

Sudden Acquired Retinal Degeneration Syndrome (SARDs) and Immune Mediated Retinitis (IMR) – primer for owners

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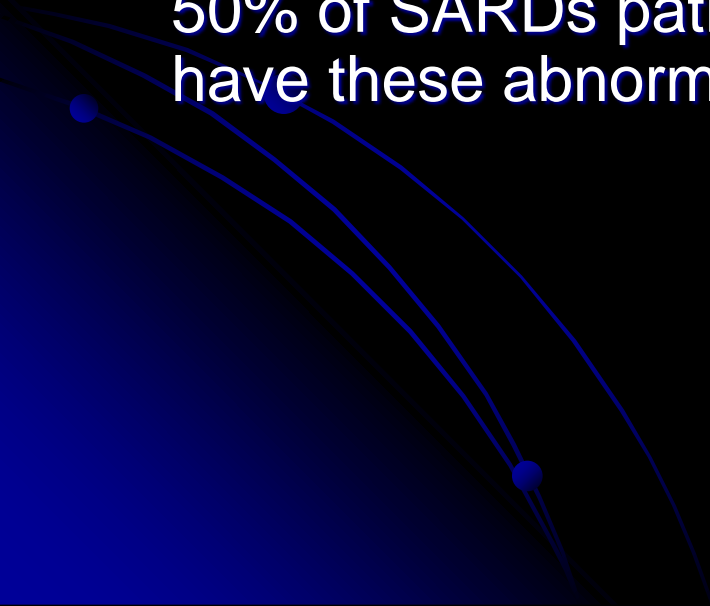
SARDs and IMR – autoimmune diseases

- SARDs and IMR are auto-immune diseases
- 90% of all patients presented to our service had a history of previous auto-immune disease :
 - a) Seasonal skin allergy (most prevalent)
 - b) Food allergy
 - c) Immune-mediated hemolytic anemia, immune mediated thrombocytopenia
 - d) Post vaccinal reactions
 - e) History of previous or current tumor (IMR patients)

What is the major difference between SARDs and IMR?

- SARDs and IMR are auto-immune diseases
- Molecular profile and clinical presentation are frequently identical for both diseases.
- In our experience SARDs has not been associated with the presence of cancer.
- Approximately 10% of all IMR patients that we have examined so far had a malignant cancer somewhere in the body.

“Survival” tips to avoid incorrect diagnosis

- **Incorrect assumptions:**
 - “Dogs with SARDs have to have elevated liver enzymes, polyuria/polydypsia (PU/PD – excessive drinking and urination) and polyphagia (excessive appetite)”
 - In our experience these symptoms are present in 40-50% of SARDs patients, while many patients do not have these abnormalities
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“Survival” tips to avoid incorrect diagnosis

- **Incorrect assumptions:**
- “SARDs and IMR affect only eyes”
- While SARDs and IMR may affect only vision, many SARDs and IMR patients may have concurrent neurological problems: partial or complete loss of hearing, partial or complete loss of smell sensation, stiff gait, excessive salivation, etc.
- PU/PD, polyphagia and weight gain can be detected months to years before development of visual deficits – spectral pupil testing and detailed ophthalmology evaluation (including the testing of vision in dim and bright light) are **ESSENTIAL** for early diagnosis before more severe vision problems develop.

Summary of systemic changes

- **Sudden onset of blindness** - 100%
- **Elevated alkaline phosphatase (Alk Phos)** - 51%
- **Elevated alanine amino transferase (ALT)** - 31%
- **Proteinuria with microalbuminuria** - 29%
- **PU/PD/Polyphagia/ Weight gain** - 22%

Elevation of ALT and Alk Phos is associated with abnormal changes in the liver function and structure.

- Kidney failure is the major cause of death in SARDs and IMR patients.

Systemic hypertension (elevated blood pressure), pancreas inflammation (pancreatitis) and hypothyroidism (low level of thyroid hormones) can be present in almost 30% of SARDs and IMR patients.

