Clinical Study: The Susac’s Syndrome International Collaborative Study (SS-ICS)

Purpose of the Study
Most of the currently available information on Susac’s Syndrome is based on analysis of case reports and relatively small series of patients. There is great need for a comprehensive, systematic, prospective and retrospective, global study of a large number of patients with SS.

The purpose of the Susac’s Syndrome International Collaborative Study (SS-ICS), therefore, is to efficiently collect, analyze, and share new, scientifically sound information regarding the clinical features, clinical spectrum, clinical assessment, natural history, treatment, clinical course, and long-term outcome of Susac’s Syndrome. The study seeks to collect clinical information on at least 50 current, 50 past and 50 future patients with Susac’s Syndrome, from around the world.

Ethics Approval for the Study
When Dr. Rennebohm was at the University of Calgary, the Susac’s Syndrome International Collaborative Study was granted ethical approval by the Conjoint Health Research Ethics Board of the Faculty of Medicine at the University of Calgary (Ethics ID: E-22423). Now that Dr. Rennebohm has moved to the Cleveland Clinic, new Institutional Review Board (IRB) approval needs to be obtained. This is in process.

All patients who participate in the Study will need to sign a Consent Form before enrolment in the Study.

The SS-International Collaborative Study Website
To announce and facilitate the SS-ICS, we have created the Susac’s Syndrome Website that you are now visiting. The Website explains the study, provides background educational materials about Susac’s Syndrome, will facilitate patient enrolment, offers treatment and management guidelines, and provides a set of the uniform data collection forms and disease assessment forms that physicians and patients can use for their own purposes (to facilitate patient care), and potentially submit for research purposes. These forms and instruments have been carefully designed to simultaneously help physicians during the day-to-day care of their patient with SS, help patients (and families) keep track of their disease progress, and facilitate data collection for study purposes. Physicians, patients, and families from around the world will be able to access the Website and the data collection forms.

When Will this Study Begin?
As soon as IRB approval is obtained from the Cleveland Clinic we will be ready to re-launch the study.

Significance of the Susac’s Syndrome International Collaborative Study
The results of this study’s sub-projects and sub-studies (see below) will add greatly to our understanding of the clinical features, clinical spectrum, clinical assessment, natural history, treatment, clinical course, and long-term outcome of Susac’s Syndrome. The study may also give us further insight regarding the immunopathogenesis (the cause) of SS.
The study, particularly its associated website, will greatly increase physician, patient, and public awareness of SS. In particular, the study will increase awareness among the medical specialists and subspecialists who are most likely to encounter patients with SS: neurologists, neuro-ophthalmologists, ophthalmologists, rheumatologists, otologists, and neuro-radiologists.

The study will help us to better appreciate how rare, or not so rare, SS is—both in the pediatric and adult populations. Although SS may be relatively rare, the study will make it more likely that people who do develop SS will be more promptly diagnosed and most appropriately treated.

The study and the website will particularly benefit patients with Susac’s Syndrome who have been misdiagnosed as having “atypical multiple sclerosis.”

Further knowledge of the immunopathogenesis, clinical course, and treatment of SS is likely to contribute substantially to our understanding of the many other, more common “autoimmune endotheliopathy disorders” such as juvenile dermatomyositis (JDM). Just as JDM has served as an instructive model for SS, SS may return the favor and serve as an instructive model for JDM and other microvascular endotheliopathies.

Principal Investigator
Robert Rennebohm, MD
Cleveland Clinic

Institutions Involved In This Study
Cleveland Clinic

Sub-Projects and Sub-Studies of the SS-ICS

The International Collaborative Study of SS includes the following sub-projects and sub-studies:

Creation of this Susac’s Syndrome Website, which serves to:
- Announce and describe the SS-International Collaborative Study.
- Provide educational materials on SS.
- Provide treatment and management guidelines for SS.
- Provide and explain data collection forms and disease assessment forms that are designed to facilitate both patient care and clinical research.

