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Research Article

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Reinvestigation on Newer Facts to Anticipate, Avoid And Mitigate The Development of Post-Dural Puncture Headache-A Prospective Cohort Study

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Abstract

Purpose: *Various researchers have described the size and the type of spinal needle used for neuraxial anesthesia as the most common risk factor for developing postdural puncture headache (PDPH). Even though the occurrence of the PDPH is rare in modern anesthesia practice, we come across many such patients despite following all guidelines or precautions. Patient-related factors for developing PDPH are relatively understudied. For that, clinical features commonly present in such patients may require a thorough investigation.*

Methods: *This prospective cohort study included fifty patients admitted for lower extremities orthopedic surgeries and developed PDPH following the neuraxial blockade. We screened all patients in this study for the presence or absence of common manifestations suggestive of connective tissue disorders (CTD). The other outcomes, like the effect of spinal needle size/type to develop PDPH and time to develop PDPH, were also measured.*

Results*: Almost all PDPH patients included in this study had common features suggestive of CTD: the ligamentous laxity (96%), high-arched palate (96%), the blue sclera (45%), joint hyperextensibility (82%), and ejection clicks (64%). PDPH occurred more frequently with the 25G spinal needle of Quincke type than 27G of Whitacre type (82% vs. 18%). The mean (SD) headache freedom time was 73.14 (24.74) hours.*

Conclusions: *The CTD might also be a causative factor responsible for the development of PDPH in some individuals. It can be considered a risk factor to anticipate, avoid, and mitigate the development of PDPH.*

Keywords: Postdural puncture headache, Connective tissue disorders, Meningeal puncture headache, Meningeal healing, Cerebrospinal fluid leak.

Introduction

Postdural puncture headache (PDPH) is always considered one of the iatrogenic complications of the neuraxial blockade. Many questions regarding the causative factors remain unanswered even though the incidence of PDPH has reduced significantly in modern anesthesia practice. Despite all preventive measures or precautions, we do come across PDPH patients in our practice. Even after analyzing a large amount of clinical data of such patients, it is still unclear whether the needle is responsible or the technique. Many studies correlated size and type of needles as an important risk factor in developing PDPH [1-6]. Despite many preventive measures, why do some patients still develop PDPH? Why do some specific patients develop PDPH, and why not others if the needle and technique used are the same? To find answers to these questions, we started looking for common etiological or associated factors in such populations for developing PDPH.

We noticed many patients having knee ligament injuries with ejection clicks on auscultation during preanesthetic evaluation in our hospital. The same auscultatory findings were frequently seen in many PDPH patients too. Hence, we tried to correlate the development of PDPH with the causes of the ejection clicks. Upon evaluating each PDPH patient, we found some features suggestive of connective tissue disorder (CTD) present in many patients. As we noticed a strong correlation between CTD and PDPH, we started screening PDPH patients for features suggestive of CTD. Between the years 2018-2021, we examined fifty PDPH patients having features of the CTD. Our observations strongly suggest CTD as one of the possible risk factors in developing PDPH.

We hypothesize that the patients with PDPH have a high frequency of connective tissue abnormalities. The main aim of this article is to find out and establish the association between CTD and PDPH. We have also tried to describe the possible association of some important manifestations suggestive of CTD, which might contribute to the development of PDPH. Such clinical features in any patient will warn the anesthetist and help them choose appropriate anesthesia to avoid PDPH.

Materials and Methods

This prospective cohort study included 50 patients (of ASA grade I and II) of all age groups admitted for lower extremity orthopedic surgeries who developed PDPH following neuraxial blockade in the postoperative period. We conducted this study from January 2018 to March 2021 with approval from our hospital institutional review board (IRB).

