AJNR

Susac's Syndrome

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This information is current as of May 17, 2025.

Susac's Syndrome

Susac's syndrome consists of the clinical triad of encephalopathy, branch retinal artery occlusions, and hearing loss. In 1975, I saw two patients with this syndrome within a matter of 3 weeks while serving in the United States Army at Walter Reed Army Hospital. The first patient was presented to me at a conference in Albany, New York, and the second was referred to me by Dr. John Selhorst. I reported these two cases at the 1977 annual meeting of the American Academy of Neurology and subsequently described these findings as microangiopathy of the brain and retina (1). None of my previous mentors at Letterman Army Hospital (Robert Daroff, Darell Buchanan, and Carl Gunderson), at the University of California (William Hoyt, Robert Fishman), or at the University of Miami (J. Lawton Smith, Joel Glaser, Daroff) had recognized this symptom complex. While at Walter Reed, I had Frank Walsh and David Cogan as consultants and neither of these senior giants in the neuro-ophthalmological field had ever encountered such patients.

Initially, I strongly considered this syndrome as a form of granulomatous angiitis (now designated "primary CNS vasculitis"), but branch retinal artery occlusions and hearing loss are not described in that disorder. I called it a "microangiopathy," since only the precapillary arterioles (<100 μm) were affected, and I presumed it to be immunologically mediated.

While in private practice in Winter Haven, Florida, I encountered two additional young women with this syndrome, and in 1986 presented one of them to Dr. William F. Hoyt at a Neuroophthalmological Symposium held in his honor. This young woman had an enigmatic encephalopathy for 6 months before she developed branch retinal artery occlusions and hearing loss. When Dr. Hoyt saw the branch retina artery occlusions, he announced the diagnosis as "Susac's syndrome." Dr. Robert B. Daroff, then Editor-in-Chief of *Neurology,* asked me to write a review in 1994 and insisted that I refer to the disorder as "Susac' s syndrome" (2). Modesty would have prevented me from by using this eponymic title, but Dr. Daroff was most persuasive and prevailed.

At that time, 1994, it seemed that Susac syndrome exclusively affected young women between the ages of 2l and 41 years: the first 20 patients reported had been women. Men were later reported, but there is a female predominance of 3 to 1, and the age range extends from 16 years to 58 years.

Headache, often severe and sometimes migrainous in character, is an almost constant complaint and may be the major presenting feature of the encephalopathy, which can manifest with cognitive changes, confusion, and memory and psychiatric disturbances. The accompanying multifocal neurologic signs usually distinguish this from a true psychiatric illness.

In 1994 at the Walsh Society meeting in Chicago, a case from the University of Michigan entitled, "The Eyes Have It," was presented. It was of a young woman admitted to a psychiatric ward with the history of being found in her bathroom "flushing the evil demons down the drain." An MR image showed multifocal white matter changes, including those in the corpus callosum. Following this, the presenter said, "A diagnostic maneuver was performed." Dr. Hoyt jumped up and said, "I guess you're going to show the branch retinal artery occlusions that Susac described." He pointed to me in the back of the room and actually spelled out my name, "S-U-S-A-C." The neuroradiologist on the panel disagreed with this violently and stated that the young woman *must* have multiple sclerosis and an unrelated process that was affecting her retinal arteries. The presenters from Michigan also rejected the Susac syndrome diagnosis. Hoyt almost had to be restrained.

MR findings in Susac syndrome always show corpus callosum involvement. We recently described this in 27 previously unreported patients in whom there was a predilection for the white mailer of both the supratentorial and infratentorial compartments (3). The lesions are typically small, multifocal, and frequently enhance during the acute stage (70%). Leptomeningeal enhancement was present in 33% and deep gray matter involvement (basal ganglia and thalamus) in 70%.

Although any part of the corpus callosum may be involved in Susac syndrome, the callosal lesions typically involve the central fibers with relative sparing of the periphery. Central callosal holes ensue as the active lesions resolve (3). In contrast to Susac syndrome, the callosal involvement in both multiple sclerosis and acute disseminated encephalomyelitis is on the undersurface of the corpus callosum at the septal interface. As encephalopathy abates, white matter lesions typically disappear, but atrophy becomes evident.

