Clinical Course

The clinical course (how the disease behaves over time) and long term outcome of SS differ from patient to patient. Many patients experience an acute or subacute “monophasic encephalopathic course” that lasts 1-3 years and is not followed by any further disease activity. If the disease during those 1-3 years is relatively mild or is otherwise successfully controlled by immunosuppressive medication, the outcome can be very good---i.e. little or no permanent damage sustained. With more severe disease, more prolonged disease, or both, there is potential for permanent, severe irreversible damage---i.e. varying degrees of dementia, visual loss, and deafness.

In addition to the “monophasic encephalopathic course,” there appears to be a somewhat milder and somewhat less worrisome (but often longer) course that is characterized chiefly by recurrent episodes of BRAO and hearing loss (the “recurrent BRAO/HL course”). Other patients appear to have somewhat of a mixed or shifting course, with a monophasic encephalopathic course that is either followed or preceded by a recurrent BRAO/HL.

Before going further, we must emphasize that most patients with SS do not have all three components of the clinical triad (encephalopathy, retinal vasculopathy, and inner ear disease) at the onset of their disease. Usually, only one or two of the three are present during the first couple of weeks (sometimes longer) of the disease. For example, in an important study of nine patients (Aubart-Cohen, et al):

- 5 of the 9 patients presented with eye symptoms and symptoms of encephalopathy (brain symptoms), but no hearing loss.
- 2 of the 9 patients, presented with only eye symptoms—the rest of the triad appearing later.
- 1 of 9 patients presented with only hearing loss.
- Only 1 of the 9 patients had all three components of the triad at onset of the disease.
- None of the 9 patients presented with isolated encephalopathy (but, this can occur).

So, eye symptoms were an initial manifestation in 8 of the 9 cases; encephalopathy symptoms were an initial manifestation in 6 of 9 cases; and inner ear symptoms were an initial manifestation in 2 of 9. Eye symptoms (visual disturbance, visual blurring, dark spots in the visual field), therefore, were the most common symptoms at disease onset, at least in this small series of patients.

On average, the triad is completed within 13 months (Aubart-Cohen). However, sometimes 2-3 years may pass before an individual patient finally develops the third component of the triad.
Regarding the long-term clinical course, review of all of the published case reports of SS, plus study of many unpublished cases with which we have become familiar, suggest several different clinical course patterns (and variations of them). These patterns are shown in graphic form (see the 5 graphs below) and are then discussed individually.

Monophasic Encephalopathic Course

Many patients present with a relatively acute onset of encephalopathy symptoms (usually accompanied by either ocular disease, inner ear disease, or both) and experience a self-limited course that spontaneously remits within 1-3 years, with no further encephalopathic disease beyond that point (i.e., a one time only, monophasic course). This is exemplified in the Figures 14 and 34.

- By “encephalopathy” we mean symptoms such as headache, memory loss, confusion, disorientation, personality change, cognitive dysfunction.
- By “acute” we mean that the patient was well and then rather suddenly developed symptoms that reach a peak within a couple or a few weeks. Often this acute onset is fulminant.
- Sometimes the onset is “subacute” or insidious, rather than acute and fulminant, meaning that the initial symptoms develop more slowly and less dramatically (but progressively) over a period of many weeks or several months. Rarely, patients experience indefinite, but at least possible hints of SS mischief, either intermittently or progressively, for a few years before their much more obvious and definite monophasic course begins.
- During the 1-3 years of active disease, the severity and intensity of the disease tends to be greatest during the first half of that time. Then the disease seems to gradually subside, as if the person’s immune system is finally able to at least gradually self correct its mistake. (That is why more
aggressive treatment is necessary early, and that is why medication, which could not be successfully tapered earlier, can be successfully tapered later.)

