Assessment of Cauda Equina Syndrome Progression Pattern to Improve Diagnosis

Jing-Chuan Sun, PhD,* Tao Xu, PhD,* Ke-Fu Chen, PhD,* Wei Qian, MMed† Kun Liu, PhD,* Jian-Gang Shi, PhD,* Wen Yuan, MD,* and Lian-Shun Jia, MD*

Study Design. Meta-analysis of individual patient data.

Objective. To date, the progression pattern of cauda equina syndrome (CES) has not been summarized. This study assessed individual patient data from CES cases, investigated the CES progression pattern to help clinicians provide timely diagnoses.

Summary of Background Data. Because there were few randomized controlled trials about CES, our research was based on case reports of CES with detailed medical history.

Methods. We searched English literature regarding CES in the PubMed database. We included a total of 198 publications involving 264 cases that met the inclusion criteria. The occurrence order of symptoms was determined by reviewing patients’ medical histories, and the progression pattern of CES was analyzed using sequential pattern mining. Finally, we summarized and reassessed the current timing of CES diagnosis.

Results. Result of sequential pattern mining demonstrated that the progression process of CES could be divided into 3 stages: early stage of CES (CESE), with bilateral peripheral nerve dysfunction characterized by progressive sensory-motor defects from unilateral to bilateral in lower extremities; incomplete CES, with reduction of sphincter functions; and CES in retention, with sphincter dysfunction. Among all the cases, 81.08% (180 cases) were diagnosed at the stage of incomplete CES or CES in retention, in which 99.4% (179 cases) had experienced CESE without being diagnosed.

Conclusion. The characteristic progressive sensory-motor CESE defects in lower extremities marked CES onset. Instead of waiting for the onset of sphincter function abnormalities, CES should be diagnosed when the CESE symptoms manifest.

Key words: cauda equina syndrome, progression pattern, diagnosis.

Level of Evidence: 3

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Cauda equina syndrome (CES) develops as a result of multiple cauda equina lesions that can be caused by lumbar intervertebral disc prolapse, intraspinal tumor, epidural hematoma, lumbar anesthesia, spinal manipulation, or infection. It is a surgical emergency that involves multiple disciplines, including orthopedics, neurosurgery, obstetrics, and anesthesiology.

Bladder, bowel, and sexual dysfunction that occur during fully developed CES cause great pain and economic burden to patients, which often result in malpractice litigation. The average compensation for litigation over CES is £336,000 per case in the United Kingdom and $549,427 per case in the United States. It is reported that the major reason for these settlements is delayed diagnosis of CES, which results in poor patient prognosis. Although typical CES onset is often described as the acute exacerbation of low back pain and/or unilateral sciatica followed by bladder and/or bowel dysfunction, how CES progresses can vary greatly depending on primary disease, spinal segments involved, speed of onset, and individual differences; therefore, the exact pattern of CES progression is still unclear. Thus, doctors have not reached a consensus whether patients with CES symptoms other than bladder or bowel dysfunction can be diagnosed with CES. These CES symptoms include bilateral motor power abnormality, bilateral sciatica, paresthesia of lower extremities and bilateral perineal region, and sexual dysfunction. The ambiguous diagnostic criteria for CES often result in delayed diagnosis in clinical practices.

The purpose of this study was to investigate the progression pattern of CES by extracting individual patient data from existing publications concerning CES. The occurrence order of symptoms of each CES case was recorded and used to analyze the progression pattern of CES using sequential pattern mining. The current timing of diagnosis was summarized and reassessed to help clinicians timely diagnose CES.
MATERIALS AND METHODS

Search Strategy
We conducted a systematic search of the MEDLINE/PubMed service of the US National Library of Medicine using the MeSH (medical subject heading) terms “polyradiculopathy” and “cauda equina syndrome” for articles published in English. We saved our searches to a PubMed “My NCBI” account and signed up for automatic e-mail updates to the searches. A total of 1272 articles were found up to May 2013.

