Case Reports in Neurology

Case Rep Neurol 2022;14:58–67
DOI: 10.1159/000521462
Received: September 30, 2021
Accepted: November 25, 2021
Published online: February 15, 2022

Case Series - General Neurology

Parsonage-Turner Syndrome Following COVID-19 Vaccination: Clinical and Electromyographic Findings in 6 Patients

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Keywords
Neurology · Parsonage-Turner syndrome · COVID-19 · Brachial plexopathy · Electromyographic studies

Abstract
Parsonage-Turner syndrome (PTS) following COVID-19 infection or vaccination is rare. The pathophysiology may involve an immune-mediated inflammatory reaction against brachial plexus nerve fibers in a genetically predisposed individual. We describe the clinical and electromyographic features of 6 patients presenting with the clinical picture of PTS following COVID-19 vaccination. All patients were referred for electromyographic studies to evaluate the acute onset of pain in the shoulder girdle/upper limb accompanied by muscle weakness in the distribution of one or more branches of the brachial plexus. Each patient had received the COVID-19 vaccine within a few weeks prior to the onset of symptoms. Patients underwent detailed neurological examinations followed by nerve conduction and EMG studies. The patients developed symptoms after a mean duration of 17 days (5 days–8 weeks) after receiving the COVID-19 vaccine. The initial symptom was pain in the shoulder girdle/upper limb, followed within days by muscle weakness. Physical examinations and EMG studies showed upper trunk brachial plexopathy in 2 patients, lower trunk plexopathy in 1 patient, posterior cord brachial plexopathy in 1 patient, and anterior/posterior interosseous nerve involvement in 2 patients. All patients either improved or attained complete resolution of the arm pain at follow-up.

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Three (50%) patients did not have any improvement in the arm/hand weakness, while 3 (50%) patients had some recovery in strength. PTS may occur after the COVID-19 vaccine and should be suspected in patients with symptoms and signs suggestive of acute brachial plexopathy. Studies of a larger series may provide insight into predisposing factors.

Introduction

Initially described in 1948, Parsonage-Turner syndrome (PTS) refers to the acute onset of shoulder pain followed by progressive motor weakness, dysesthesia, and numbness of the upper extremities [1]. Also known as acute brachial plexus neuropathy or neuralgic amyotrophy, this condition is usually unilateral and has an incidence of 1.64 cases per 100,000 individuals (although may be as high as 20–30/100,000 due to missed cases or misdiagnosis) [1–3]. While the etiology is unknown in many cases, several causes have been reported, including prior viral infections, vaccination, surgery, and trauma [1, 4]. Myriad immunizations have been associated with the development of PTS, including varicella zoster, hepatitis B, tetanus toxoid and antitoxin, diphtheria, pertussis, tetanus vaccine, smallpox, and swine flu [1]. It has been suggested that the viral antigen in the vaccine may trigger the development of PTS post-vaccination [1].

During the first 6 months of 2021, we noted an increase in the number of cases of PTS diagnosed in our diagnostic facility. Further analysis showed that the increase was apparently related to patients receiving COVID-19 vaccine, which prompted us to study these patients in more detail.

Since the initial reports of "pneumonia of unknown etiology" in Wuhan, China, on December 29, 2019, which was identified as the novel coronavirus or the severe acute respiratory syndrome coronavirus 2, this global pandemic has profoundly affected all aspects of society, resulting in 726,846 fatalities in the USA as of October 25, 2021 [5]. On December 11, 2020, the US Food and Drug Administration granted the emergency use authorization for the BNT-162b2 severe acute respiratory syndrome coronavirus 2 vaccine for individuals >16 years [6]. As of October 25, 2021, over 416 million doses have been administered in the USA, representing 61% of the population who have been fully vaccinated [5]. The safety profile of this vaccine specified short-term, mild-to-moderate pain at the injection site, fatigue, and headaches. Numerous short- and long-term side effects of the peripheral nervous system from the COVID-19 infection have been reported, including nerve pain and skeletal muscle injury, Guillain-Barrė syndrome, Bell's palsy, tinnitus, cranial polyneuritis, neuro-ophthalmological disorders, neurosensory hearing loss, neuromuscular junction disorders, and dysautonomia [7]. Rare cases of PTS following COVID-19 infection or vaccination have been described [2, 3, 7–12]. It has been suggested that peripheral nervous system abnormalities may be attributed to dysregulation of the systemic immune response due to COVID-19 [12]. In this manner, COVID-19 infection results in an increased number of antibodies against peripheral nerve myelin leading to inflammation with macrophage activation [2].