- During the 1-3 years of active disease, the intensity of disease activity may fluctuate only minimally, but often the disease either fluctuates widely or waxes and wanes at least moderately. In fact, sometimes the fluctuation is so wide that the disease seems to be episodic (remitting, relapsing, remitting again, relapsing again) within those 1-3 years (as in Figure 34).
- It is probably more common for the disease to remit within 9-18 months, than to continue for a full 2-3 years.
- Sometimes, however, the monophasic course extends beyond 3 years. When this happens, remission usually occurs within 3-4 years. In rare instances the disease remains active, usually in a waxing and waning fashion, for 5 or more years. There is one published report of a patient who experienced unrelentingly active disease for 10 straight years.
- On the other hand, some patients experience a monophasic course that seems to remit within 6 months, even within a few months.
- Although the vast majority of patients who appear to be experiencing a monophasic encephalopathic course do, in fact, go into remission and never experience a recurrence of encephalopathic disease, there are rare patients who experience a recurrence of encephalopathic disease. One patient experienced a recurrence 18 years after her initial encephalopathic course.
- Although patients who experience an encephalopathic monophasic course are not expected to experience a recurrence of encephalopathic disease, many do go on to experience recurrent episodes of retinal vasculopathy or inner ear disease, or both (see the BRAO/HL course described below), even for several years after the encephalopathic phase has resolved. See Figure 36.

Recurrent BRAO/HL Course

Many patients primarily experience repeated episodes of branch retinal artery occlusion (BRAO), or of hearing loss (HL), or of both—with either a minimum of encephalopathy symptoms (if so, usually only at the beginning of their disease), or no encephalopathy symptoms at any time. Below is what we know, don’t know, or partially know about the Recurrent BRAO/HL Course:

- When we say BRAO, we should also be aware that retinal vasculopathy can involve only retinal vessel “leakage,” without apparent occlusion. So, we should probably use the term “retinal vasculopathy,” which would refer to BRAO, “leakage,” or both. “Leakage” is a milder phenomenon than BRAO, but can lead to BRAO. Some patients experience recurrent episodes of retinal vessel “leakage,” without actual BRAO and even without symptoms.
- How frequently do these “recurrent episodes” occur?
  - Some patients, early in their disease, might experience a new episode of BRAO, HL, or both, quite frequently (e.g. monthly, even weekly) at least for awhile.
  - We know that some experience episodes only 1-3 x/year and may even skip a year or two between episodes.
- How long do the individual episodes typically last (remain active)?
  - We suspect, but do not know for sure, that some of these episodes may spontaneously resolve within days or weeks—particularly episodes of leakage, without BRAO.
Can an individual episode take several months, though, before it finally and completely resolves? We suspect that some episodes could be more intense and stubborn than average and may take a few months to fully remit, even many months---but, this is unclear.

- Is their disease truly in remission between episodes?
  - Between episodes of BRAO or “leakage,” is there truly nothing active going on in the retinal vasculature? It seems possible that this is truly the case, but we do not know for sure. If so, no medication would be necessary between episodes.
  - Or, could there be at least some low-grade active disease going on in the retina (way out in the periphery, for example) and/or inner ear that may not be clinically apparent (between the obvious episodes), but could, cumulatively, cause regrettable harm? This seems quite possible. If so, it might be important to maintain at least some treatment between episodes, at least for awhile.
  - Are we sure that subclinical, asymptomatic CNS vasculopathy is not occurring along with the retinal and/or inner ear vasculopathy---either during the individual BRAO/HL episodes or even between them? This is unclear. If so, this initially inapparent CNS involvement could, cumulatively and eventually, become regrettably apparent.

- For how many years can a patient continue to experience these recurrent episodes?
  - We know of one patient who has been experiencing recurrent episodes of BRAO (without encephalopathy) now for 30 years, with an episode occurring every few years? (She initially had mild encephalopathy at the beginning of her SS, but never had evidence of encephalopathy after that.) She probably represents an exception.
  - Other patients have had recurrent episodes for at least 6-10 years.
  - Some patients have had only 1-2 isolated episodes, ever.

- How much encephalopathy do these patients experience, and when do they experience it?
  - Do some truly never experience any clinically evident encephalopathy? Probably so, but we don’t know what percentage.
  - Do some experience some initial mild encephalopathy, but none after that, despite continued recurrent episodes of BRAO/HL? Yes, this appears to be the case.
  - So far, almost all patients in this recurrent BRAO/HL subset have had definite and typical SS MRI abnormalities (often mild), at least at some point during the course of their disease---but, there appear to be exceptions.
  - Do some patients present with the full, even florid, triad---but then proceed to experience only a recurrent BRAO/HL course, without any further encephalopathy? Yes, and we would say they started with the monophasic encephalopathic form of SS and then their disease shifted into the BRAO/HL form. That is, they experienced an encephalopathic onset, but subsequently followed a recurrent BRAO/HL course.
  - Do some start with a BRAO/HL onset, but later develop an encephalopathic episode? Yes, there are examples of this, but the encephalopathic episode usually occurs sooner, rather than much later. That is, some patients appear initially to have the BRAO/HL subset, but soon develop the encephalopathic form of the disease.
  - Do some patients who are following a recurrent BRAO/HL course experience subclinical, asymptomatic CNS involvement that only becomes evident years later, in retrospect? We don’t know.