Inclusion and Exclusion Criteria
Inclusion criteria were a definite diagnosis of CES and a detailed medical history of CES in the publications. Cases were excluded if the occurrence order of CES symptoms was not or could not be recorded, that is, the authors did not report the occurrence order of each CES symptom in detail; it was difficult to obtain the medical history due to long disease duration; or the patients were too young to describe the symptoms or unable to undergo thorough physical examinations.

Data Management
After removing duplicate cases, a total of 198 publications involving 264 cases were included. All publications were independently read by 2 clinicians, and a third clinician was consulted in the event of disagreement. The sex, age, nationality, primary disease, injured spinal segment, and symptoms of primary diseases were input into EpiData software (EpiData Association, Denmark).24 Symptoms prior to CES onset included low back pain, referred pain, unilateral sciatica, and paresthesia in unilateral lower extremity. Patient medical histories were reviewed, and the occurrence order of 12 CES symptoms was recorded. Each symptom was represented with a corresponding code (E01-E12, Table 1) separately in the software, and the occurrence order was numerically expressed: 1 indicated the initial symptom, and 2 indicated the secondary symptom. Symptoms that occurred simultaneously were recorded with the same number. All data processing and analyses were performed with R software (version 2.15.1; “R & R” of the Statistics Department of the University of Auckland, Auckland, New Zealand). Varying descriptions of CES symptoms were summarized into 12 CES symptoms as described in Table 1.

CES Progression Pattern Analysis
The medical histories of all patients with CES were read carefully, and the occurrence order of the 12 CES symptoms was recorded. Cases with simultaneous occurrence of all symptoms, with sphincter dysfunction, were defined as acute onset. Given that these patients’ symptoms had no occurrence order, these cases were not included in the CES progression pattern analysis. After acute onset cases were

<table>
<thead>
<tr>
<th>TABLE 1. Analysis of the Initial Symptoms in Nonacute Cases</th>
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<tbody>
<tr>
<td>CES Symptoms</td>
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<tr>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>Bilateral lower extremity pain</td>
</tr>
<tr>
<td>Bilateral lower extremity paresthesia</td>
</tr>
<tr>
<td>Motor power abnormality of bilateral lower extremity</td>
</tr>
<tr>
<td>Bilateral sciatica</td>
</tr>
<tr>
<td>Paresthesia in perineal region</td>
</tr>
<tr>
<td>Pain in perineal region</td>
</tr>
<tr>
<td>Reduction in bladder function</td>
</tr>
<tr>
<td>Reduction in bowel and anal function</td>
</tr>
<tr>
<td>Reduction in sexual function</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
</tr>
<tr>
<td>Bowel and anal dysfunction</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

| Bilateral lower extremity paresthesia included hyporesthesia, numbness, reduction, and loss of sensation. Motor power abnormality of bilateral lower extremity included weakness, decreased muscle strength, tendon reflex abnormality, and paralysis. Reductions in bladder function included urinary difficulties, altered urinary sensation, loss of desire to void, poor urinary stream, and the need to strain to micturate. Reduction in bowel and anal function involved no desire to defecate, reduced anal tension, and uncontrollable flatulence. Reduction in sexual function included erectile dysfunction (male) and reduced vaginal discharge and decreased libido (female). Bladder dysfunction included compromised urinary retention or incontinence. Bowel and anal dysfunction included constipation or fecal incontinence. |

*Because some patients experienced concurrent initial symptoms, the total percentage of cases is more than 100. CES indicates cauda equina syndrome.
excluded, a total of 222 cases were included in the final analysis. The occurrence orders of symptoms in all cases were analyzed using sequential pattern mining to obtain the common CES progression pattern. Sequential pattern mining was first proposed by Agrawal and Srikant for analyzing customer purchase behavior. It looks for repeating patterns that identify potential associations between different events, and it has been widely applied to analyze web access patterns, scientific experiments, disease treatment, natural disasters, and protein formations. Symptom subsequence of each case was generated by software after symptom occurrence order was input, and the frequencies of all subsequences were calculated. For example, if 3 symptoms of A-B-C occurred sequentially in a case (presented as A-B-C with “-“ indicating the occurrence order), 7 subsequences including A, B, C, A-B, A-C, B-C, and A-B-C were generated, and the frequency for each was one. The subsequences of the symptoms in all cases were integrated, and the total frequencies were calculated. Finally, CES progression pattern was inferred according to the subsequences with higher frequencies. Analyses were performed using the TraMineR package (version 1.8–2; Matthias Studer, Institute for Demographic and Life Course Studies, University of Geneva, Switzerland) in R software, and minimum support of sequential pattern mining was predefined as 0.02.