Herein, we report 6 patients with PTS temporally related to the COVID-19 vaccination, who were referred for electrodiagnostic (EDX) evaluation for acute onset of pain and weakness of the upper extremity. The presenting symptoms, physical examination, EDX findings, MRI results, history of COVID-19 vaccination, treatment, and follow-up are discussed. The mechanism linking PTS and COVID-19 is examined. The diagnosis, management, and prognosis of PTS as well as the importance of EDX studies are also discussed.

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Methods

We performed a retrospective analysis of patients referred to our facility for EDX investigation of pain and weakness of the upper extremity. All patients underwent EDX studies following standard protocol in our laboratory [13]. The EDX tests focused on detecting focal demyelination, conduction block, axonal loss, and localizing the site of involvement by nerve conduction studies and needle EMG. Numerous metrics were documented including presenting symptoms, physical examination, EDX findings, history of COVID-19 vaccination, treatment, and outcome. Other potential triggers of PTS such as active COVID-19 infection, recent illness, surgery, or strenuous exercise were excluded.

Standard Protocol Approvals, Registrations, and Patient Consents

The University of Louisville Institutional Review Board determined that this study was exempt according to 45 CFR 46.101(b) under Category 4. The IRB number is 21.0567. Written informed consents were obtained from all patients in this study.

Results

Four patients with PTS received the Pfizer-BioNTech COVID-19 vaccine, and 2 patients were inoculated with the Moderna COVID-19 vaccine prior to symptom onset (mean duration: 17 days, range: 5 days–8 weeks) (Table 1). The symptoms arose on the ipsilateral side to the injection site in 5 patients and on the contralateral side in 1 patient. The onset of symptoms occurred after the 1st dose of the vaccine in 2 patients, while 4 patients developed symptoms after the 2nd vaccine dose. Presenting symptoms included arm pain in 5 patients and shoulder pain in 3 patients followed by the acute onset of muscle weakness in all patients (Table 1). Physical examination and EDX studies showed abnormalities suggesting localization to a part of the brachial plexus or to one or more of its branches. Topography of denervation changes on needle EMG in selected upper extremity and cervical paraspinal muscles further confirmed the localization. The clinical picture coupled with EDX findings supported the diagnosis of PTS. The upper trunk/lower trunk was involved in 3 patients, posterior cord in 1, anterior interosseous nerve (AIN) in 1, and posterior interosseous nerve (PIN) in 1. Figure 1 depicts weakness of flexor pollicis longus in Patient #2 with AIN palsy. In Patient #1, stimulation at the right Erb's point evoked a small compound muscle action potential with fibrillations over the deltoid, which showed fibrillations and positive sharp waves indicating significant axonal involvement.

Five patients underwent a cervical spine MRI which did not show abnormalities that could be related to the motor or sensory deficits. Only 1 patient (Patient #1) underwent a brachial plexus MRI which revealed no abnormalities of the brachial plexus.

Treatment included prednisone/prednisolone in 4 patients, gabapentin in 2 patients, and physical therapy (PT) in 4 patients. All 6 patients in our study attained either improved or complete resolution of the arm pain at follow-up (Table 1). Three patients did not have any improvement in the arm/hand weakness, while 3 patients had some recovery in muscle strength.

Discussion

PTS is a clinical diagnosis and depends on an accurate history and neurological examination. The differential diagnosis includes several conditions including cervical radiculopathy; cervical myelopathy; adhesive capsulitis, rotator cuff, or labral tear of the shoulder;