Creation of an International Disease Registry (IDR) of Patients with SS:

Fewer than 250 cases of Susac’s syndrome have been reported in the world’s medical literature. It is unclear how many other people, world-wide, have suffered with Susac’s syndrome. It is possible that Susac’s syndrome is much more common than has been realized—but, we do not know. We do not know how many new cases appear each year. We do not know whether Susac's syndrome is more common in certain ethnic groups or in certain countries. We do not know whether mild cases are more common than severe cases, or vice versa. We do not know whether partial versions of Susac’s syndrome are less common than full versions, or more common.
To help answer these questions, we have developed an International Disease Registry (IDR) to collect basic information on as many patients as possible, world-wide (patients who either currently have Susac's syndrome, or have had Susac's syndrome in the past, even the distant past). A simple, one-page IDR Form has been created to collect these basic data. The information on the IDR Form contains no patient identifying information. It contains only the following patient information:

- Patient’s age at time of diagnosis
- Patient’s gender
- Patient’s country of residence
- Patient’s ethnicity
- Yes/No answers to the following questions:
  - Did the patient experience encephalopathy?
  - Did the patient experience retinal vasculopathy (e.g. BRAO)?
  - Did the patient experience inner ear disease (e.g. hearing loss)?
  - Did the patient’s MRI reveal corpus callosal lesions?

The only other information on the IDR Form is a “registering physician code” (e.g. TB092465) that indicates who the registering physician is. Only that physician and the SS-ICS research team know the physician name (and a physician email address) associated with the registering physician code. Only the registering physician knows the name of the patient. The IDR Form does not contain the patient's name, address, or any other patient identifying information.

We are encouraging all physicians who know of patients with Susac's syndrome to consider registering such patients in the IDR. For further information regarding how patients can be registered properly (i.e. registered in a way that protects the privacy and confidentiality of the patient), physicians are encouraged to email Dr. Rennebohm (rennebr@ccf.org). If patients are interested in registering themselves, they may also contact Dr. Rennebohm for further information.

The International Disease Registry (IDR) represents a separate project from the other projects of the SS-International Collaborative Study (ICS). Whereas the IDR involves no patient identifying information, the other SS-ICS projects do involve patient identifying information.

Patients and physicians are certainly allowed to participate in only the IDR project and none of the other SS-ICS projects. In other words, participation in the IDR project does not obligate the physician or patient to participate in other SS-ICS projects. Patients who do wish to participate in other SS-ICS projects are certainly allowed to participate at any level they wish—from minimal or partial participation to maximal, full participation. In other words, signing up for participation in SS-ICS projects does not obligate the patient to do any more than what they wish and have time to do.

**Creation of Uniform Data Collection Forms and Disease Assessment Instruments:**

The data collection forms listed below have been designed to simultaneously facilitate the physician’s day-to-day care of the patient, to help the patient/family track the progress of their own disease, and to generate data for research purposes. It is our hope that the physician and patient/family will quickly find that serial completion of the forms (e.g. the SS-Disease Activity Score and the Medication Flow Sheet) will be very useful to them—in that serial documentation of the scores and medications will provide an easier, more efficient, and more accurate way to follow the progress of the patient.
The majority of the forms are designed as patient/family “self-report” forms. The rest of the forms—e.g. SS-CML (Cumulative Manifestations List), SS-DAS (Disease Activity Score), SS-DA-GA (Disease Activity Global Assessment), SS-PAM (Points of Active Mischief), and SS-DDS (Disease Damage Score)—will be completed by the Principal Investigator of the SS-ICS (and his Team) after the patient has signed the Consent Form and the patient’s medical records have been sent to the Principal Investigator.

To facilitate management of their own patient, physicians are encouraged to maintain the SS-MEDS (Medication Flow Sheet) and serially and prospectively use the disease assessment forms that they and their patient find particularly useful, clinically. The patient and family may also want to maintain the Medication Flow Sheet and use some of the forms, so that they can keep track of the patient’s progress.

The Forms and Documents:

- SS-International Disease Registry Form (SS-IDR)
- SS-Cumulative Manifestations List (SS-CML)
- SS-Disease Activity Score (SS-DAS)
- SS-DAS Scoring System (SS-DASS)
- SS-Definitions and Gradations (SS-DG)
- SS-Disease Activity-Global Assessment (SS-DA-GA)
- SS-Points of Active Susac’s Mischief (SS-PAM)
- SS-Hearing Loss Scale (SS-HL)
- SS-Tinnitus Self Assessment Scale (SS-TSAS)
- SS-Mini-Tinnitus Questionnaire (SS-Mini-T)
- SS-Health Assessment Questionnaire (SS-HAQ)
- SS-Quality of Life (QOL) Score (SS-QOL)
- SS-Disease Damage Score (SS-DDS)
- SS-SAGE Test: Cognitive Assessment (SS-SAGE)
- SS-Medication Flow Sheet (SS-MEDS)
- SS-MRI Assessment Form (SS-MRI)
- SS-Ophthalmologic Assessment Form (SS-OP)
- SS-Formal Neuro-Psychology Assessment (SS-FNPA)
- SS-Investigations Flow Sheet (SS-IFS)
- SS-Timeline for Evaluations, Questionnaires and testing (SS-TL)
- SS-Clinical Progress Score Sheet (SS-CP)

