REPORT

https:/doi.org/10.64611/XANZ9910

PATHOGENESIS OF ADHESIVE ARACHNOIDITIS: RISK FACTORS INCITING EVENTS, VIRAL REACTIVATION, INFLAMMATION AND AUTOIMMUNITY

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Published by

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JULY 2026

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INTRODUCTION

Adhesive arachnoiditis was defined in medical dictionaries in 1873 as inflammation of the arachnoid membrane. Over the past 153 years the disease has tended to have singular causes. In the 1800's and early 1900's before the advent of antibiotics, the infectious diseases of gonorrhea, syphilis, and tuberculosis were the main causes. In the latter half of the 1900's, dyes used in myelograms proved toxic to some people and caused adhesive arachnoiditis. At the start of this century, AA seemed to be increasing in incidence and prevalence due to an increase in epidural spinal injections and spine surgery related to degenerative disc disorders. In the year 2017, the Tennant Foundation initiated Arachnoiditis Hope with a mission to bring diagnosis and treatment of AA to every community. To accomplish our mission our first efforts were to learn more about the disease and to develop diagnostic criteria and treatment protocols. Over the past eight years our studies of today's persons with AA, show that most AA patients have acquired the disease quite differently from the past when it had a singular identifiable cause.

For AA to develop it has to have an inciting event that causes cellular damage and inflammation to the arachnoid membrane. The most common initiating events are the medical procedures of epidural injections, spinal puncture, and surgery. Rather than heal as usual with an inflammatory lesion, the inflammation continues due to an autoimmune disorder. The Epstein-Barr virus appears responsible for the ongoing autoimmune process. The virus can reactivate and develop an autoimmune disorder. In summary, to develop AA, there is an inciting event that causes cellular damage and inflammation. Healing doesn't take place and an autoimmune process takes over and instills a long-term inflammation that leads to AA. In our studies we have found a subgroup of AA patients who have an inciting event such as spine trauma or an infection that may take place in early life. Epstein-Barr virus was reactivated, and an autoimmune disorder initiated. These persons went on to develop multiple pain conditions and eventually developed AA. Due to these new observations and their profound significance, this report has been written to explain step-by-step how we arrived at the pathogenesis for this terrible disease.

THE INFLAMMATION MYSTERY

Arachnoiditis was defined as an inflammatory disease of the arachnoid membrane in 1873. Since that time, tissues examined at autopsy of AA victims have confirmed the presence of chronic inflammation. In 2017, no blood test confirmation of chronic inflammation had ever been done so we measured inflammatory markers to determine if AA patients show chronic inflammation in blood. Our studies clearly showed that AA is a chronic inflammatory disease. A major question remained. What caused inflammation to develop in the arachnoid membrane and cauda equina in the first place and to the point that it produced adhesions that fused the two tissues together? After all, inflammation is usually the body's response to tissue injury, and it subsides as healing takes place. A big mystery looms. The cause of inflammation in the

arachnoid and cauda equina is clear (i.e., epidural), but why doesn't the inflammation resolve itself?

SPINAL CALAMITY

In starting to review AA cases a shock hit. Essentially, all cases reported a wide variety of spinal disorders. The attached Table shows spinal manifestations of 80 cases of AA. The number of epidural injections and surgery are incredible. With this kind of repetitive spine trauma; no wonder it triggers AA. The presence of such ubiquitous spinal disorders that accompanied AA led to a question. Why did this group of patients have so many spine disorders besides AA. Which came first, AA or the spine disorders? Interestingly, patients almost universally didn't know they had a spine problem until they sought medical help for back pain. Few could give a history of back trauma or an injury such as overlifting or a fall.

TABLE ONE

Clinical Profile of 80 MRI-Documented
Cases of Adhesive Arachnoiditis

	NO.
1. Females	65 – 81%
2. Males	15 – 19%
3. Age Range in Years	18 to 80
4. Mean Age ± S.D. in Years	48.9 ± 13.7
5. No. with a Predisposing Spinal Condition	61 – 76.3%
a. Herniated discs	44 – 55%
b. Spondylolisthesis	17 – 21.25%
c. Osteoporosis	6 – 7.5%
d. Spine arthritis	23 – 28.75%
e. Scoliosis	9 – 11.25%
f. Tarlov cysts	9 – 11.25%
6. No. with One or More Spinal Surgeries	43 – 53.8%
7. Total No. of Spine Surgeries in 43 Cases	91
8. Range of Surgeries in 43 Cases	1 to 8
9. No. Who Had 2 or More Spine Surgeries	22 – 27.5%
10. No. Who Had One or More Epidural Injections	69 – 86.3%
11. Total No. Epidural Injections in 69 Cases	236
12. Range of Epidural Injections in 69 Cases	1 to 20
13. No. Reported Over 8 Epidural Injections	16 – 20.0%
14. Symptoms and Complications Reported by Over 55% of Cases	
a. Pain Relief on standing	70 – 87.5%