Table 1. Patients with Parsonage-Turner syndrome following the COVID-19 vaccine

Patient No	Age, years/ Gender	COVID-19 vaccine (1st/2nd dose, type, side of innoculation)	Presenting symptoms	Physical examination	Interval between symptom onset and EMG/NCV	EDX studies	Treatment/follow-up
1	36/F	COVID-19 1st dose Pfizer vaccine 1 week before right arm symptoms; vaccine ipsilateral to symptoms	Right neck and shoulder pain; right arm weak	Weakness of right deltoid, biceps, infraspinatus	5 weeks	Fibrillations, PSWs, and loss of motor units in right biceps, deltoid, infraspinatus; normal pattern in other muscles including cervical paraspinals *Right upper trunk brachial plexus*	Prednisone, gabapentin, PT; improved arm pain and weakness 3 months after onset
2	74/M	COVID-19 2nd dose Pfizer vaccine 2 weeks before left arm symptoms; vaccine ipsilateral to symptoms	Pain left forearm, weakness of left thumb flexion	Weakness of flexion of left thumb at the IP joint	3 months	Marked decrease in motor unit recruitment in the FPL; normal FDP, APB, PrT, EI, and EDC *Left AIN fascicles to FPL*	PT, electric stimulation of muscles; forearm pain resolved, weakness thumb persisted 4 ½ months after onset
3	50/M	COVID-19 2nd dose Moderna vaccine 5 days before right arm symptoms; vaccine ipsilateral to symptoms	Right neck/shoulder pain, arm weak	Weakness of right deltoid, biceps, brachioradialis, triceps, infraspinatus; decreased pinprick sensation right upper arm	2 months	Fibrillations, PSWs, and decreased motor units in the right deltoid, brachioradialis, triceps; increased polyphasic units in deltoid, biceps, brachioradialis, triceps; normal cervical paraspinals *Right upper trunk brachial plexus*	Corticosteroid, methylprednisolone, PT, chiropractor; arm pain resolved, weakness improved 4 months after onset
4	53/M	COVID-19 1st dose Pfizer vaccine 2 weeks before left arm symptoms; vaccine ipsilateral to symptoms	Left shoulder pain radiating to fingers; paresthesia ulnar 3 fingers, weakness of hand	Weakness of left triceps, EDC, FDI, ADM, APB	2 months	PSWs and decreased motor unit recruitment in FDI, ADM; decreased motor unit recruitment EPL, EDC, APB, triceps; normal pattern in cervical paraspinals *Left lower trunk brachial plexus*	Prednisone, gabapentin; improved shoulder and arm pain, continued weakness of index and middle fingers 3 ½ months after symptom onset
5	84/F	COVID-19 2nd dose Pfizer vaccine 8 weeks before left arm symptoms; vaccine contralateral to symptoms	Left forearm pain, weakness of left hand	Weakness of extension of left digits at MP joint	6 weeks	No CMAP over EI or EDC; fibrillations and PSWs in EDC and EPL; normal pattern in ECRL, triceps, APB, FDI, biceps, deltoid *Left PIN fascicles*	No treatment; pain resolved, continued hand weakness 3 months after symptom onset
6	46/F	COVID-19 2nd dose Moderna vaccine 6 days before left arm symptoms; vaccine ipsilateral to symptoms	Difficulty with left shoulder movements; left arm pain; unable to flex/extend left fingers	Weakness of extension of left digits, weak shoulder abduction	3 months	Decreased motor unit recruitment and increased polyphasics left deltoid, triceps, EDC, EI; normal pattern in FDI, APB, PrT, biceps and cervical paraspinals *Posterior cord brachial plexus*	Corticosteroid injection; significant improvement in left arm pain, improvement in weakness

APB, abductor pollicis brevis; FPL, flexor pollicis longus; FDP, flexor digitorum profundus; FDI, first dorsal interosseous; ADM, abductor digiti minimi; EPL, extensor pollicis longus; EDC, extensor digitorum communis; EI, extensor indicis; IP, interphalangeal joint; MP, metacarpophalangeal; PIN, posterior interosseous nerve; PSWs, positive sharp waves; PrT, pronator teres.