“Survival” tips to avoid incorrect diagnosis

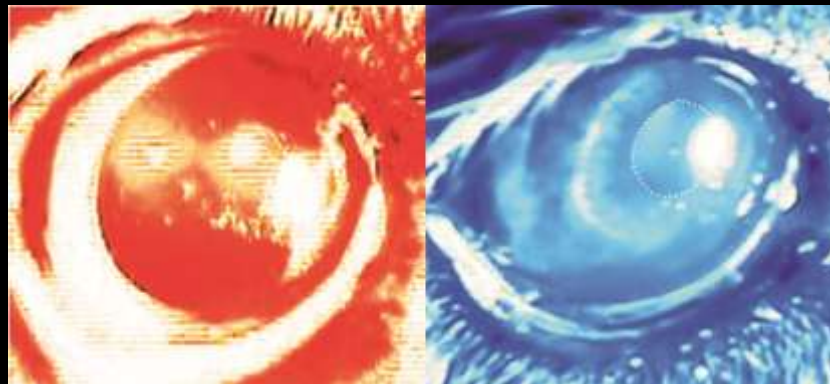
“SARDs and IMR are diseases with sudden onset” – not always correct

- PU/PD, polyphagia and weight gain can be detected months to years before development of visual deficits – spectral pupil testing and detailed ophthalmology evaluation (including the testing of vision in dim and bright light) are ESSENTIAL for early diagnosis of disease before severe vision and systemic problems develop.
- Sudden onset of night vision loss may precede the complete vision loss for weeks to months (particularly in IMR patients)

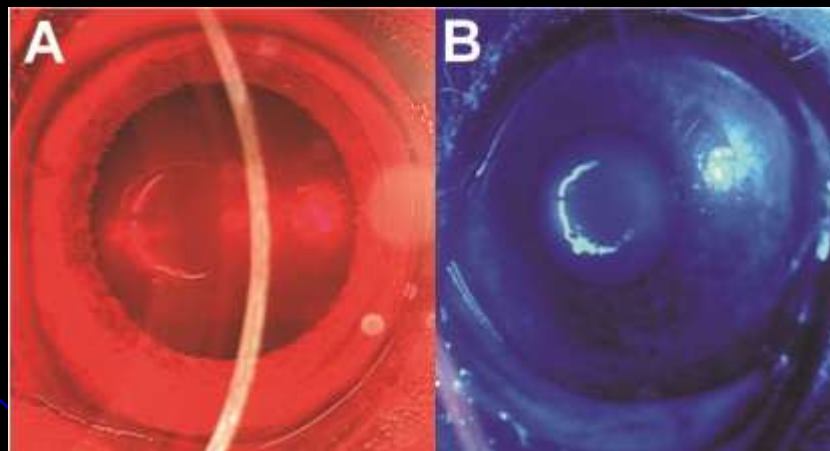
My dog is diagnosed with SARDs – does it have a Cushing's disease?

- While many SARDs patients may have clinical signs of Cushing's disease (excessive thirst and urination, pot-bellied appearance, excessive panting) these clinical symptoms usually completely resolve within the 6 months of onset of clinical problems.
- In rare cases SARDs patients may have a true Cushing's disease, which may require clinical treatment.
- It is not unusual for SARDs patients to have different endocrine problems.

SARDs or IMR – how to diagnose?