The plan is to establish email correspondence with physicians (as many as possible, from around the world) who are (or have been) involved in the clinical management of patients with SS. We will refer them to the SS Website and ask them to consider providing us (after obtaining consent from the patient/family) with clinical information on their patient(s). For consenting patients, the above listed clinical data gathering forms will be used to both retrospectively and prospectively collect those data.

Creation of National SS-ICS Teams in Countries throughout the World:

Our intention is to develop at least one National SS-ICS Team in as many countries as possible—with all of these National Teams working together as branches of the SS-ICS. These National SS-Teams will consist of a small group of neuro-ophthalmologists, neurologists, and rheumatologists who are willing to take the lead in coordinating SS-ICS efforts in their country.
Each National Team will be encouraged to organize efforts to increase patient, physician, and public awareness of SS in their country. Each Team will maintain a National SS-Disease Registry. National Teams will advertise the existence of this Registry, as well as the SS Website, through their local medical journals (particularly, journals of ophthalmology, neurology, rheumatology, radiology, and otology) and through their local medical societies and subspecialty list serves. The National Teams will share their National Registries with the International Registry. Each Team will serve as a Consultation Resource for physicians in their country who have patients with suspected or definite SS.

Validation of the SS-ICS Disease Assessment Instruments:

Where possible, we will be using already validated disease assessment instruments. However, we have had to create two new SS-specific instruments---SS-DAS (Disease Activity Score), SS-DDS (Disease Damage Score). These new disease assessment instruments/forms have been designed to be as non-frustrating and as clinically helpful/useful as possible for the patients and their physicians---otherwise the physicians and patients will not use them. The goal has been to make them so rewarding to fill out, that the physicians will feel uncomfortable trying to follow their patient's progress without serially using and referring to the forms (and the serial scores produced by them) in their day-to-day management of the patient.

The same is true for the patients/families, regarding their completion of forms. In other words, on a scale of 1 to 10 (with 10 being the highest positive rating) we want the physicians who are being asked to complete the forms to rate them as a “10,” regarding the clinical usefulness/helpfulness of the forms in their week-to-week management of their patient; and we want our research team to rate them a “10,” regarding the sufficiency and quality of the data. The study will fail if the latter rating is “10,” but the physician’s rating is “3,” because the physician probably will not complete the form, or will complete it begrudgingly (since it feels like such a burden), or is more likely to complete it in a hurried and lower quality way.

Fortunately, the physicians we will be asking to use these forms will typically have only one patient with SS. This should ease the sense of burden added to their already busy practices. Furthermore, the patients/families will likely have a huge vested interest in seeing to it that the forms are used---particularly if the scores from the forms help everyone to more accurately appreciate patient progress, or lack of it.

These newly developed SS-clinical assessment instruments will need to be validated---for inter-rater reliability, construct validity, and responsiveness to change. The data generated by these forms will also be compared to data generated by the already validated instruments.

Use of the SS-ICS Disease Assessment Instruments:

The key objective of the SS-ICSG is to enrol as many patients as possible (world-wide---at least 50 current, 50 past, and 50 future patients) in both the retrospective and prospective use of SS-ICSG forms and instruments listed earlier. Use of these forms/instruments, particularly prospective use of them, will allow us to capture important information about the clinical features, clinical spectrum, natural history, treatment needs, clinical course, and long-term outcome of SS. These forms/instruments will also be used to document the results of open, non-randomized study of the treatment of SS, and will be used in any future randomized clinical trials.

