deficiency Anemia in Tuberculosis Patients
Results
Overall, 217 patients were examined in this study amongst those 198 new smear-positive TB patients were enrolled according to inclusion and exclusion criteria. Ninety-one (45.9%) of the patients had anemia (hemoglobin below 13 g/dl in men and 12 g/dl in women). Based on IDA criteria and considering the transferrin saturation less than 20%, seventy-two out of 91 patients had iron deficiency anemia. Therefore, the overall prevalence of IDA was 36.3 percent.

The mean age of patients with IDA was 51.38 ± 14.88 years of whom 35 (48.6%) were male and 37 (51.4%) were female. The frequency of functional iron deficiency anemia was 54 (75%) and absolute IDA was reported 18 (25%). The comparison between functional and absolute IDA, based on gender, age and duration of TB symptoms before treatment were not significantly different in TB patients (p=0.341, p=0.887, p=0.750, respectively) (Table 2).

At the end of two-month anti-TB therapy, 68 patients remained smear positive (37.3% with IDA compared to 29.2% without IDA). The difference of sputum conversion in TB patients with and without IDA was not statistically significant (p=0.278) (Table 3).

Table 2 – Distribution of gender, mean age and duration of symptoms in sputum smear-positive tuberculosis patients with iron deficiency anemia

<table>
<thead>
<tr>
<th>Gender</th>
<th>Functional IDA</th>
<th>Absolute IDA</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>28 (51.9%)</td>
<td>7 (38.9%)</td>
<td>35 (48.6%)</td>
<td>0.341</td>
</tr>
<tr>
<td>female</td>
<td>26 (48.1%)</td>
<td>11 (61.1%)</td>
<td>37 (51.4%)</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>54 (100%)</td>
<td>18 (100%)</td>
<td>72 (100%)</td>
<td></td>
</tr>
<tr>
<td>Age (year) ± SD</td>
<td>51.44 ± 13.99</td>
<td>51.94 ± 13.16</td>
<td>51.37 ± 14.88</td>
<td>0.877</td>
</tr>
<tr>
<td>Duration of symptoms (day) ± SD</td>
<td>24.70 ± 8.07</td>
<td>24.00 ± 8.06</td>
<td>24.38 ± 7.66</td>
<td>0.750</td>
</tr>
</tbody>
</table>

Table 3 – Sputum conversion rate at the end of the second month in TB patients with and without iron deficiency anemia

<table>
<thead>
<tr>
<th>Smear results</th>
<th>IDA</th>
<th>Non-IDA</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>21 (29.2%)</td>
<td>47 (37.3%)</td>
<td>68 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>51 (70.8%)</td>
<td>79 (62.7%)</td>
<td>130 (65.7%)</td>
<td>0.278</td>
</tr>
<tr>
<td>total</td>
<td>72 (100%)</td>
<td>126 (100%)</td>
<td>198 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

TB – tuberculosis; IDA – iron deficiency anemia
The frequency of positive sputum smear after 2 months of treatment with anti-TB in patients with functional and absolute IDA was 15 (27.8%) and 6 (33.3%), respectively with no significant difference (p=0.766) (Table 4).

Discussion
Tuberculosis remains a public health threat, especially in developing countries and is still a major cause of death and suffering worldwide. This devastating disease is much higher among people infected with HIV, and also higher among people affected by risk factors such as under-nutrition, diabetes and smoking (Antonucci et al., 1995; Espinal et al., 2000; Ferrara et al., 2012). On the other hand, anemia is also a major public health problem in many parts of the world. According to a study done by World Health Organization (WHO) on anemia, worldwide prevalence of anemia was 25% from 1993 to 2005 (World Health Organization, 2008). Nutritional anemia is a serious health problem globally which is primarily due to iron deficiency. The prevalence of anemia in all patients with TB was reported between 30–94% in several studies (Cameron and Horne, 1971; Oppenheimer, 2001; Lee et al., 2006). Iron deficiency may also contribute to the development of TB disease because iron deficiency compromises the immune function and reduced body capacity against infection control.