**CES Initial Symptom Analysis**

The initial symptom or concurrent initial symptoms in non-acute CES cases were defined as the initial symptoms. The frequency and percentage of each initial symptom was calculated to analyze the early manifestations of CES.

**Validation of CES Progression Pattern**

After the CES progression pattern was determined, the patients’ original occurrence orders of CES symptoms were used to validate the pattern. The cases were classified into 2 groups: conforming or nonconforming to the progression pattern gained by sequential pattern mining, and the frequency and percentage of each group was calculated.

**Analysis of the Current Timing of Diagnosis**

To summarize the current timing of diagnosis and reassess it by CES progression pattern, we investigated when cases were diagnosed according to their most severe symptom and calculated the number and percentages of cases diagnosed at different stages.

**RESULTS**

**Baseline Description**

A total of 264 cases were included, including 227 cases from case reports and 37 cases from retrospective studies that supplied detailed patient medical histories. Of the 264 cases, with a mean age of 44.75 ± 17.10 years (range, 1–79 yr), 63.26% (167 cases) were male. Baseline characteristics of patients with CES are listed in Table 2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>19 (7.20)</td>
</tr>
<tr>
<td>18–24</td>
<td>8 (3.03)</td>
</tr>
<tr>
<td>25–44</td>
<td>100 (37.88)</td>
</tr>
<tr>
<td>45–64</td>
<td>90 (34.09)</td>
</tr>
<tr>
<td>≥65</td>
<td>46 (17.42)</td>
</tr>
<tr>
<td>Undescribed</td>
<td>1 (0.38)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>167 (63.26)</td>
</tr>
<tr>
<td>Female</td>
<td>97 (36.74)</td>
</tr>
<tr>
<td>Continent</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>124 (46.97)</td>
</tr>
<tr>
<td>Europe</td>
<td>75 (28.41)</td>
</tr>
<tr>
<td>Asia</td>
<td>55 (20.83)</td>
</tr>
<tr>
<td>Oceania</td>
<td>4 (1.52)</td>
</tr>
<tr>
<td>South America</td>
<td>3 (1.14)</td>
</tr>
<tr>
<td>Undescribed</td>
<td>3 (1.14)</td>
</tr>
<tr>
<td>Total</td>
<td>264 (100.00)</td>
</tr>
</tbody>
</table>

CES indicates cauda equina syndrome.

**Primary Disease Information**

Detailed primary disease information is listed in Table 3 because of the restriction on the length of the article.

**CES Progression Pattern**

Simultaneous occurrence of CES symptoms (with sphincter function abnormalities) was observed in 15.91% (42 cases) of all 264 cases. Lumbar puncture, trauma, and postoperative hematoma were the primary diseases for 66.67% (28 cases) of the acute onset cases. Conversely, CES symptoms in 84.09% (222 cases) of the cases occurred successively. The order of these CES symptoms was obtained from each case, and the progression pattern of CES was analyzed using sequential pattern mining. To avoid repetition, this study only displayed subsequences containing only 2 symptoms (Figure 1). After considering the subsequences with higher frequencies and the widely accepted classification of CES originally reported by Gleave and MacFarlane, according to sphincter function abnormality severity, 3 stages of progression process of CES from mild to severe were inferred: early stage of CES (CESE), incomplete CES (CESI), and CES in retention (CESR). CESE mainly involved bilateral peripheral nerve dysfunction and were characterized by sensory-motor defects in lower extremities, including bilateral lower extremity pain, paresthesia,
and motor power abnormality; perineal region pain and paresthesia; and bilateral sciatica (no obvious occurrence order of these symptoms, not all were necessarily present in a single case). CESI occurred after CESE and was characterized by reduced sphincter function (bladder and bowel). CESR was considered the advanced stage of CES and was characterized by complete loss of sphincter function, including bladder and bowel dysfunction.