- Should this subset be treated differently than the typical encephalopathic patient? Possibly so. (See section on treatment.)
Mixed or Shifting Course

- Some patients shift from one course to the other, or experience both course types simultaneously.
- As mentioned above, some patients start off with an apparent recurrent BRAO/HL course, but then experience a typical monophasic encephalopathic course. Usually, the longer a patient experiences only a recurrent BRAO/HL course, the less likely it is that they will ever experience a monophasic encephalopathic course. In other words, if a patient presents with BRAO and/or Hearing Loss and does not develop encephalopathy within about two years, the chances are very good that such a patient will never develop encephalopathy.
- Some patients initially experience a monophasic Encephalopathic course, which fully resolves, but is followed, even for years, by at least a mild recurrent BRAO/HL course (more commonly involving recurrent retinal disease than recurrent inner ear disease).
- Some patients primarily experience an encephalopathic monophasic course, but seem to also be experiencing a recurrent BRAO/HL course during that same block of time.

How predictable is a given patient's clinical course?

Early in the course of a patient’s disease, it appears to be very difficult to predict what kind of a course, how severe a course, and how long a course that patient will experience. Some patients who present with very severe and very worrisome encephalopathic disease turn out to experience only a short course and have an excellent outcome (especially if treated promptly and aggressively while the disease is active). Other patients, who initially appear to have only mild disease, go on to experience a very difficult course. As the patient’s disease unfolds and more or less declares its intentions (i.e. the course type becomes more recognizable), then it becomes easier to more accurately predict the patient’s subsequent experience.

One of the primary purposes of the SS-International Collaborative Study is to gather more details so that we can more accurately understand the natural clinical course of SS—including early predictors of likely clinical course and outcome.

Outcome of SS

The outcome of SS depends on several factors:

- The clinical course type
- The clinical course duration
- The severity/intensity of the disease (particularly the encephalopathy) while it is active
- How promptly and aggressively the disease is treated.

The worst outcome will likely occur in a patient who experiences a particularly severe and particularly prolonged encephalopathic course that is difficult to control with immunosuppressive medications. Such patients may end up with severe cognitive impairment, even dementia.
Patients whose encephalopathic course is either of short duration, or of only mild severity, or both, are likely to have a good outcome, particularly if they receive prompt, appropriately aggressive, and appropriately sustained therapy. They may return to normal intellectual function, or may have only subtle deficits.

Patients who experience a recurrent BRAO/HL course do much better than do those who experience a monophasic encephalopathic course, particularly those who never develop any clinically evident encephalopathic features. The main concern in these patients is the extent of irreversible visual impairment or irreversible hearing loss they might develop. (Our other concern, though, is our worry that a subtle, but important, amount of subclinical, asymptomatic encephalopathy could, possibly, be accompanying the BRAO and HL.)

Although many episodes of BRAO resolve without any clinically apparent residua, recurrent and/or severe BRAOs sometimes cumulatively eventuate in markedly restricted visual fields. In severe cases, a person’s vision might approximate that of looking through toilet paper cylinders---i.e. no peripheral vision at all. Usually, even in cases of severe visual field loss, visual acuity is well preserved.

When hearing loss first occurs, it is difficult to predict the likely amount of irreversible hearing loss that will develop. If the initial ischemic injury to the cochlea is very quick and very severe there may not be sufficient time for even the most prompt and aggressive therapy to save the hearing. Such patients may develop profound deafness and may need (and benefit from) cochlear implants. Less severe, less prolonged, and less frequent “hits” to the cochlea will lead to less irreversible hearing loss.

So, in the worst case scenario, SS can cause dementia (including profound personality change), blindness, and deafness---but, this would be very rare. In the best case scenario, the patient may experience no residual effects, other than minor visual field loss and mild hearing loss. But, with the encephalopathic form of the disease mild-moderate permanent neurocognitive dysfunction is always a potentiality.

A major purpose of the SS-International Collaborative Study is to learn more about the very best way to treat the various courses of SS, so that improved outcome may occur.