In our study we evaluated TB patients who had IDA in Zahedan, a big city situated in Sistan and Baluchestan, south-eastern Iran with the highest prevalence of TB in Iran. The incidence of all form of TB and sputum smear positive pulmonary TB was estimated 30.21 and, 19.03 per 100,000 populations, respectively in the year 2017 in Zahedan (Center for Disease Control and Prevention, 2019).

Based on the results of this study it was found that nearly half of our patients were anemic and most of them (79.1%) had IDA. The overall prevalence of iron deficiency anemia in this study was 36.3%.

According to the study done by Isanaka et al. (2012), the overall prevalence of anemia in TB patients was 64% that more than one-half of them were related to IDA. The results of this study showed no association between overall anemia or iron deficiency anemia at baseline and the risk of treatment failure at 1 month after initiation. The prevalence of anemia in our study was less than the mentioned study,

<table>
<thead>
<tr>
<th>Smear results</th>
<th>Functional IDA</th>
<th>Absolute IDA</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>15 (27.8%)</td>
<td>6 (33.3%)</td>
<td>21 (29.2%)</td>
<td>0.766</td>
</tr>
<tr>
<td>–</td>
<td>39 (72.2%)</td>
<td>12 (66.7%)</td>
<td>51 (70.8%)</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>54 (100%)</td>
<td>18 (100%)</td>
<td>72 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

TB – tuberculosis; IDA – iron deficiency anemia
but similar to our study, the majority of the patients had IDA and we did not found any association between two groups of IDA and non-IDA for sputum conversion.

In a study conducted by Lee et al. (2006), anemia was mostly associated with the female and older age and during or after anti-TB treatment, anemia was resolved in 64.6% of patients without iron intake. On the contrary, we did not find any significant relationship based on gender in the two groups of IDA and non-IDA patients and the mean ages of our patients were similar.

In another study, in female with pulmonary tuberculosis in their reproductive age, 67.5% had IDA and using tardiferon helped in enhancing the efficiency of treatment for tuberculosis in the presence of IDA (Mukhtarov and Sultanova, 2009).

It seems that geographical areas and nutritional base of the patients play important roles to determine the prevalence of IDA in TB patients and subsequently, predict their response to tuberculosis treatment (Cegielski and McMurray, 2004; Mulenga et al., 2017). Approximately, more than one-third of our TB patients had IDA and it seems reasonable that most of them owned the criteria for functional IDA which is more prevalent than absolute IDA. Expectedly, functional iron deficiency is much more prevalent than absolute iron deficiency. Based on epidemiological studies on iron deficiency showed prevalence rates varying between 29–46% for functional iron deficiency and for iron deficiency-associated anemia prevalence rates between 7–42% (Kuvibidila et al., 2004; Ludwig et al., 2013).

Being underweight has been associated with a higher risk of tuberculosis in developing countries. The fact that undernourishment can also influence iron metabolism, it would have been better to calculate BMI (body mass index) which is one of the limitations of this study.

Although the results of our study did not show any association between sputum conversion and treatment response in IDA and non-IDA patients, further research with larger sample size in different geographical regions is required to increase reliability of the studies.

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Iron Deficiency Anemia in Tuberculosis Patients
Acute Massive Pulmonary Embolism with Direct Visualization of a Free-floating Right Heart Thrombus Successfully Treated with Fibrinolysis: A Case Report

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Key words: Pulmonary embolism – Right heart thrombus – Fibrinolysis – Bedside echocardiography

Abstract: A male patient with a history of immobilization due to motor weakness, was transferred to our emergency department after syncope during physiotherapy, with recorded hypotension. Transthoracic echocardiography showed severe dilatation of the right ventricle (RV), with apex hypercontractility and almost akinetic RV free wall. The above findings, in addition to the unexpected visualization of a large, free-floating, right atrial thrombus, a rare finding associated with high mortality, readily confirmed the clinical suspicion of acute pulmonary embolism (PE) causing circulatory collapse. Intravenous fibrinolysis and vasopressor therapy were successfully administered, and hemodynamic instability was soon alleviated.