Retrospective and Prospective Study of SS in Children and Adolescents:
Only 8 cases of SS in children/adolescents have been reported in the international medical literature. It is likely, however, that SS has been under-diagnosed and under-reported in children, as well as in adults. Most pediatricians, including pediatric rheumatologists, ophthalmologists, and neurologists, have either never heard of SS or are minimally aware of it. The primary objectives of this sub-study are:

- To increase physician awareness of SS in children
- To survey the international pediatric rheumatology community, the pediatric ophthalmology community, and the pediatric neurology community (via professional List Serves) to determine how many cases of pediatric SS have been noted by members of these medical communities.
- To retrospectively collect and analyze data on the patients so identified, with particular attention to:
  - Clinical characteristics at the time of diagnosis
  - Treatment, including response to various treatments
  - Clinical course
  - Outcome
  - Comparison of SS in children vs. SS in adults

**Retrospective Study of Treatment of SS with Rituximab:**

The current recommendations for treatment of severe encephalopathic SS are based on the treatment of severe juvenile dermatomyositis (JDM)—a better known and more extensively studied autoimmune microvascular endotheliopathy disorder. The immunosuppressive therapies that have seemed to benefit patients with JDM have included oral prednisone, pulses of methylprednisolone, IVIG, methotrexate, and Cyclophosphamide. These same therapies have appeared to benefit patients with SS.

The most recently studied therapy for JDM has been rituximab—an anti-CD20 B cell antibody. Rituximab has been shown to be a promising therapy for a number of autoimmune diseases, including rheumatoid arthritis, lupus, Sjögren’s syndrome, ITP, and autoimmune hemolytic anemia—as well as juvenile and adult dermatomyositis. Because rituximab appears to be a promising option for treatment of dermatomyositis, it has been mentioned as a reasonable innovative option for treatment of SS (2-4).

We are aware of a number of physicians (approximately 10) who have opted to treat SS with rituximab. They and their patients have usually chosen this option because they have viewed it as a less risky alternative to Cyclophosphamide and because rituximab has shown potential to be effective and steroid sparing. Preliminary feedback suggests that the majority of patients (and their physicians) who have used rituximab believe it has been effective.

Since rituximab is increasingly being used for a variety of autoimmune diseases, including dermatomyositis and SS, it is important to conduct a formal retrospective study to determine the extent to which rituximab has benefited patients with SS. To determine whether rituximab is worthy of inclusion in any future clinical trial of treatment for SS, it is obviously important to retrospectively and systematically study patients with SS who have already been treated with rituximab.

**Long-Term Outcome of SS:**

Little is known about the long term outcome of patients who have had SS. By “long term outcome” we mean the status of patients 5, 10, 20, 30 years after onset of their disease.

- What are patients with SS like 5, 10, 20, or 30 years after disease onset?
- How much irreversible damage has the disease caused?
• How well are patients functioning, cognitively, physically, and emotionally?
• How much memory deficit?
• How much impairment of “executive function”?
• What has their “Quality of Life (QOL)” been since developing SS?
• To what extent did their experience with SS necessitate vocational changes or adaptations?
• How are they doing emotionally?
• How much irreversible visual disturbance?
• How much irreversible hearing loss?

No adequate formal studies of the long-term outcome of SS have been conducted. The one long-term outcome study that has been published does not include formal neurocognitive or quality of life evaluations.

In this Sub-Study, patients will be asked to complete a series of outcome assessments (at the times suggested on the SS-TL), including:

- SS-Disease Damage Score
- Formal, extensive neuro-cognitive testing
- Quality of Life Questionnaires
- Functional Status Questionnaires
- Vocational Status Questionnaire
- Formal visual field and OCT testing
- Formal audiometry evaluation

Qualitative Research:

In addition to conducting the aforementioned “quantitative” study of SS, we also plan to conduct “qualitative” research. Willing patients and families will be interviewed about their experiences with SS, so that we can hear their voices and document and study what they have to say. We will be looking for themes that might not necessarily be generated by the quantitative research.

Patient Generated Clinical Course Graphs:

To supplement the quantitative study of the long term clinical course of SS, willing patients will be asked to draw a free-hand graph of their clinical course----one graph for CNS involvement, one for ophthalmologic involvement, one for hearing loss, and one for tinnitus. These free hand graphs will be filed in a Compendium of SS Free Hand Clinical Course Graphs and will be compared to other clinical course data generated by the SS-ICS.

To our knowledge, this will be the first such Compendium developed for a chronic disease. So, it will serve as a model for future study of other chronic diseases whose long term clinical courses have been difficult to discern and study.