No strict clinical correlation exists between the degree of encephalopathy and the number of lesions evident on the MR image. There may be only a few white matter lesions in a patient who is profoundly encephalopathic. A prime example of this was in a 58-year-old man whose hemispheric white matter lesions could have easily been misinterpreted as age related, except for the characteristic callosal lesions of Susac syndrome.

What frustrates me is that with current MR imaging, the small cortical microinfarctions are not seen. They are almost certainly there, because every time a brain biopsy is done, microinfarctions are seen in the cortex as well as in the white matter and leptomeninges. There are occasional enhancing lesions within the cortex, but only rarely are the cortical microinfarctions evident on FLAIR, proton density–weighted, or T2-weighted images.

The cranial nerves are not involved in Susac syndrome. The hearing loss is due to cochlear involvement and the vertigo, if present, is due to semicircular canal involvement. We have been unsuccessful in detecting microinfarcts in either of these structures with gadolinium-enhanced T1-weighted imaging.

I asked Dr. Hoyt why this syndrome was not more frequently recognized and his response was, "The branch retinal artery occlusions were always hard to find." Thus, we recommend that in any unexplained encephalopathy predominantly involving the white matter, but also the gray matter and leptomeninges, a neuro-ophthalmologist or retinal specialist should evaluate the patient with a dilated funduscopic examination. If the branch retinal artery occlusions are not seen at the very onset, the examination should be repeated at frequent intervals, because occlusions may develop later in the course. These specialists are well attuned to the characteristic fundus picture of the branch retinal artery occlusions that are often associated with Gass plaques (4) and the multifocal fluorescence that Dr. Gass believes is pathognomonic for Susac syndrome.

Another reason Susac syndrome is under-diagnosed is that radiologists and neuroradiologists are not familiar with it. Frequently, the MR image is interpreted as "typical" for MS or acute disseminated encephalomyelitis. Other diagnoses that are entertained include meningeal carcinomatosis, aseptic meningitis, Lyme disease, cardioembolic disorder, complicated migraine, chronic encephalitis, and even Creutzfeldt-Jakob disease.

Extensive diagnostic laboratory studies will not show any evidence of connective tissue disorder, procoagulant state, or infectious disease. EEG findings are diffusely slow during encephalopathy. Lumbar puncture usually reveals a high spinal fluid protein and occasionally mild pleocytosis, usually lymphocytic. On occasion, an elevated IGG Index or synthesis rate and oligoclonal bands will be evident, leading to a mistaken diagnosis of multiple sclerorosis. Cerebral arteriography findings are almost always normal, because the involved precapillary arterioles (<100 μm) are beyond the resolution of arteriography. Fluorescein angiography, however, is extremely useful and will often show the branch retinal artery occlusions as well as the pathognomonic multifocal fluorescence of the branch arterioles.

The clinical course of Susac syndrome is usually self-limited, fluctuating, and monophasic. It lasts from 2–4 years but may be as short as 6 months or as long as 5 years in duration. Although some patients recover with little or no residual disease, others are profoundly impaired with cognitive deficits, gait disturbance, and hearing loss. Usually, vision is not seriously impaired.

The pathogenesis of this syndrome is unknown. Since these patients tend to improve spontaneously, it is difficult to evaluate the results of treatment, but treatment with intravenous methylprednisolone followed by oral steroids, in conjunction with cyclophosphamide or immunoglobulin, seems helpful. Some patients seem to respond to monotherapy with steroids, cyclophosphamide, or immunoglobulin. Anticoagulation has no role in the treatment of this disorder.

There is a form fruste of the disease in which recurrent branch retinal artery occlusions and hearing loss occur in the absence of encephalopathy. Even in these cases, MR imaging may show white matter changes, especially in the corpus callosum.

Finally, I would like to stress to neuroradiologists that lesions of the corpus callosum are not pathognomonic of multiple sclerosis and when they involve the central fibers, sparing the periphery, think Susac syndrome.