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Introduction
Venous thromboembolism is a major health problem with acute pulmonary embolism (PE) being its most serious clinical presentation (Cohen et al., 2007). PE occurs when a portion of a clot from a deep vein thrombosis breaks off, travels through the right heart, and eventually lodges in the pulmonary vasculature (Giordano et al., 2017). To this day, epidemiology of PE is difficult to determine, and its incidence is estimated around 100 to 200 cases per 100,000 people (Huang et al., 2014; Martinez et al., 2014). Well known risk factors that increase likelihood of developing PE include surgery, trauma, prolonged immobility, cancer and estrogen use (Giordano et al., 2017). Prompt diagnosis may be difficult, since its clinical signs and symptoms (dyspnea, pleuritic chest pain, cough) are non-specific. Arterial hypotension and shock are rare but important clinical presentations, indicating massive PE or severely reduced hemodynamic reserve. Given the fact that PE is a major cause of morbidity, mortality and hospitalization, when clinical presentation raises the suspicion of PE, further objective testing should be prompted (Konstantinides et al., 2014).

Case report
A 63-year-old male was transferred to our emergency department after syncope during physiotherapy, with recorded hypotension. He had a history of essential arterial hypertension [amlodipine 10 mg once daily (od), valsartan 160 mg od, nebivolol 2.5 mg od], dyslipidemia (simvastatin 10 mg od, ezetimibe 10 mg od), symptomatic hyperuricemia (allopurinol 100 mg od), depression (sertraline 50 mg od, lorazepam 1.25 mg od) and benign prostate hyperplasia (solifenacin 6 mg od, tamsulosin 0.4 mg od). He had also been diagnosed with Parkinsonism [levodopa 50 mg twice daily (bid), benserazide 12.5 mg bid, pramipexole 2.1 mg od] and syringohydromyelia with severe motor weakness, due to which he remained bedridden. The patient had been recently hospitalized because of progressive motor weakness and hyponatremia and was discharged on prophylactic anticoagulation therapy [3,500 international units (IU) of tinzaparin od] and physiotherapy recommendation.

Initial clinical examination revealed blood pressure of 70/50 millimetres of mercury (mm Hg), heart rate of 125 beats per minute, temperature of 36.6 °C and oxygen saturation of 97% on room air. His electrocardiogram showed sinus tachycardia with right bundle branch block pattern. Laboratory investigations were as follows: hemoglobin: 11.8 g/dl, total leucocyte count: 18,760 per μl with 82.5% neutrophils, serum urea: 67.46 mg/dl, AST: 85 U/l, ALT: 93.2 U/l, LDH: 387.5 U/l, CRP: 1.01 mg/dl, potassium: 2.79 mmol/l, D-dimers of 2.23 mg/dl (upper normal limit: 0.05 mg/dl) and a negative troponin test.

Patient was conscious and hypotension was initially treated with fluid resuscitation, unsuccessfully. Because of recent history of immobilization, in conjunction with persistent hemodynamic instability and D-dimers count rise, acute
Figure 1 – Bedside echocardiography revealed a large, elongated, free-floating thrombus (white arrow) in the right atrium (RA – right atrium; TV – tricuspid valve; RV – right ventricle).