IMR pupil response

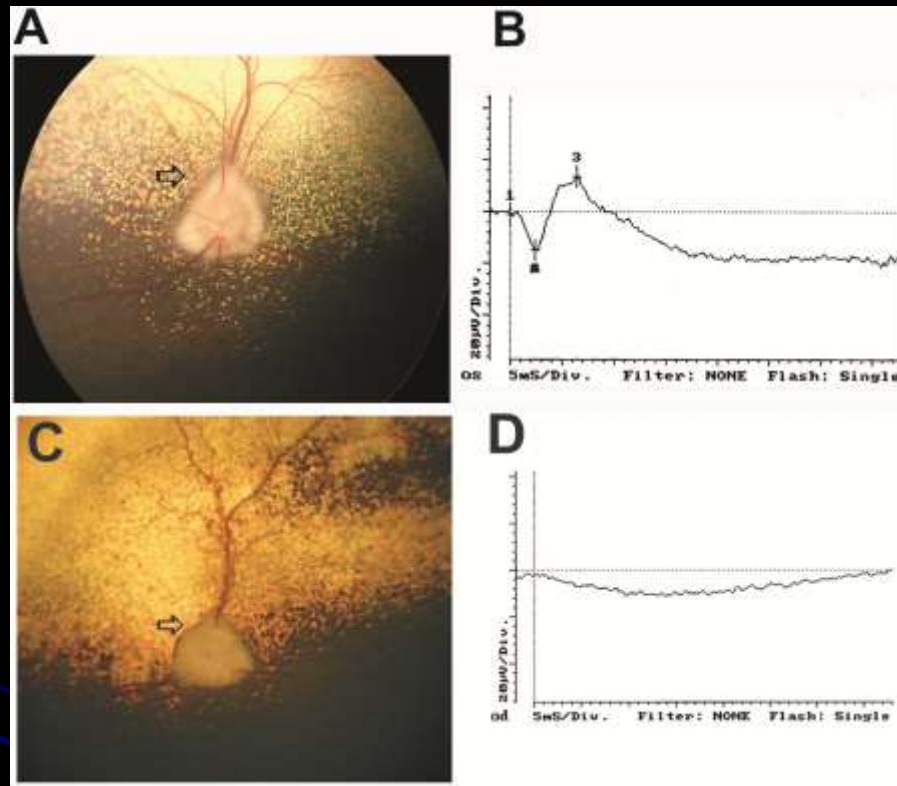


SARDs pupil response

IMR – poor or moderately strong pupil response to the red light (but always present), good pupil response to the blue light

SARDs – no response to the red light, good response to the blue light

SARDS or IMR - how to diagnose?



IMR retinal electrical activity

SARDS retinal electrical activity

IMR – retinal electrical activity (ERG) is usually present (but can be flat!), normal fundus or arterioral attenuation (arrow in image A)
SARDS – flat ERG, relatively normal fundus appearance (image C – arrow shows significant decrease in arterioral diameter)

SARDs pupil – no red, good blue response



White light can elicit normal pupil responses or the pupil response may appear incomplete and delayed in SARDs patients