In our study, the duty anesthetist made the diagnosis of PDPH in these patients based on the clinical symptoms like positional headache (aggravated in sitting/erect position and improved in supine position), location (mainly in the frontal/occipital region), and onset (between 12 hours-5 days) after the neuraxial blockade. The severity of the headaches was graded based on the visual analog scale (VAS) from 0-10 (where 0 = no pain and 10 = the worst pain imaginable) and the functional grading (FG) from 1-3 scale (where, 1= headache not interfering with regular daily activity, 2= headache requiring periodical bedrest to get relief, and 3= severe headache not allowing the patient to sit up and eat). Combining both scores, the severity of postdural puncture headache graded as grade 0- no headache, 1- mild (corresponds to FG 1+ and VAS 1-3), 2- moderate (corresponds to FG 2+ and VAS 4-7), and 3- severe (corresponds to FG 3 and VAS 8-10) [7].

The patients' demographics, type of neuraxial anesthesia, size/type of spinal needle, and the onset of PDPH symptoms were noted. We also screened all the patients for CTD by looking for five important features (Table 1) the high-arched palate, blue sclera, hypermobility of knee joint, hyperextensibility of fingers, and an ejection click (Figure 1). We recorded the presence and absence of these features into the chart (Table 2), and graphs were plotted accordingly (Figure 2). The outcomes such as the effect of spinal needle size/type to develop PDPH, time to develop PDPH (headache freedom time), and presence of features suggestive of CTD in the PDPH patients were measured. All patients included in this study or their next-of-kin provided informed consent for anonymous data recording and sharing concerning this procedure.

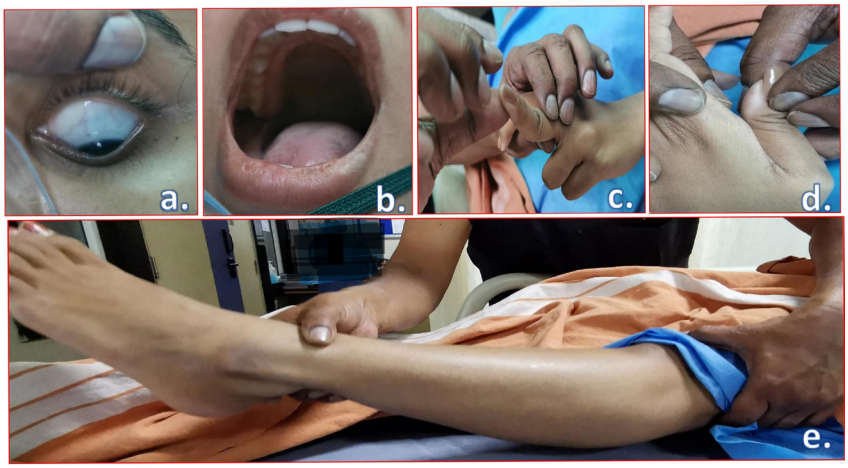
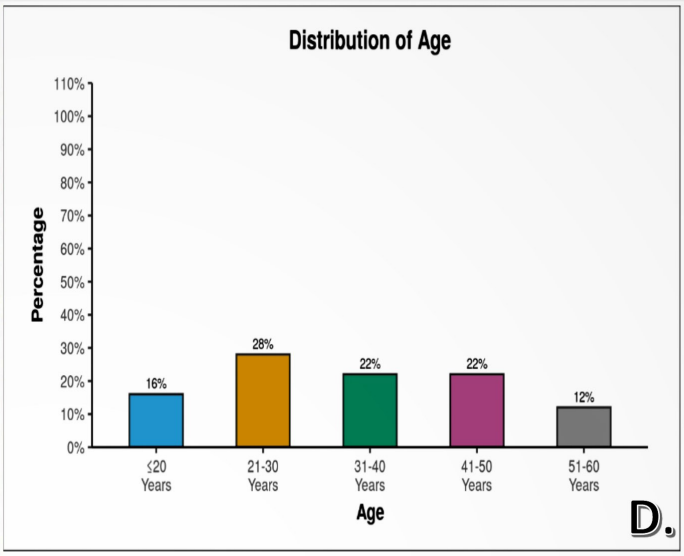
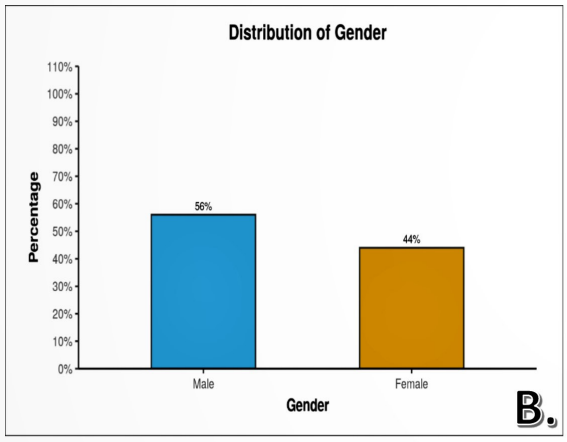