Figure 2 – Right atrial thrombus (white arrow) protruding through the tricuspid valve into the right ventricle, during end diastole (RA – right atrium; TV – tricuspid valve; RV – right ventricle).
PE was suspected, and bedside transthoracic echocardiography was performed. The RV (right ventricle) was severely dilated (right/left basal ventricular diameter ratio: 1.2), with apex hypercontractility, while RV free wall was almost akinetic (McConnell’s sign). RV systolic pressure (RVSP) using tricuspid regurgitation flow was calculated 58 mm Hg. Findings above were highly indicative of massive PE. Unexpectedly, direct visualization of a large, elongated, free-floating, right atrial thrombus (Figure 1), originating from the inferior vena cava and protruding through the tricuspid valve during end-diastole (Figure 2), readily confirmed the diagnosis.

No further imaging was deemed necessary. Five thousand IU of unfractionated heparin were infused intravenously, and the patient was admitted to the coronary care unit (CCU). Since cardiothoracic surgery department is not available on site, and due to the patient’s hemodynamic instability, fibrinolysis with 100 mg of intravenous recombinant tissue plasminogen activator (rtPA – Alteplase) was initiated, along with norepinephrine, a vasopressor with known beneficial effect on RV contractility. Fibrinolytic and vasopressor therapy soon alleviated hemodynamic instability, while no right heart thrombus was visible one hour after fibrinolysis completion. Twelve hours later, vasopressor therapy was gradually withdrawn, and the patient started treatment with therapeutic dose of tinzaparin (14,000 IU od).

During his two-day stay in the CCU the patient remained hemodynamically stable. Computed tomography pulmonary angiogram (CTPA) before his discharge

Figure 3 – CTPA after fibrinolysis and hemodynamic stabilization revealed a large, residual thrombus (white arrow) in the main branch of the right pulmonary artery (CTPA – computed tomography pulmonary angiogram; RPA – right pulmonary artery).

Mobile Heart Thrombus in Pulmonary Embolism
from the CCU to the ward, demonstrated a large thrombus in the main branch of the right pulmonary artery (Figure 3). Follow-up transthoracic echocardiography on the fifth hospital day revealed normal contractility of the RV, its size being marginally normal (right/left basal ventricular diameter ratio: 0.9), RVSP of 35 mm Hg and absence of thrombi in right heart chambers. After one week of hospitalization, patient was discharged on warfarin, with an international normalized ratio (INR) target of 2.5 (between two and three).

**Discussion**

In this report, we present a case of an acute massive PE with direct echocardiographic visualization of a large, free-floating, right atrial thrombus, protruding through the tricuspid valve during end-diastole. The differential diagnosis in our case, a combination of syncope and hemodynamic instability, included acute coronary syndrome, pulmonary embolism, acute valvular dysfunction, tamponade and aortic dissection. Bedside transthoracic echocardiography is the most useful initial test in this situation and, thus, it was immediately performed. The simultaneous presence of a mobile right heart thrombus (RiHT) with severe RV dysfunction essentially confirmed the diagnosis of PE (Konstantinides et al., 2014). RiHT can be detected by echocardiography in ∼4% of PE patients, its presence being associated with high mortality (Torbicki et al., 2003; Koc et al., 2016). They can easily embolize to the pulmonary arterial tree compromising pulmonary circulation, causing severe hypoxia and sudden cardiac death, thus rendering their immediate treatment mandatory (Chapoutot et al., 1996).