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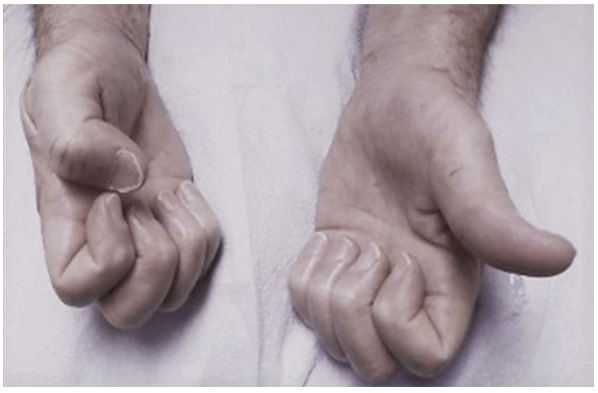

Fig. 1. Patient #2 showing inability to flex the IP joint of the left thumb from weakness of the FPL due to involvement of AIN fascicles. FPL, flexor pollicis longus; IP, interphalangeal; AIN, anterior interosseus nerve.

and glenohumeral osteoarthritis [2, 3, 11]. A vague and unreliable history and confusing findings on physical examination may lead to misdiagnosis. EDX studies are crucial to confirm localization of the disorder to the brachial plexus/branches. They are valuable in supporting the diagnosis of PTS and excluding mimics like acute cervical radiculopathy based on the distribution of denervation and the presence or absence of SNAPs [3]. While the upper trunk is most commonly involved, there is often widespread denervation of the involved muscles and often patchy damage to any portion of the brachial plexus [1, 3]. Our earlier study showed a predilection for fascicles of the AIN or PIN in a significant proportion of patients with PTS [4]. EMG/NCV studies may or may not reveal absent SNAPs, reduced CMAPs, and prolonged F responses [14]. In van Alfen et al. [15] publication of sensory nerve conduction studies in PTS, 80% of clinically affected nerves had normal SNAPs. EMG/NCV tests are also helpful to demonstrate reinnervation of the affected muscles when studies are performed serially. A cervical MRI may reveal findings such as a disc herniation that may cause symptoms similar to PTS, while an MRI of the shoulder and brachial plexus often demonstrates intramuscular denervation changes and a uniformly increased T2 signal of the supraspinatus, infraspinatus, teres minor, teres major, and deltoid muscle characteristic of PTS [1, 11, 14]. High-resolution MR neurography may show hourglass constrictions in fascicles of nerves involved in PTS [1].

PTS is usually self-limited and does not require surgical intervention. Medical management may consist of corticosteroids, opioid and nonsteroidal anti-inflammatory medications, and PT. The pain often resolves within 1–2 weeks. Approximately, 70–80% of patients attain improvement in muscle strength at 2–3 years; however, 70% often experience residual weakness [11, 14]. Additional common residual symptoms include pain and fatigue [16]. A recent report suggests that motor impairment in PTS may improve after intravenous immune globulin [17]. If hourglass-like constrictions are observed on imaging, surgical treatment may be beneficial for persistent weakness [16].

Very few case reports/series have been published in the literature describing PTS as a sequelae of COVID-19 infection or vaccination (Table 2) [2, 3, 7–12, 18–20]. In 5 of these articles, patients had contracted COVID-19, after which they developed shoulder and/or arm pain followed subsequently by arm/hand paresthesia and weakness [2, 7, 9, 11, 12]. Five case reports/series featured similar presenting symptoms after receiving the COVID-19 vaccine [3, 10, 18–20]. One case report described pure sensory PTS after COVID-19 infection [8]. The physical examinations, EDX studies, and MR imaging in these published cases excluded other causes that may have precipitated the patients' symptoms. Most patients were treated with prednisone/prednisolone or an anti-inflammatory medication in conjunction with PT with varying degrees of improvement in pain and weakness of the arm/hand (Table 2).

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Table 2. Patients with Parsonage-Turner syndrome following COVID-19 infection or vaccine in the literature