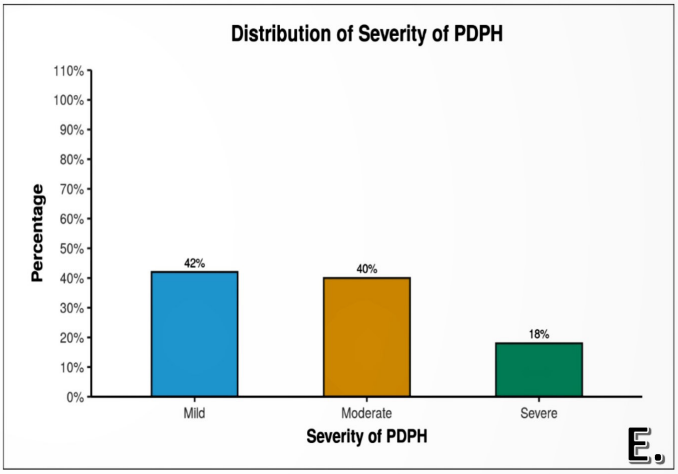
Figure 1: Clinical features suggestive of connective tissue disorders
(a): Blue sclera **(b)**: High-arched palate **(c)**: Hyperextension of fingers
(d): Hyperextension and subluxation of the thumb **(e)**: Hyperextension of knee joint

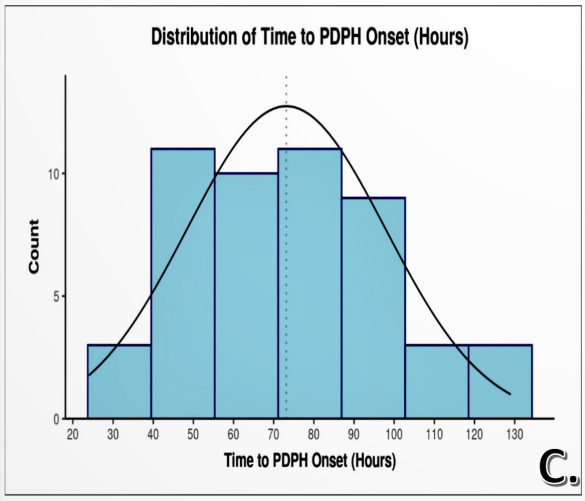
Basic Details	Mean ± SD || Median (IQR) || Min-Max || Frequency (%)
Age (Years)	34.26 ± 12.28 || 32.50 (24.00-43.75) || 11.00 - 60.00
Age	
≤20 Years	8 (16.0%)
21-30 Years	14 (28.0%)
31-40 Years	11 (22.0%)
41-50 Years	11 (22.0%)
51-60 Years	6 (12.0%)
61-70 Years	0 (0.0%)
Gender	
Male	28 (56.0%)
Female	22 (44.0%)
ASA Grade	
I	42 (84.0%)
II	8 (16.0%)
Severity of PDPH	
Mild	21 (42.0%)
Moderate	20 (40.0%)
Severe	9 (18.0%)
Time to PDPH Onset (Hours)	73.14 ± 24.74 || 72.00 (53.50-92.00) || 24.00 - 129.00
Type of Neuraxial Anesthesia	
SAB	37 (74.0%)
CSEA	13 (26.0%)
Type of Spinal Needle	
25G	41 (82.0%)
27G	9 (18.0%)

A.