SARDs pupil – no red, good blue response

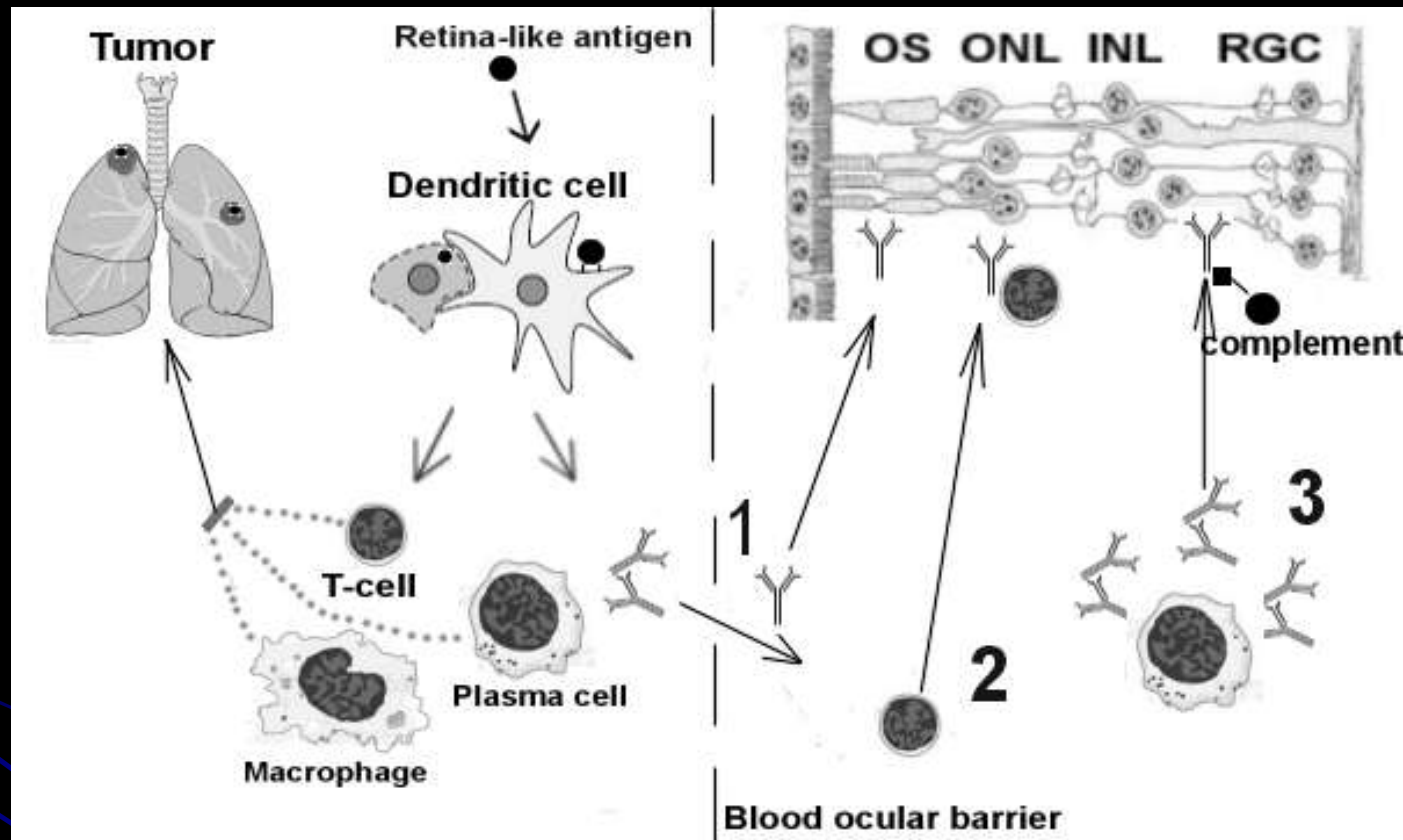


- White light is an unreliable source for evaluation of PLR responses in dogs with SARDs and IMR.
- Deficient/incomplete or absent PLRs after white light stimulus can frequently be seen in dogs with SARDs

IMR pupil response – the red light response is always present, however it is usually very slow, incomplete and with prominent escape (blue response is always normal)



Proposed mechanism of SARDs and IMR autoimmune mechanisms



1. Infiltration of auto-antibodies from blood stream in the retina
2. Infiltration of cytotoxic T-cells and macrophages
3. Infiltration of plasma cells with localized production of auto-antibodies
4. Excessive complement activation

Treatment for SARDs and IMR

- SARDs and IMR are auto-immune diseases which are not curable, but they are controllable. These diseases should be treated carefully, but with therapy aggressive enough to preserve vision, or more importantly, the systemic well being of the patient.
- Many of these patients do have systemic organ diseases, which can be lethal if left untreated. In a significant number of patients, presence of kidney, liver or endocrine diseases can have a significant impact on the overall well being.
- Adequate medical and dietary management can dramatically improve the quality of life and slow down the decline of systemic health.

Treatment options for SARDs and IMR

- Immunosuppressive medications: systemic steroids, cyclosporine, leflunomide. Systemic steroids can cause severe liver reactions (acute function worsening or even failure) in some SARDs patients
- Systemic intravenous immunoglobulins (IVIG) – should not be given to patients with pre-existing liver, kidney and heart disease and patients with systemic hypertension. Treatment requires 4 day long hospitalization
- Intraocular injection of IVIG + steroid combination – treatment is very safe, since drugs are given in a very small dose locally in the eye.
- Overall success of treatment for SARDs and IMR is 30-40% if no advanced retinal degenerative changes are present during the ophthalmology examination.

Mechanism of IVIg action

- Complement inhibition
- Activation of auto-antibody degradation
- Blockade of macrophage activation receptors
- Activation of inhibitory subpopulation of macrophages
- Activation of dendritic cells which regulate activation of T cells

IVIg treatment criteria

1. Presence of any residual vision is an excellent prognostic factor
2. Diffuse hyper-reflective lesions/retinal degenerative changes—
POOR PROGNOSIS if patient is completely blind (true for SARDs, IMR patients seem to be responding better to therapy even when hyper-reflective lesions are present)
3. Good systemic organ function (for systemic IVIg therapy):
 - Presence of kidney, liver and heart disease, systemic hypertension are clear contraindications for systemic IVIg treatment
 - Patients which can not receive systemic treatment due to presence of underlying organ disease, can be treated with intraocular IVIg injection
4. Presence of uncontrolled auto-immune diseases before and after treatment is a negative prognostic factor for the long term maintenance of vision

For how long the therapeutic effect lasts?