Study	Age, years/ Gender	COVID-19 infection/Vaccine	Presenting symptoms	Physical examination	EDX studies	Treatment/follow-up
Ismail et al. [9]	32/M	COVID-19 infection	Bilateral shoulder pain, proximal weakness, hand/left shoulder/forearm numbness	Weakness of left shoulder abduction/flexion/external rotation, elbow flexion, flexion of DIP of left thumb and index finger; weakness of right shoulder abduction/flexion, elbow flexion	Low CMAP amplitude musculocutaneous, axillary, suprascapular bilaterally; long thoracic and AIN on left	Acetaminophen, pregabalin, tramadol, steroid/lidocaine injection to shoulder; partial relief of pain, no improvement in strength
Mitry et al. [11]	17/F	COVID-19 infection	Joint pain left shoulder/hand	Normal	Not performed	Oral prednisone
Siepmann et al. [12]	52/M	COVID-19 infection	Right shoulder pain, paresthesia index/longer fingers; weakness right hand	Weakness of right FDP, FPL, AP, OP	Decreased motor unit recruitment APB, OP, FP	Oral prednisolone; partial pain relief, no improvement in weakness
Alvarez et al. [2]	46/F	COVID-19 infection	Pain/weakness left shoulder/ arm, weakness of left shoulder abduction/flexion, elbow flexion	Decreased strength of left shoulder abduction/extension; left shoulder atrophy; tenderness subacromial region	Motor unit recruitments consistent with chronic left upper trunk plexopathy with reinnervation	Meloxicam, PT; strength improved
Han et al. [7]	52/M	COVID-19 infection	Pain left forearm/hand, weakness left UE	Weakness of biceps, triceps, wrist/finger extensors, wrist/finger flexors, forearm pronation, forearm supination, superficial and deep finger flexors, intrinsic hand muscles	Fibrillations and PSW in all muscles of left UE except deltoid; recruitment absent in left triceps, brachioradialis, ECR, EDC, EI	Wrist splint, PT; gabapentin, oxycodone, acetaminophen; pain resolved, some improvement in strength, severe muscle atrophy of left triceps/forearm
Cacciavillani et al. [8]	52/M	COVID-19 infection	Pain, hypoesthesia, dysesthesia left arm/wrist	Sensation abnormalities reflected presenting symptoms	Reduced SNAP amplitude of left lateral antebrachial cutaneous nerve	Acetaminophen; pain resolved, continued hypoesthesia and dysesthesia
Diaz-Segarra et al. [3]	35/F	COVID-19 vaccine 9 days earlier	Weakness, numbness, paresthesia left arm	Weakness of left deltoid, supraspinatus, biceps brachii, triceps brachii, ECR, EDC, EIP, FDS, FDP	Denervation dorsal scapular, suprascapular, musculocutaneous, axillary, radial nerves	High-dose prednisone; numbness/ paresthesias resolved; strength improved

Table 2 (continued)

Study	Age, years/ Gender	COVID-19 infection/Vaccine	Presenting symptoms	Physical examination	EDX studies	Treatment/follow-up
Majahan et al. [10]	50/M	COVID-19 vaccine 1 week earlier	Left periscapular/forearm pain, weakness of handgrip/wrist extension	Weakness of left finger extension/ handgrip, DI, ED, EI, FCU	Decreased motor unit recruitment left 1st DI, FCU, ADM, ED, EI	Oral prednisone, OT; pain improved; minimal improvement in strength
Crespo Burillo et al. [18]	38/M	COVID-19 vaccine 4 days earlier	Left shoulder pain/scapular/ arm	No motor or sensory deficit	Fibrillations and positive waves in EDC, ADM, 1st dorsal interosseus, APB	IV methylprednisolone, oral prednisone; symptoms resolved within 2 weeks
Queler et al. [20]	(1) 49/M (2) 44/M	(1) COVID-19 vaccine 13 h earlier (2) COVID-19 vaccine 18 days earlier	(1) Left forearm pain (2) Left lateral deltoid pain; inability to abduct left shoulder beyond 20°	(1) Atrophy left volar forearm, weakness in left forearm pronation/ wrist flexion (2) Weakness left shoulder abduction/ external rotation; diminished pinprick sensation radial nerve distribution	(1) Normal EDX tests (2) Slowing of left median and radial sensory responses; denervation with poor motor unit recruitment in infraspinatus	(1) IV anti-inflammatory medications, oral prednisone; pain resolved with persistent weakness 3 months after symptom onset (2) Gabapentin, PT; strength/range of motion improved 3 months after symptom onset
Koh et al. [19]	(1) 50/M (2) 44/M (3) 58/M	(1) COVID-19 vaccine 25 days after 1st dose (2) COVID-19 vaccine 4 days after 2nd dose (3) COVID-19 7 days after 2nd dose	(1) Right arm pain/weakness/ numbness (2) Neck/shoulder pain; right forearm/hand numbness; right hand weakness (3) Shoulder/left arm pain; left hand numbness/weakness	(1) Upper and middle trunk brachial plexus (2) Lower trunk brachial plexus (3) Lower trunk brachial plexus	(1) Normal EDX tests (2) EDX tests showed lower trunk brachial plexus involved (3) EDX tests showed lower trunk brachial plexus involved	(1) Corticosteroid; symptoms improved within 7 weeks (2) No treatment; symptoms improved within 8 weeks (3) Corticosteroid; symptoms improved within 5 weeks