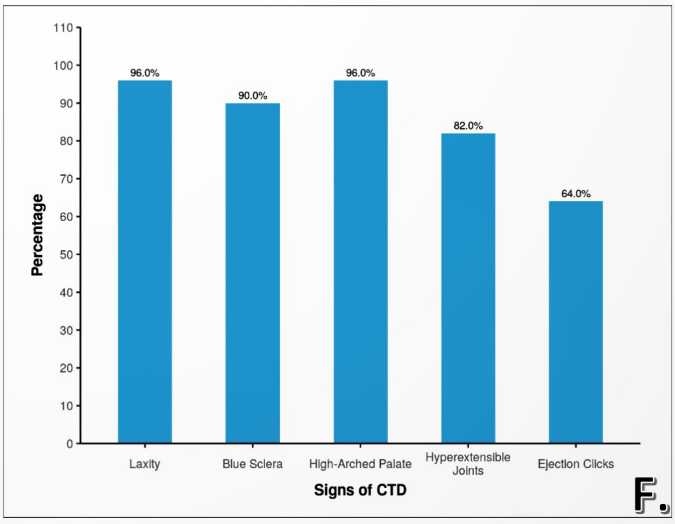


Figure 2: Patients' demographics and graphs displaying statistical analysis
(a): Patients' demographic chart **(b)**: Distribution of gender **(c)**: Distribution of time to PDPH
(d): Distribution of age **(e)**: Distribution of severity of PDPH **(f)**: Percentages graph displaying signs of CTD
(**PDPH**: Postdural puncture headache, **CTD**: Connective tissue disorders/diseases)

Table 1: Common manifestation of CTS and differential diagnoses
(CTD: Connective tissue disorders/diseases)

Common manifestations of CTD – Differential diagnoses			
1.	Joint Laxity	• Hypermobility syndrome • Ehlers-Danlos syndrome • Marfan syndrome • Osteogenesis imperfecta	• Down syndrome • Bony dysplasia • Osteoarthritis
2.	Blue Sclera	• Osteogenesis imperfecta • Marfan syndrome • Ehlers-Danlos syndrome	• Pseudoxanthoma elasticum, • Willems De Vries syndrome
3.	Hypermobility of Joints	• Marfan syndrome • Ehlers-Danlos syndrome • Joint hypermobility syndrome	• Joint hypermobility syndrome
4.	High arched palate	• Allergic rhinitis • Apert syndrome • Crouzon syndrome • Down syndrome • Ehlers-Danlos Syndrome • Fragile X syndrome	• Incontinentia pigmenti • Marfan syndrome • Treacher Collins syndrome • Upper Airway Resistance Syndrome
5.	Ejection click	• Marfan syndrome • Ehlers-Danlos syndrome • Ebstein anamaly	• Muscular dystrophy • Graves' disease • Scoliosis

Table 2: Total number of patients with presence of various manifestations of CTD
(CTD: Connective tissue diseases/disorders)

Signs of CTD	Yes	No
Laxity	48 (96.0%)	2 (4.0%)
Blue Sclera	45 (90.0%)	5 (10.0%)
High-Arched Palate	48 (96.0%)	2 (4.0%)
Hyperextensible Joints	41 (82.0%)	9 (18.0%)
Ejection Clicks	32 (64.0%)	18 (36.0%)

Statistical Analysis

Data were collected and recorded in the MS Excel spreadsheet program and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences, software version 23.0, IBM Corp., Chicago, USA). Descriptive statistics were elaborated in means/standard deviations and medians/IQRs for continuous variables, frequencies, and percentages for categorical variables. Data were presented graphically wherever appropriate for data visualization using histograms/box-and-whisker plots/column charts for continuous data and bar charts/pie charts for categorical data. Statistical significance was kept at $p < 0.05$.