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Peripheral Nerve Imaging and the Magic Angle

High-resolution MR imaging of the peripheral nervous system (MR neurography) has gained acceptance as a clinical tool in the diagnosis of peripheral neuropathy and plexopathy. Clinical indications include the following: 1) suspected mass involving a peripheral nerve, 2) entrapment syndrome, 3) traumatic nerve injury, 4) post-treatment evaluation, and 5) symptoms unexplained by clinical examination (1). Morphologic and MR signal intensity characteristics of individual nerves or nerve plexuses are assessed visually in determining whether a nerve is normal or likely to have pathologic changes. Secondary imaging characteristics such as muscle denervation changes are used to aid in identification of the affected nerve(s). Focal or diffuse enlargement, a markedly nonuniform fascicular pattern, and loss of surrounding fat planes, as well as postcontrast enhancement of a nerve, are features that have been associated with neuropathy in the clinical settings noted above. The feature that has been most often used as a marker of disease is hyperintensity on short tau inversion recovery (STIR) or fat-saturated (fatsat) T2-weighted fast-spin-echo (FSE) images. This feature, as pointed out by Chappell et al in their article in this issue of the

AJNR, must now be evaluated more cautiously because normal peripheral nerves can exhibit increased signal intensity, mimicking disease, depending on the orientation of the nerve relative to the main magnetic field B_o of the MR system—"the magic angle" effect. In retrospect, this orientational dependence of signal intensity may be one of the factors—along with partial volume effects, signal intensity variation associated with the use of surface coils, inhomogeneous fat suppression with fatsat acquisitions, and differences between investigators in the choice of pulse sequence parameters—that have complicated the qualitative and quantitative differentiation of diseased nerves (especially the components of the brachial plexus) with mild or moderate hyperintensity from normal nerves, which are usually described as isointense to mildly hyperintense to adjacent muscle on STIR or fatsat T2-weighted FSE images.

Chappell et al have provided evidence of a magic angle effect for peripheral nerves by showing that there is a 46–175% increase in signal intensity in the median nerve as its orientation relative to the main B_o magnetic field changes from 0° (parallel to B_o) to 55° (the magic angle), accompanied by an increase in mean T2 relaxation times from 47.2 to 65.8 ms. Images depicting the signal intensity changes in the ulnar and sciatic nerves and brachial plexus as a function of orientation relative to B_o suggest that the effect is likely to be generalized for peripheral nerves and nerve plexuses. By presenting data acquired at 0.5 and 1.5 T, the authors demonstrate that the effect is not an "artifact" limited to one system or field strength. Finally, the authors show that a two-compartment model with chemical exchange, in which one compartment has protons with angle-dependent T2 and the other compartment has protons with angle-independent T2, provides a good fit to the data for the median nerve and the flexor tendon. The similar fit for peripheral nerve and tendon data strengthens the argument for a magic angle effect and implicates collagen as the structural component responsible for the effect.

The magic angle effect in tendons has been well characterized and results from the abundance of collagen, which has a highly ordered structure with bound water molecules (2–4). The protons in the bound water typically produce very short T2 values because of dipole-dipole interactions between nearby spins that result in dephasing of the MR signal intensity. Hence, tendons usually appear dark on MR images. The dipole-dipole interactions however, are minimized when the collagen fiber makes an angle of 55° (or 125°) with the direction of B_o. This contribution to relaxation is then diminished and results in increased T2 and higher signal intensity within tendons. As illustrated by Chappell et al in Figure 1 of their article, and as described by many earlier investigators (3), the mean T2 for tendons is generally short enough, and the dependence on orientation narrow enough, that tendons often remain visibly dark on STIR or T2-weighted images even as the magic angle is approached. The mean T2 for the median nerve reported by Chappell et al, though, is longer than the value for tendons, and as the magic angle is approached, the isointense or mildly hyperintense nerve becomes

visibly brighter as a result of the increase in signal intensity. Figure 1 demonstrates clearly that the magic angle effect for nerves may be more evident to the eye of the radiologist than the effect for tendons.