b. Standing Too Long Causes Need to Lie Down	69 – 86.3%
c. Hurts to Lie Flat on Back	67 – 83.8%
d. Pain Always Present	66 – 82.5%
e. Shooting Pains, Tremors, or Jerking in Legs	64 – 78.8%
f. Burning Pains in Feet	63 – 78.8%
g. Cold Hands or Feet	58 – 72.5%
h. Crawling of Insects on Skin	58 – 72.5%
i. Water Dripping/Running Down Legs	53 – 66.3%
j. Difficulties Starting Urination/Defecation	51 – 63.8%
k. Leg Raise Hurts Back	50 – 62.5%
l. Blurred Vision	47 – 58.8%
m. Pain Behind Eyes	45 – 56.3%

MEDICAL CONDITIONS BEFORE AA

The prior section described the almost unbelievable presence of other spinal conditions in persons with AA. Our studies also showed that some AA patients have a very high prevalence of non-spine medical conditions before they developed AA. Table Two shows medical conditions in 64 cases of AA.

TABLE TWO
Previous or Concomitant Medical Conditions in 64 Cases of AA
(More than one prior condition may be listed per participant)

	Condition	N	%
1	Disc bulging/herniation	47	73.4%
2	Infectious mononucleosis	21	32.8%
3	Ehlers-Danlos Syndrome	15	23.4%
4	Fibromyalgia	12	18.8%
5	Autoimmune – unspecified	11	17.2%
6	Hashimoto's	8	12.5%
7	Sjogren's	5	7.8%
8	Rheumatoid arthritis	3	4.7%
9	Tarlov cysts	3	4.7%
10	Psoriasis	3	4.7%
11	Lupus	2	3.1%
12	Scoliosis	1	1.9%

Lori Verton and her associates of Arachnoiditis & Chronic Meningitis Collaborative Research Network (ACMCRN) compiled a brilliant description of 1105 cases of AA. They found that 72.2% of AA patients had one or more medical conditions prior to AA. The top 20 conditions from their research are listed in Table Three.

THE AA PATIENT IS IN A COMPLEX OF DISORDERS

Our studies came to the startling conclusion that some AA patients have many pathologic pain disorders. The obvious question was, "how and why did all the co-morbidities occur in the AA patient?" Furthermore, almost all the co-morbidities are known to have an inflammatory underpinning. But how and why did the process start? Simply put, the patient with AA seemed to be one component of an inflammatory disease process that affected many bodily tissues.

TABLE THREE
Medical Conditions in 1105 Cases of AA

Condition	N	%
Degenerative disc disease	268	32.3
Spinal stenosis	210	25.3
Fibromyalgia	207	25.0
Hypertension	112	13.5
Osteoarthritis	103	12.4
Arthritis (unspecified)	99	11.9
Cauda equina syndrome	91	11.0
Scoliosis	85	10.3
Clinical depression	84	10.1
Migraine	83	10.0
Failed back surgery	82	9.9
Tarlov cysts	81	9.8
Herniated disc	70	8.4
Hypothyroidism	69	8.3
Anxiety/generalized anxiety disorder (GAD)	68	8.2
Ehlers-Danlos Syndrome	66	8.0
Diabetes mellitus	56	6.8
Bulging discs	53	6.4
Complex regional pain syndrome	50	6.0
Rheumatoid arthritis	47	5.7

The message in this Table is that AA patients have many different medical conditions prior to the development of AA. This picture suggests that AA is one disease in a disorder with multiple manifestations.

RISK FACTORS

A risk factor makes one more susceptible to a disease. It doesn't necessarily mean you will acquire the disease. There are several risk factors to develop AA. (See Table.) The various

Risk factors have different genetic abnormalities that make an individual with one or more factors susceptible to AA.

People who have Ehlers-Danlos Syndrome and other connective tissue diseases have a compromised immune system and a collagen defect in tissues that render them more easily damaged and inflamed. Tarlov cysts and structural spine abnormalities appear to cause tissue damage by pressure or friction with subsequent inflammation in the arachnoid membrane. Basically, the mechanism is constant rubbing and friction from pressure or misalignment of anatomic structures. Autoimmune diseases and infectious mononucleosis have deficient immune systems that are unable to prevent viral reactivation and chronic inflammation. Tethered cord involves the cauda equina and it is usually a result of chronic inflammation.