Results

All fifty enrolled patients completed the study successfully without any exclusion due to the noninterventional nature of the study, entirely based on the patient's clinical examination.

- The variable age of the patient was normally distributed (Shapiro-Wilk Test: $p = 0.295$). It ranged from 11-60 years with a mean (SD) of 34.26 (12.28) years and median (IQR) of 32.50 (24-43.75) years. PDPH occurred more frequently in patients younger than 40 years than their elder counterparts (56% vs. 34%).
- The number of male patients who developed PDPH was more than females (56.0% males and 44.0% females).
- The majority of the PDPH patients were healthy without comorbidities: 42 (84.0%) patients of ASA grade I and 8 (16.0%) patients of ASA grade II.
- The 21 (42.0%) patients had a mild headache, 20 (40.0%) patients had a moderate headache, and 9 (18.0%) patients had a severe headache.
- The variable time of PDPH onset (headache freedom time) in hours was normally distributed (Shapiro-Wilk Test: $p = 0.422$). It ranged from 24-129 hours with the mean (SD) of 73.14 (24.74) hours and the median (IQR) of 72.00 (53.5-92) hours.
- PDPH occurred more frequently in patients with spinal anes-

thesia than CSEA (74% vs. 26%) and with the needle of 25 G of Quincke type than 27 G of Whitacre type (82% vs. 18%).

- The ligamentous laxity and the high-arched palate were the most common features in PDPH patients suggestive of CTD, followed by the blue sclera, joint hyperextensibility, and ejection clicks.

Discussion

In this prospective noninterventional observational study, we found a strong association of CTD in the development of PDPH. Diagnosing CTD using various investigations is complex and time-consuming. Hence, we sorted common manifestations representing almost all types of CTD in this study. The presence of any of such manifestations can be considered a high risk for the development of PDPH. We believe that all possible precautions and steps should be taken while performing neuraxial blocks or avoid and use alternative anesthesia techniques in CTD patients considering its potential role in developing PDPH. To establish and justify the association of PDPH with CTD, a basic understanding of types and functions of connective tissues, the meningeal connective tissue, the meningeal tear healing process, and manifestations of CTD leading to PDPH is essential.

The connective tissues connect, separate, and support all other tissues in the body and distribute as cellular and extracellular. The cellular connective tissues include fibroblasts, macrophages, mast cells, plasma cells, lymphocytes, leukocytes, and adipose cells. The extracellular connective tissues include fibers (reticular, elastic, and collagen) and ground substance (macromolecule and multi adhesive glycoproteins). They play an important role in support (epithelium), strength (ligaments), storage (fat cells), transport (of water, ions, and electrolytes), packing (adipose tissue), repairing (wound healing), and defense (plasma cells, macrophages, lymphocytes, monocytes and eosinophils). Connective tissues constitute two proteins: collagen (found in tendons, ligaments, skin, cornea, cartilage, bone, and blood vessels) and stretchy elastin that resembles a rubber band (found in ligaments and skin).

The inflammation of connective tissues leads to CTD. Among more than 200 different CTD types, some are autoimmune (like systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis), and some are with genetical inheritance (like Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome) [8]. The Marfan syndrome (MFS) involves mutations in the gene coding for fibrillin-1 (FBN1), the Loeys-Dietz syndrome (LDS) involves mutations in the transforming growth factor-beta (TGF-β) receptor genes (TGFBR1 or TGFBR2), and the Ehlers-Danlos syndrome (EDS) of classic type involves mutations in the genes encoding for type V collagen (COL5A1 or COL5A2) [9–13].

The condition with more than one CTD is known as an "overlap" syndrome, or sharp syndrome, or mixed connective tissue disease (MCTD) [14]. Body parts (Table 3) that may be affected include bones, joints, skin, heart, blood vessels, lungs, head, face, and height. Diagnosis of all these CTD can be established clinically by physical examination to detect clinical manifestations in the affected body parts or by blood tests to detect abnormally higher levels of specialized antibodies.