- First SARDs and IMR treatments have been initiated in the early 2007.
- We are still following some patients which remain visual since receiving the initial treatment.
- The use of systemic immunosuppressive medications and hypoallergenic diet after initiating the treatment seems to have a beneficial effect on the maintenance of vision.
- We have reports of some patients losing vision 2-12 months after the initial treatment.
- In majority of reported cases with the vision loss after the initial treatment, there was an occurrence of systemic autoimmune diseases or systemic diseases, which required discontinuation of the systemic medications (pancreatitis being the most frequently reported).

How many patients we have treated so far?

- Since the March 2007, we have treated total of 216 patients
- Almost 90% patients showed clinical signs of the improvement in the general condition (decreased lethargy and depression, increased mobility, improvement in the overall behavior)
- 80% of patients diagnosed with the early stage of the disease are still visual after initiating the treatment
- Between 30-40% of all patients which presented with very poor or absent vision successfully improved their visual status after being treated

SARDs – response to systemic immunosuppressive therapy



The goal of therapy is to establish a crude navigation skills against objects with a good contrast against the background in patients which are completely blind.

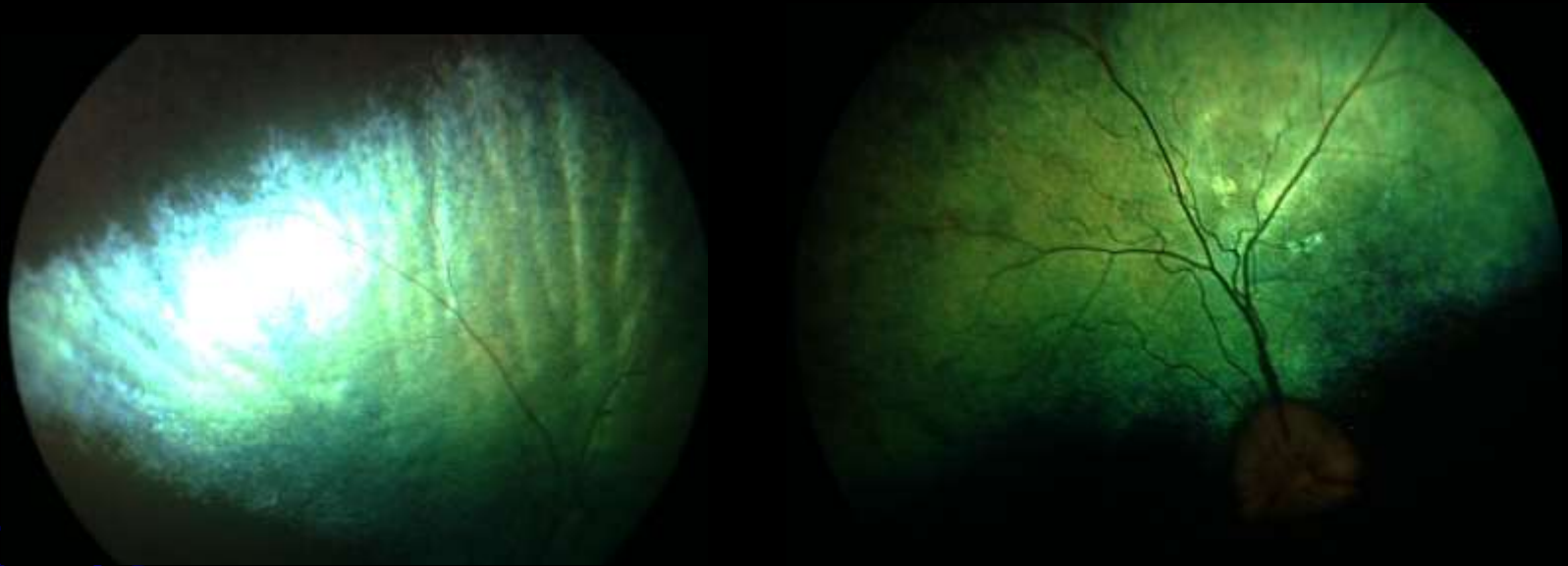
This patient responded well to therapy and has good navigational skills, however it still could not detect the large object in the front of eyes (no detection of the hand motion).