TABLE FOUR
Risk Factors for Adhesive Arachnoiditis

Ehlers-Danlos Syndrome
Tarlov cysts
Structural spine abnormalities (scoliosis, spondylolisthesis)
Autoimmune disease
Infectious mononucleosis
Tethered cord

INCITING EVENTS

To develop AA there must be an inciting event that produces cellular damage and inflammation in the arachnoid membrane. Inciting events are in one of two categories: (1) medical spinal procedure, (2) non-medical disorder.

TABLE FIVE
Common Inciting Events

Medical	Non-Medical
Spinal puncture Epidural injection Surgery	Spine trauma Infection (pneumonia, meningitis, Lyme, infectious mononucleosis) Contaminant in spinal fluid
An inciting event is one that causes cellular damage and inflammation to the arachnoid membrane.	

Our studies indicate that the pathologic pathway to AA may actually be initiated in childhood or adulthood long before AA symptoms occur. The autoimmune process that produces

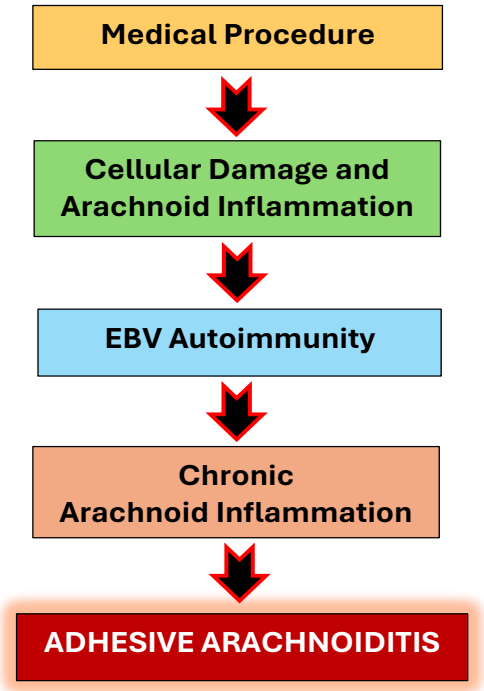
inflammation in spinal tissues such as the arachnoid may be very slow, insidious, and asymptomatic for years before enough tissue damage and inflammation causes pain and other symptoms.

If one asks an AA patient what caused their AA, the majority will say it was an epidural injection or spine surgery. They are correct. If the inciting cellular damage and inflammation do not heal, an autoimmune process (usually EBV) will propagate inflammation and AA may develop. Persons who have an epidural injection or surgery may already have an autoimmune disorder from a viral reactivation or genetic disease, and the medical procedure further stresses the immune system and makes the development of AA more likely. The medical procedure itself is a stressful occurrence and can cause viral reactivation.

MEDICAL PROCEDURES AS INCITING EVENTS

The prevalence and incidence of AA in this century have risen primarily due to medical procedures that involve the spine. This includes epidural injections, spinal punctures, and surgery. These medical procedures may cause EBV to reactivate, or if EBV reactivation and/or autoimmunity already exists, the medical procedure may accelerate the pathologic process that leads to AA.

THE USUAL PATHWAY TO AA
AFTER A SPINAL PUNCTURE, EPIDURAL, OR SURGERY



THE EPSTEIN-BARR STUDIES

For some time Epstein-Barr virus had been associated with autoimmune diseases including systemic lupus, rheumatoid arthritis, and Sjogren's Syndrome. Surprisingly, recent scientific announcements have concluded that EBV is also a causative factor in the development of multiple sclerosis (MS). Most interesting is that some persons with AA have MS. AA is a lower spine condition, and MS is in the upper spine. A review of the reports linking EBV to MS are persuasive.

EBV TESTING OF AA PATIENTS

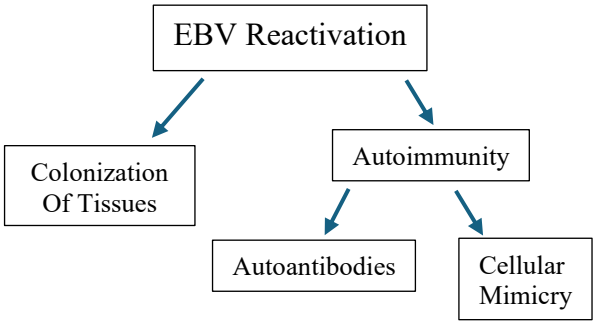
Since EBV was linked to MS we believed it essential to test AA patients to see if there was also an association of high EBV antibodies in AA patients.