**Validation of CES Progression Pattern**

The statistical analysis demonstrated that CES symptoms progressed from mild to severe according to the 3 stages of CES progression pattern in 69.82% of nonacute cases (Table 4). Among all the nonacute cases, only 11.26% (25 cases) did not fully conform to the mild to severe pattern. The primary diseases of these 25 cases were ankylosing spondylitis 64% (16 cases) and lumbar puncture 16% (4 cases). The other 18.92% (42 cases) of the nonacute cases could not be analyzed if they conformed to the mild to severe pattern because they only presented CESE symptoms.

**CES Initial Symptom Analysis**

Analysis of the initial symptoms in cases with nonacute onset (Table 1) revealed that bilateral lower extremity pain was the initial symptom in 69 cases (31.08%), including 17 cases that progressed from unilateral to bilateral lower extremity pain. Paresthesia of the bilateral lower extremity was observed as the initial symptom in 54 cases (24.32%), including 4 cases that progressed from unilateral to bilateral paresthesia. Paresthesia in perineal region was initial symptom in 49 cases (22.07%). Motor power abnormality of bilateral lower extremity was found as the initial symptom in 48 cases (21.62%), including 7 cases that progressed from unilateral to bilateral motor power abnormality. Bilateral sciatica was identified as the initial symptom in 21 cases (9.46%), including 6 cases that progressed from unilateral to bilateral sciatica. Sphincter dysfunction as the initial symptom was observed in 28 patients (12.61%) in which ankylosing spondylitis were the major primary disease (57.14%, 16 cases).

**The Current Timing of CES Diagnosis**

Among the 222 cases with nonacute CES onset, 18.92% (42 cases), 21.62% (48 cases), and 59.46% (132 cases) received a diagnosis at the stages of CESE, CESI, and CESR, respectively. Among the cases that were diagnosed at the stage of CESI or CESR, 99.4% (179 cases) had experienced CESE without being diagnosed.

**DISCUSSION**

It is widely recognized that patients will face a poor prognosis of their bladder and bowel symptoms after being diagnosed with CES, and this is thought to be attributable to surgery timing, symptom severity, and disease course. We reconsidered the underlying cause for poor prognosis of CES, with the goal of exploring the progression pattern of CES, which is vital to diagnosis but still unclear. English literature that provided definite diagnoses and described the occurrence order
of CES symptoms were included. Because of ethical issues, it is difficult to conduct a prospective study to investigate the progression pattern of CES. Therefore, most of the included publications were retrospective studies or case reports. The included data may be subject to information bias due to inter-clinician variations among approaches to obtaining CES medical history. Although almost all the available data from published literature were included, we were unable to rule out publication bias and selection bias. The potential errors of collected studies and case reports might have introduced bias, and the potential effect of such bias is difficult to predict. However, we consider that the bias is tolerable because the symptom occurrence order and progression pattern of CES summarized in this study are mainly consistent with results from other studies.

Shephard\textsuperscript{30} reported 2 groups of CES: slowly developed and rapidly developed.\textsuperscript{32} We found that 15.91% (42 cases) of the total cases included in this study had acute CES onset.
attributable to specific causes, such as trauma, lumbar puncture, and postoperative hematoma. They experienced symptoms simultaneously and rapidly progressed to sphincter dysfunction, which are the typical symptoms of CES that enable clinicians to provide a rapid diagnosis. However, 84.09% (222 cases) of the cases had relatively slow disease development, and the CES symptoms varied from case to case, which made it difficult to provide a prompt diagnosis.