Table 3: Common connective tissue disorders with systemic manifestations
(CTD: Connective tissue diseases/disorders)

CTDS	Joints	Skeleton	Skin	Eyes	CVS
Marfan's Syndrome	Hypermobility	Marfanoid habitus	Hyperextensibility	Ectopia lentis	Aortic dilatation, mitral valve prolapse
Ehlers-Danlos Syndrome	Hypermobility	Osteoporosis	Hyperextensibility	-	Mitral valve prolapse, intracranial aneurysm
Osteogenesis Imperfecta	Hypermobility	Osteoporosis	Hyperextensibility	Blue sclera	Mitral valve prolapse
Benign Joint Hypermobility Syndrome	Hypermobility	Marfanoid habitus Osteoporosis	Hyperextensibility	Lid laxity, Blue sclera	Varicose veins
Loeys-Dietz Syndrome	-	Marfanoid habitus Cervical spine instability	Velvety skin	Hypertelorism	Arterial tortuosity, Multiple arterial aneurysms

The meninges are the membranous connective tissue coverings of the brain and spinal cord. They contain both collagen and elastin fibers [15]. Meninges provide a supportive framework for the cerebral and cranial vasculatures and protect the CNS from mechanical damage by acting with CSF- the spinal cord's first line of defense [16].

The outer layer also referred to as pachymeninges or the dura mater, is the toughest, thick, dense, and white fibrous (inextensible) connective tissue. The dura is composed of fibroblast and dense interlacing bundles of collagen and elastic fibers [17]. The elastic fibers provide considerable flexibility upon stretching during movements, and the collagen provides tensile strength and pro-

tects the spinal cord. It contains a rich vascular network, an extensive nerve supply, and lymphatic drainage channels. The dura mater (around 400 μm thickness) has randomly distributed fibers arranged around 80 concentric layers, known as dural laminas [18, 19]. The dura mater rests on the arachnoid mater, with a small amount of lubricating fluid between them.

The middle layer, the arachnoid mater, is a thin layer of connective tissue with fine trabeculae connected to the underlying pia mater and form a meshwork through which CSF recirculates. It resembles a cobweb in appearance and is composed of collagen and elastic fibers [20]. Unlike dura, it lacks its own innervation and blood supply, likely deriving all of its metabolic support from the CSF itself. The arachnoid mater (around 40 μm thickness) has several cell layers with frequent tight and occluding junctions that function as a barrier limiting CSF escape [19, 21–29]. Its outer (dural) aspect is smoother than the inner (pial) aspect from which trabeculae emerge to bridge the subarachnoid space.

The innermost layer, the pia mater, is a thin and delicate membrane firmly adherent to the brain and spinal cord. Like dura, it is highly vascularized. The pia and the arachnoid mater together constitute the leptomeninges. The pia mater's elasticity helps the spinal cord maintain its shape. It is composed of collagen and reticular fibers. The reticular tissue is wrapped closely around the spinal cord underneath the bundles of the collagen fibers. The thickness of the pial cellular layer includes 8-15 μm at the spinal cord level and 3-8 μm overall on the nerve roots [30]. There are fenestrations within the pial cellular layer at the thoracic-lumbar junction, conus medullaris, and spinal nerve roots.

Iatrogenic meningeal tears can result from injury, epidural injections, lumbar punctures, or spine surgery complications. In the case of the neuraxial procedures, the CSF leakage from the lesion (produced by the needle) is entirely dependent on the elasticity of the arachnoid layer, which retracts to close the defect and stops CSF leakage. The volume of CSF lost is also likely related to the speed of closure of the arachnoid lesion. For this reason, the meningeal tears are also referred to as "dura-arachnoid" lesions. The pattern of the meningeal tears may differ with the needle types. The non-traumatic pencil-point needle causes microscopic burst-type le sions associated with extensive fiber damage, which promotes inflammatory response and paradoxically results in faster lesion closure reducing the incidence of PDPH. In contrast, the cleaner tear produced by cutting needles leads to a less inflammatory response resulting in delayed closure of the lesion and increasing incidence of PDPH. Unlike pencil-point needles, cutting needles cause more damage to the nerve fibers due to associated needle tip deformation after colliding against bone [31, 32].