Why do peripheral nerves exhibit T2 anisotropy, resulting in the magic angle effect? Probably because peripheral nerves, like tendons, have collagen as a major structural component. Tendons consist of thick bundles of parallel, densely packed, Type I collagen fibers, and these hydrated fibers account for the T2 anisotropy. The largest peripheral nerves have three distinct layers of connective tissue: 1) endoneurium, which invests the axon–Schwann cell complex, is a loose connective tissue consisting of small, variably oriented, collagen fibrils, along with cellular elements and extracellular fluid; 2) perineurium, which ensheaths the endoneurium/axon–Schwann cell complexes forming fascicles, is more dense and consists of flat fibroblast-like cells interleaved with layers of longitudinally oriented collagen fibers and a few elastic fibers; and 3) epineurium, which envelops the nerve and sends extensions to surround the separate fascicles, is a dense, irregular connective tissue dominated by longitudinally oriented collagen fibers. As noted by Chappell et al, 49% of the total protein in whole nerve is collagen, primarily type I, and most of the collagen is located in epineurium, which occupies 22–88% of the nerve cross-sectional area.

Thus, the T2 anisotropy of peripheral nerves results from densely packed hydrated collagen, which is primarily located in epineurium. Although this conclusion seems reasonable, scrutiny of Figure 1 raises questions about the strict analogy with tendon. First, the marked increase in signal intensity in the median nerve at the magic angle (55°) in Figure 1 appears to be located within the perineurium-lined fascicles and not within the surrounding epineurium. This apparent discrepancy between the expected and the apparent location of the magic angle effect may be clarified by a correlative MR-anatomic study of the median nerve from cadaver wrist specimens, analogous to the work of Ikeda et al (5). Second, intrafascicular tissue, which appears to be responsible for the magic angle effect, has mild hyperintensity at 0° rather than the marked hypointensity of collagen in tendon. The etiology of this difference may be clarified by studies of the multicomponent T2 relaxation time behavior of peripheral nerves in vivo and in vitro (6) with histologic correlation.

In summary, Chappell et al have made a significant contribution to the literature on MR imaging of peripheral nerves. Neuroradiologists performing MR neurography studies should be just as aware of the magic angle effect for peripheral nerves as musculoskeletal radiologists are of the effect for tendons and ligaments. The potential for confusion in image interpretation should be considered when positioning the patient for the MR study, when employing unusual orientations or provocative tests involving flexion or extension of joints, and when evaluating the brachial and lumbosacral plexuses. Although the anatomic basis for orientational dependence of the signal inten-

sity of peripheral nerves in vivo will require additional studies, Chappell et al have established the importance of recognizing the clinical diagnostic implications of the magic angle effect. Furthermore, they have suggested that the effect, rather than being viewed as a pitfall in interpretation, may be exploited as a tool to assess the integrity of nerves. A decrease in the magic angle effect, secondary to an abnormal accumulation of free water or disruption of highly ordered structures like collagen, may be sought as a sign of an injured or diseased nerve.

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Back Surgery Begets Back Surgery

You probably last heard that old saying not very long ago when you and a colleague were reviewing the spinal MR images of some unfortunate patient with a history and pictorial evidence of multiple prior spine surgeries and the ominous history of "Failed Back Syndrome." It didn't matter if it was the cervical, thoracic, or lumbar spine. Everyone from the MR imaging technicians to the maintenance people knew exactly what this was all about: the patient had a simple starter laminectomy many years ago, which didn't cure the symptoms and had had two or more spine surgeries since. That patient is now either addicted to painkillers, being considered for yet another surgery, or both. He may also have arachnoiditis. He probably gets frequent flier miles for his hospitalizations. He is never going to be pain-free.

Why is this "failed back" syndrome such a common entity? Although it is true that patients sometimes simply do not respond to the best, most targeted, and correct surgical procedure for their symptoms, most often the "failed back" patient didn't get better, because the most appropriate surgical procedure may not have been the one he received. Or it wasn't enough. In turn, this error may have been due to the original diagnosis not being precise enough. The problem goes all the way back to the multiple overlapping possible causes of back pain.

Back pain is such a protean condition that not any one simple etiology is usually the cause, unless the patient has a very specific radiculopathy due to a very specific extruded disk fragment seen at MR imaging to be sitting directly on that irritated nerve root. Then it can be reasonably expected that, if the fragment is removed, the radiculopathy will disappear and not recur unless the disk extrudes again in the same anatomic location. This is the appropriate course of action in this situation, emergently if there is severe neurologic deficit, and after conservative therapy fails in other situations. Clinically, this disk impingement causing radiculopathy is actually less frequently encountered than the scenario in which a patient has vague but real back pain, with or without radiculop-

athy, and a good contribution of facet pain, muscle spasm pain, and psychogenic overlay. How does the clinician ever figure out which anatomic component is responsible for which pain component, and how much? Is operating on the intervertebral disk going to relieve this patient's pain?