Gleave and MacFarlane suggested that CES could be classified into 2 stages according to sphincter function abnormality severity. Our findings demonstrate that the progression process of CES can be divided into 3 stages. CESE is characterized by bilateral sensory-motor defects in the lower extremities. CESI is characterized by sphincter abnormalities. Sphincter dysfunction was presented when CESE or CESI progressed to CESR. Many studies have demonstrated that the prognosis of patients with CESI seems to be more favorable than that of the patients with CESR, which suggests that earlier diagnosis and treatment can achieve better outcomes. Todd proposed 3 stages: CESI, CESR, and CESS (suspicious CES). CESS is inferred when there is bilateral sciatica or signs of bilateral cauda equina compression without sphincter dysfunction. CESS is similar to CESE described here, except CESS indicates a lack of radiological or further evidence other than symptoms or signs of bilateral lower extremity radiculopathy such as bilateral sciatica. Thus, CES is suspected but not clinically proven, whereas CESE is the early stage of CES prior to CESR. When there is radiological evidence of cauda equina compression (e.g., large central disc herniation), cases should be diagnosed as CES, further classified as CESE.

Our statistical analyses of the current timing of CES diagnosis included cases from all continents except Africa and Antarctica (rare cases of CES were reported in Africa) and showed that 81.08% (180 cases) of patients were diagnosed or treated at the stage of CESI or CESR. This finding highlights the issue that clinicians worldwide tend to diagnose after abnormalities of sphincter function were evident other than symptoms or signs of bilateral lower extremity radiculopathy which may be the reason for the symptoms not always being present at the same time. These CESE symptoms usually developed from unilateral extremity pain, paresthesia, and motor power abnormality. Instead of waiting for the onset symptoms to manifest, clinicians should consider the possibility of CES when these characteristic symptoms are present, especially when they progress from unilateral to bilateral.

Use of these initial symptoms for CES diagnosis enhances sensitivity but may lead to reduced specificity. Therefore, the evidence of bilateral cauda equina lesions should be identified before a definitive diagnosis of CES, and the cause of the initial symptom should be differentially diagnosed.

In this study, 11.26% (25 cases) of the cases did not fully conform to the 3 stages. Most of these patients had simultaneous damage to multiple segments of cauda equina due to ankylosing spondylitis. Arachnoid diverticula and inflammatory process in patients with ankylosing spondylitis are usually extended over several lumbosacral levels, and each segment may have different degrees of injury to the local cauda equine, which may be the reason for the symptoms not always progressing in a predictable pattern.

Although the symptoms in most patients progressed from mild to severe, and each stage has its own characteristic symptoms and signs, there are still difficulties in identifying CES symptoms, such as reduced function of bladder and bowel or paresthesia of perineal region in bedridden patients. These can lead to delayed diagnosis. It has been demonstrated that electrophysiological abnormalities in bilateral lower extremity and sphincter can detect multiple cauda equina lesions prior to the presence of CES symptoms. Although this observation underscores the potential value of early CES diagnosis, there are few clinical studies regarding electrophysiological findings in early stage CES. Therefore, further studies should be carried out to validate this possibly useful finding.

CONCLUSION
Result of sequential pattern mining of patients’ medical history demonstrated that the progression process of CES could be divided into 3 stages: CESE, CESI, and CESR. The characteristic progressive sensory-motor CESE defects in lower extremities marked CES onset. Instead of waiting for the onset of sphincter function abnormalities, CES should be diagnosed when the CESE symptoms manifest.

Key Points
➢ To date, the progression pattern of CES has not been summarized, which may lead to delayed diagnosis.
We found the progression process of CES could be divided into 3 stages: CESE, with bilateral peripheral nerve dysfunction characterized by progressive sensory-motor defects from unilateral to bilateral in lower extremities; CESI, with reduction of sphincter functions; and CESR, with sphincter dysfunction.

Instead of waiting for the onset of sphincter function abnormalities, CES should be diagnosed when the CESE symptoms manifest.

Acknowledgments
Jing-Chuan Sun, PhD, and Tao Xu, PhD, contributed equally to the manuscript.

References