The presence of a mobile RiHT, however, renders optimal treatment significantly different than anticoagulation alone, which is the standard treatment in uncomplicated PE (Torbicki et al., 2003). Recommendations for mobile RiHT treatment include fibrinolytic therapy and surgical pulmonary embolectomy. Current European Society of Cardiology (ESC) guidelines indicate systemic fibrinolysis as the treatment of choice for patients with PE and hemodynamic instability, leaving surgical embolectomy as an alternative in case fibrinolysis is absolutely contraindicated or has failed to improve hemodynamic status (Konstantinides et al., 2014). Furthermore, in 2018, Burgos et al. published a systematic review comparing the treatment strategies for patients with free-floating RiHT, reaching to the conclusion that fibrinolysis and surgical embolectomy show similar results and that the treatment of choice relies on proper individualization of the risks and benefits of both techniques. Of note, although novel anticoagulants (NOACs) are a convenient choice for long term, orally administered anticoagulation in patients with uncomplicated PE, patients who received fibrinolysis were excluded from relevant studies, leaving vitamin K antagonists (warfarin) as the only evidence-based choice for orally administered therapy in this specific population (Schulman et al., 2009, 2014; Buller et al., 2012; Agnelli et al., 2013).
Conclusion
This case demonstrates the value of bedside echocardiography in diagnostic assessment of hemodynamically compromised patients. Furthermore, acute massive PE should be a diagnosis to consider in patients presenting with hemodynamic instability. Finally, echocardiographic visualization of a mobile RiHT is a rather rare finding associated with high mortality. Thus, prompt treatment, either with fibrinolysis or with surgical thrombectomy, can be life-saving.

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Spinal Cord Tethering, a Very Rare Cause of Cauda Equina Syndrome after Lumbar Disk Surgery: A Case Report

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Abstract: Tethered cord syndrome (TCS) may rarely remain asymptomatic until degenerative or nondegenerative lumbar diseases superimpose in adulthood and expose the hidden anomaly. In such cases, different treatment options can be selected and simultaneous detethering might be considered too. We are reporting an undiscovered TCS in a young lady who underwent lumbar discectomy due to symptomatic disk extrusion and suffered complete cauda equina syndrome (CES), postoperatively.

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Introduction
In 95% of the general population, the spinal cord normally ends above or at the level of inferior aspect L2 vertebral body (Srinivas et al., 2012). Some pathologies such as thickened filum terminale, or a lipomatous lesion cause to the cord ends at the level below than L2 and result in low-lying tethered cord. In childhood, during the growth of the spine, longitudinal traction on the tethered cord can result in a neurological impairment named tethered cord syndrome (TCS). Rarely, the patients remain asymptomatic to adulthood. In some of these patients, precipitating factors such as trauma or spinal degenerative conditions exacerbate neurological symptoms, and patients can present with tethered cord syndrome (Srinivas et al., 2012; Carpineta et al., 2017). On the other hand, TCS is an error of spinal cord developmental process which could show neurological signs and symptoms in childhood or adulthood due to tension on conus medullaris (Lapsiwala and Iskandar, 2004; Yamada et al., 2004).

Injury or irritation of distal lumbosacral roots in cauda equina may lead to a complex syndrome of sensory, motor, and sphincter disturbances which named cauda equina syndrome (CES). CES or horsetail syndrome is a clinically important and troublesome condition and rarely occurs following lumbar spine surgery (Duncan and Bailey, 2011). We are going to report a case of postoperative CES in a patient with a symptomatic extruded disc with undiagnosed TCS. We report the clinical scenario and will also discuss the possible mechanisms of postoperative complications.

Case report
A 32-years-old healthy woman referred us due to intractable bilateral L5 and S1 radicular pain, mild to moderate low back pain, and feet paresthesia since three months ago. She hadn’t any sphincter problems such as frequency, urgency or incontinence. Physical examination revealed positive bilateral Lasegue’s sign, no motor or sensory deficit, and no upper motor neuron sign. On magnetic resonance imaging (MRI), we noted a voluminous extruded disk at L4/L5 level with significant compression on thecal sac (Figure 1).

The patient scheduled for lumbar discectomy. During surgery after L4 coronal hemilaminectomy and bilateral foraminotomy, we found bilateral conjoined roots; and discectomy was performed with gentle retraction of exiting roots without any intraoperative complication. Just postoperatively, we faced with a CES for which we didn’t have any explanation (except for intraoperative trauma to nerve roots secondary to the aforementioned abnormality). The patient presented with urinary retention and saddle anesthesia without any motor deficit even in S1 myotomes.