In January 2023 we asked persons with documented AA in our study group to take EBV blood tests under supervision of their personal physician. Testing was done by their local laboratory resource. One-hundred-ten persons submitted their results along with some basic demographic data. There were 94 (85.5) females and 16 (14.5% males. Ages ranged from 26 to 80. Table Five shows the test results. All were tested for VCA IgG and EBNA IgG antibodies. Ninety-four (94.3%) showed antibody levels of both antibodies to be above normal range for their testing laboratory. Perhaps significant is that over 50% of the cases of VCA IgG and EBNA IgG had antibody levels above their laboratory's maximal testing threshold suggesting that EBV reactivation had repeatedly taken place in the past. Forty-one patients were tested for early EBNA IgG antibody which is a marker for Current EBV reactivation, and 29 (70.7%) were found to be positive. It is important to note that a high EBNA antibody suggests the presence of chronic autoimmunity.

Most study participants gave a history compatible with multi-site, migratory pain and inflammatory diseases that preceded their development of AA. Others were generally healthy and developed AA after an epidural, spinal puncture, or surgery. All suffered intractable pain and required daily pain relief medications. About 20% said they had experienced infectious mononucleosis. Given our test results we have to conclude that EBV reactivation and autoimmunity play a causative role in essentially all AA patients.

TABLE FIVE Epstein-Barr Virus (EBV) Antibodies in 110 Patients with Adhesive Arachnoiditis			
	No. Tested	No. + Positive	%
EBV Viral Capsid IgG Antibody (VCA)	106	105	99.1
EBV Nuclear Antigen IgG (EBNA)	105	99	94.3
EBV Vira Capsid IgM Antibody (VCA IgM0	94	5	5.3
Early Nuclear Antigen IgG Antibody (EA-EBNA IgG)	41	29	70.7
A positive test was an antibody level above the laboratory's normal test range. Elevated VCA and EBNA antibodies indicate reactivation and are considered markers for autoimmunity. EBNA is believed to be the major carrier of EBV autoantibodies. VCA IgM indicates symptomatic active, current infection such as infectious mononucleosis. I am uncertain why five patients tested positive for EBV IgM antibodies other than they may have an unknown active EBV infection. Early-EBNA indicates current reactivation of EBV.			

HOW REACTIVATION CAUSES TISSUE DESTRUCTION AND PAIN



EBV PREDILECTION FOR NEURAL TISSUE

EBV colonization and autoimmunity have a predilection for neural tissues. This explains the high rate of disc degeneration and AA with EBV. Once EBV establishes an autoimmune process it produces inflammation in tissues which causes AA. EBV reactivation requires a temporary state of immune suppression. Most AA patients could relate to such a state occurring in their teenage or young adult years. The inciting events were trauma such as an automobile accident or a severe infection such as pneumonia or meningitis. About 20% had infectious mononucleosis.

ACUTE SPINE TRAUMA

Some persons with AA develop it after spine trauma such as a fall, auto accident, or surgery. We have heard the argument that EBV isn't involved in these cases. This is apparently not so. EBV

may reactivate at the time of the spine trauma and is causative in formulation of the ongoing inflammatory process.

TARLOV CYSTS

Tarlov cysts inside the spinal canal are outpouchings of the arachnoid membrane. These cysts may become inflamed and lead to AA. Tarlov cysts may grow and rub on the arachnoid membrane and cause cellular damage and inflammation that can lead to AA. EBV may reactivate and colonize tissues around Tarlov cysts.

CONCLUSION

AA is the end result of an inflammatory-autoimmune disorder resulting from an inciting event and EBV reactivation. EBV autoimmunity may cause other painful conditions besides AA accounting for the high prevalence of co-morbidities seen in AA patients. Medical procedures are the most common inciting event, and they appear to be the major cause that AA is increasing in the population in this century.

ALTERNATE CONCLUSION

At this point in time, I see no other explanation for the pathologic development of AA. I welcome challenges and alternative explanations to my conclusions.

SUMMARY

Adhesive arachnoiditis doesn't just happen. It is the end result of risk factors, inciting events, viral reactivation, and an inflammatory-autoimmune disorder. In simple terms, AA is initiated by an inciting event such as an epidural injection or spine trauma, but its long-term existence is the result of an autoimmune process.

This report has been written to inform all parties why we came to the conclusion presented here. It is recognized that our conclusions on AA causation are new and may be considered controversial. This gives any party the opportunity for dissent and rejection. Our view is that understanding the pathway to AA provides clinical understanding that permits the development of prevention and treatment measures.

NOTE OF INTEREST

Dr. Antonio Aldrete, in his book "Silent Epidemic," states that an autoimmune process caused the long-term inflammation of AA. His conclusion is the same as ours. Medical procedures are causing a "silent epidemic" and autoimmunity propagates inflammation.

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