ECR, extensor carpi radialis; EDC, extensor digitorum communis; EIP, extensor indicis proprius; FDS, flexor digitorum superficialis; FDP, flexor digitorum profundus; DI, dorsal interossei; ED, extensor digitorum; EI, extensor indicis; FCU, flexor carpi ulnaris; ADM, abductor digiti minimi; OT, occupational therapy; FPL, flexor pollicis longus; AP, abductor pollicis; OP, opponens pollicis; APB, abductor pollicis brevis; FP, flexor pollicis; SNAP, sensory nerve action potential; PSW, positive sharp waves.

Three mechanisms have been proposed to explain the development of PTS following COVID-19 infection [2]. COVID-19 may enter any host cell by binding to the angiotensin-converting enzyme 2 receptor which is located in many cell types including the lungs, heart, intestines, and kidneys. In this respect, the COVID-19 virus may act as a direct neuropathogen that invades the peripheral nerves. The COVID-19 virus may also cause peripheral nerve damage through direct cytotoxic effects or through molecular mimicry, the latter involving antibodies against viral surface glycoproteins that target similarly structured glycoconjugates in the human nervous tissue.

Strengths and Limitations

Our study is the largest series to date in the literature that features patients who developed PTS following the COVID-19 vaccine. While the patients' clinical history and physical examination suggested PTS, the EDX testing further corroborated this diagnosis and excluded other causes such as cervical spondylotic/disc disease and rotator cuff pathology.

The limitations of the present work include its retrospective nature and lack of a conclusive diagnostic test for PTS. Few studies have reported the time between vaccine administration and symptom onset [3, 10, 18–21]. In Tsairis et al. [21] study of 14 post-immunization patients, the interval between the innoculation and symptoms ranged between 3 and 21 days. In the patients who developed PTS post-COVID-19 vaccine depicted in Table 2 [3, 10, 18–20], the time duration between the vaccine and onset of symptoms ranged between 13 h and 25 days. The time interval between the vaccine and symptom onset in Patient #5 of our study was 8 weeks which represents an outlier. An additional limitation is that only 1 patient in our study underwent a brachial plexus MRI.

Conclusion

Physicians should be aware of the potential for development of PTS in patients who have experienced either COVID-19 infection or been vaccinated for this novel virus. Timely recognition and early treatment of this condition with corticosteroids and PT offer the best outcome, although complete recovery may not always occur. Additionally, prompt and accurate diagnosis avoids needless testing or surgery of the cervical spine or the rotator cuff. EDX testing is valuable in localizing the problem to the brachial plexus and to exclude other conditions that may cause overlapping signs and symptoms of PTS. With the rampant surge in the number of COVID-19 cases due to virus variants coupled with an increase in COVID-19 vaccinations, physicians should anticipate more patients with PTS, as has been our recent experience. Further analysis into the mechanisms that trigger neurological complications following COVID-19 infection or vaccine is warranted.

Acknowledgment

We acknowledge Norton Healthcare for their continued support.

Statement of Ethics

Written informed consent was obtained from the patients for publication of this case series and any accompanying images. The University of Louisville Institutional Review Board determined that our study was exempt according to 45 CFR 46.101(b) under Category 4. The Institutional Review Board number is 21.0567.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that there were no funding sources for their work.

Author Contributions

Lisa B.E. Shields: data conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript and gave final approval. Vasudeva G. Iyer: data conception, design, acquisition, analysis, and interpretation; critically revised the manuscript and gave final approval. Yi Ping Zhang: data conception, design, acquisition, analysis, and interpretation; critically revised the manuscript and gave final approval. John T. Burger: data conception, design, acquisition, analysis, and interpretation; critically revised the manuscript and gave final approval. Christopher B. Shields: data conception, design, acquisition, analysis, and interpretation; critically revised the manuscript and gave final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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