Fortunately, more recent trends in spinal disease diagnosis and therapy place much more emphasis on obtaining the most precise anatomic diagnosis the *first* time around, before any surgery takes place at all. Recent trends also strongly favor conservative trials, such as physical therapy and anti-inflammatory medications before even considering surgery. Very often, nothing else is necessary and in the natural course of things large numbers of patients get over the acute phase and can exist symptom–free, or relatively so, without ever going under the knife. This course of action seems much more likely to ensure successful symptom relief for the suffering patient than trying to figure it out over many years and many trial-and-error surgeries in a futile effort to eliminate one possible cause after another until the patient has nothing left but enough titanium to set off the metal detectors at the airport.

Under this conservative scenario, surgery become a last choice, when conservative therapy fails. Outcomes are much better when surgery is thus targeted, more focused and selective, with the correct procedure now likely to be applied to the correct anatomic or biomechanical diagnosis the first time around. Not every case of back pain needs a laminectomy and diskectomy, and not everyone needs screws and plates.

Part of the this evolving better understanding of the individual but interdependent causes of spinal pain syndromes has come courtesy of the orthopedic spine surgeons, who emphasized biomechanics. Neither neuroradiologists nor neurosurgeons had much of any understanding of this concept before the orthopedics started talking about it. The first Interdisciplinary Spine Conference held in Snowbird, Utah in 1989 was the first time most participants ever heard

anyone take the biomechanical theories of Punjabi and White seriously. These concepts make a great deal of sense, because the spine is not a static construct and is actually designed to function through a wide range of movement, and have subsequently led to increased considerations of biomechanics in every surgical procedure.

Most tellingly, it is now desirable to leave the postoperative spine patient with some muscle and tendon dorsally in the operative site to support the spine when laminectomies alone are performed. If wide decompression surgery is contemplated, some sort of fusion procedure will be necessary to lend support afterward. Hardware development for spinal fusion became a growth industry and companies that manufactured the devices enjoyed phenomenal initial public offerings in the late 1990s. Primary instrumentation and stabilization came to be considered beneficial in cases of spinal instability, with or without decompression. Disk space cages, interbody fusion devices, and, on the horizon, disk replacement devices were designed and helped many patients.

Perhaps even more important, practitioners recognized that not all spinal pain syndromes started and ended with the intervertebral disks, and facets and other tissues could be involved in pain production. Disks did not even need to protrude or extrude (or herniate) and could hurt all on their own without compressing neural tissue. It is easy to forget how revolutionary these concepts were not that long ago.

In this issue of the *AJNR,* Cyteval et al present a clinical approach to spine disease than we as neuroradiologists may be accustomed to. Interventional neuroradiologists have been at the forefront, with clinical outcomes articles that have gone a long way toward the ultimate acceptance of embolization techniques in vascular diseases of the brain and vertebroplasties in the spine. This article brings us further into an era in which the efficacy of spinal injection procedures may finally be subjected to necessarily rigorous clinical studies to determine their ultimate usefulness.

For as many nerve root sleeve blocks, facet blocks, and diskographys neuroradiologists perform, there are no well-designed long- or even short-term clinical studies in the neuroradiology literature to support the efficacy of these techniques. We write articles about techniques, but cannot seem to define the problems well enough to examine the efficacy. There are some studies to be found in the orthopedic, physical therapy and rehabilitaion, and anesthesia literatures, but these spinal injection procedures are still performed by those specialties (and by us) very much in a spirit of empiricism. Long-term studies are difficult for many reasons, not the least of which is the question of how to define "long-term relief." Without any specific endpoint, some authors consider long-term relief to be up to and including 3 months. Others have no problem with long-term relief because they argue that the only reason to perform a nerve root block or facet block is to define the pain generator for the surgeon and then to ensure a better ultimate surgical outcome. This really is not a bad goal and may actually be the most important use of the procedures after all.

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