On postoperative lumbosacral MRI, thecal sac and neural elements were decompressed, but unexpectedly we detected cord tethering and a low lying conus at L4/L5 level (Figure 2). Reviewing the preoperative images revealed that this
pathology sneaked due to bolded herniated disk. So, a revision surgery for cord untethering offered to the patient but she refused.

Alternative conservative treatments such as steroids, anticholinergics and physical therapies for pelvic floor muscles failed and electrodiagnostic studies showed severe injury to S2 to S4 roots. On the last follow-up, one year after surgery, the patient revealed no significant improvement.

**Discussion**

TCS was described the last three decades and was previously known as an only pediatric defect; now, however, there is good evidence on the occurrence of tethered cord in adults and although rare is more common than previously thought.

Figure 1 – Preoperative T2 weighted sagittal and axial magnetic resonance imaging of lumbar spine showing bulky disk extrusion at L4/L5 level compressing conus medullaris of the tethered cord and exiting roots.
In most of these cases, precipitating factors such as trauma (trauma during surgery could be considered as precipitating factor in our case) or rarely spinal degeneration such as disk diseases, initiate or exacerbate symptoms and deficits (Ahn et al., 2000; Gleave and Macfarlane, 2002; Srinivas et al., 2012). Management of adult-onset tethered cord syndrome is controversial and choosing surgery is debated in literature till now, although the necessity of surgery as the main choice in pediatric cases is well-established (Iskandar et al., 2001; Kang et al., 2003; Aufschnaiter et al., 2008). It has been shown in studies that after a precipitating factor such as coughing, bending, or strenuous physical activity, all as a mechanical longitudinal traction, some symptoms may become apparent that could mimic symptoms of lumbar disc disease (maybe as was seen in our case) or spinal stenosis, but true radicular pain is rare (Srinivas et al., 2012).

The incidence of postoperative cauda equina syndrome is between 0.02 to 1% in different studies (Henriques et al., 2001). In the majority of cases, the cause is
retained disk fragment, gelfoam, excessive tension on dural sac during discectomy, epidural abscess, placement of a free epidural fat graft, vascular insufficiency and very rarely dural sac shift and venous congestion (Henriques et al., 2001; Maki et al., 2017). Our case presents postoperative CES as a complication of lumbar discectomy for spinal disc protrusion in a patient with an unknown tethered cord till adulthood. Theoretically, the cause of postoperative CES after that surgery could be the result of tension on sacral nerve roots and the tethered cord. In such cases, motor deficit is almost always present and its return signals a better prognosis (Ahn et al., 2000; Jensen, 2004) in contrast to what happened to our patient.

Reviewing the preoperative MRI sequences demonstrated low lying conus and tethered cord, but the massive disk herniation misled us and obscured coexisting TCS, so the surgical technique was chosen as a routine lower lumbar discectomy procedure. Surely, these special cases should be managed as a thoracic disc herniation. In this case, decompression of neural elements must be performed with minimal traction on the dural sac, for example using transfacet or even anterolateral approaches (Endo et al., 2014; Carpineta et al., 2017). Moreover, intraoperative neuromonitoring could be used before the surgery, if the diagnosis of TCS would be made preoperative. We think it could be helpful for the avoidance of neurological complications; although neuromonitoring findings are not always predictive (Cole et al., 2014).

Although untethering procedure during or after the decompressive surgery in such cases is still in question, especially if patients symptoms could be attributed only to herniated disk and nerve root compression (Endo et al., 2014; Carpineta et al., 2017); it seems that untethering in our case after clarifying underlying disease should be advisable. However, a bright signal on T2 weighted images on postoperative MRI in conus medullaris points to concomitant traumatic contusion within the terminal of cord and poor prognosis for any further treatment (Ramon et al., 1997).

Conclusion
Although TCS is a rare incidental finding in adult patients, it should be searched in imaging of any patient whose main problem in lumbar spine is a different pathology. In such cases diagnostic and therapeutic measures would be remarkably different too.

References


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