The healing of dural tears is a slow and gradual process, sometimes requiring more than six weeks [33]. Since connective tissue plays an essential role in the wound healing process, the disorders affecting connective tissue also cause disturbed wound healing of the dural hole. Spontaneous meningeal tears can result from the defect in the wound healing or repairing process associated with CTD. Such tears may lead to leaking of the CSF out of the dura - disrupting CSF homeostasis - loss of buyont effect - dragging and stretching of neural structure - development of PDPH symptoms.

The CTD patients have four-fold increased incidence of PDPH and nearly three-fold increased epidural blood patch (EBP) requirement to resolve their headaches [34]. Thus, the CTD can be a risk factor for both the development of PDPH and the need for EBP. The important manifestations of the CTD leading to the development of PDPH are spontaneous CSF leaks, joint laxity/hypermobility, and dural ectasia.

Spontaneous CSF leaks in CTD are due to associated thinning (than normal) and the excessive fragility of the spinal dura leading to the formation of fragile meningeal diverticula or simple dural rents allowing CSF to leak into the extradural space [35]. Such spontaneous CSF leaks from the dural sac have been reported in Marfan syndrome. The spontaneous CSF leaks in CTD are common in females that suggest hormonally-mediated effects on the dural integrity [36]. Similar female biases are also found in congenital hip dislocation, scoliosis, and joint hypermobility [37-39]. Thus, spontaneous spinal CSF leaks may be part of this developmental spectrum.

Joint laxity or hypermobility is another biomarker of CTD, mainly the Type I (gravis type) and Type II (mitis type) EDS, Down's syndrome, Marfan syndrome, osteogenesis imperfecta, and benign joint hypermobility syndrome [40]. The joint laxity is maximal at birth, declining rapidly during childhood, less rapidly during the teens, and more slowly during adult life. It is more common in women than men of all ages and associated with a wide ethnic variation [41]. Around 20% of women and 10% of men have more flexible and fragile tissues than average [42]. The primary cause of joint hypermobility is the fibrous protein genes encoding collagen, elastin, and fibrillin that determine ligamentous laxity [43]. It is seen in up to 10% of individuals in Western populations and up to 25% in other populations [44, 45]. The pauciarticular (less than five joints involved) is even more highly prevalent than the polyarticular variety [46]. Joint hypermobility can also result from the sheer hard work of training like ballet dancing, gymnastics, and acrobatics.

Dural ectasia is another biomarker of CTD, mainly MFS and LDS [47]. It is an enlargement of the outer layer of the meningeal sac leading to ballooning or widening of the dural sac, which can be associated with the herniation of nerve root sleeves through the neural foramina [48–50]. These changes occur predominantly in the caudal portion of the spinal column, probably due to the effect of the greatest hydrostatic pressure in that location [51]. Due to this, the patient may develop chronic back pain, radiculopathy, PDPH (due to stretching of nerves and traction mechanisms),

spontaneous cerebrospinal fluid leaks, fixation failure during spine surgery, and inadequate spinal anesthesia.

This cohort study is subject to gender bias and selection bias that must be considered when generalizing the sample data to the general group of patients with CTD. However, our study results cannot be generalized to all patients with PDPH.

Conclusion

We finally concluded that the PDPH might not be only a neuraxial complication but also a side effect of the body bio-physiological changes present in some individuals. Future studies, including long-term follow-up on this cohort, are needed to understand the impact of an underlying CTD on patients' natural history and management with PDPH. We propose a clinical basis for considering PDPH as a clinical manifestation of CTD and that individuals with PDPH should be evaluated for connective tissue abnormalities.

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