Treatment criteria – menace and ERG vs. visual maze testing



- Absence of the menace response and ERG activity is not the evidence of blindness.
- Visual maze test should be checked in dim and bright light conditions before making diagnosis of blindness.
- Both patients showed in movies were referred to us with the absent ERG activity and diagnosis of blindness.
- Patients with the residual vision are the best candidates for treatment regardless of the retina status – if not treated complete blindness usually develops within 4-8 weeks after the first start of clinical symptoms.

Importance of retinal degenerative changes in SARDs patients



Peripheral retinal “ridging” or change in reflectivity is a negative treatment prognostic factor in SARDs patients which are COMPLETELY BLIND. Dogs which still have any residual vision are good candidates for the treatment regardless of the retinal status.

When looking in the SARDs and IMR retinas, an ophthalmologist should carefully observe the area centralis, perivascular spaces, and peripheral retina – early retinal degenerative changes can be frequently detected in these regions.

Systemic IVIg treatment

Is systemic IVIg infusion safe?

- IVIg is considered very safe when all precautionary measures are applied (Bianco et al, J Vet Intern Med. 2009 Sep-Oct;23(5):1071-8.)
- IVIg is routinely used in patients with severe hemodynamic disturbances with excellent safety profile (sepsis, auto-immune blood cell diseases, auto-immune kidney diseases).
- IVIg has been associated with liver failure, heart failure, kidney failure, anaphylactic reactions, stroke and other complications in human patients (percent of complications vary between studies and it is usually less than 1%), however data from the larger cohorts of veterinary patients are still lacking.
- Systemic IVIg can have pro-inflammatory and pro-thrombotic effects in healthy dogs (Tsuchiya et al, J Vet Intern Med. 2009 Nov-Dec;23(6):1164-9.)

Mortality associated with systemic IVIg treatment in SARDs and IMR patients

Non-Iowa treated patients:

- 1 patient died due to the anaphylactic reaction (no IV dexamethasone was given before the infusion)
- 1 patient died from the kidney failure (unknown kidney status prior to the infusion)
- 1 patient died from the liver failure (3 days after IVIg infusion) – had pre-existing liver disease

Iowa treated patients:

- 1 patient died 10 months after IVIg infusion due to the kidney failure

*** The major reported cause of death in non-treated SARDs and IMR patients is the kidney failure**

Intraocular IVIg treatment – is it safe?

- Intraocular IVIg treatment has an excellent systemic safety due to the minimal amount of drug being delivered to the body.
- Any intraocular injection can potentially result in the intraocular bleeding, damage to the retina or other ocular structures which can result in the loss of the eye.
- In a very limited number of patients we have noticed beneficial effects of the intraocular IVIg injection on the systemic parameters (improvement in kidney and liver function, clearance of retinal auto-antibodies from the systemic circulation.
- Considering that the intraocular IVIg can potentially have systemic immuno-modulatory effects, we do not recommend the use of intraocular IVIg in patients with malignant tumors.

Mortality and morbidity associated with intraocular IVIg treatment in SARDs and IMR patients

Non-Iowa treated patients:

- 1 patient developed uveitis and secondary glaucoma after intraocular injections resulting in the bilateral eye removal
- 1 developed bilateral intraocular inflammation (uveitis) which resolved after treatment with anti-inflammatory medications

Iowa treated patients:

- 1 patient died 4 weeks after intraocular IVIg treatment due to the pulmonary thromboembolism. This patient had a cancer (brain meningioma)
- 1 patient developed intraocular hemorrhage after the injection, which resolved within 3 weeks
- Approximately 50% of patients develop benign subconjunctival hemorrhage as a result of intravitreal injection, which resolves within 7-10 days after injection.

SARDs visual response after IVIg therapy



- Menace recovered 2 weeks after treatment in this patient. Patient remained visual 16 months after treatment until developed pancreatitis and complete blindness again

This patient remained visual for 24 months until it was lost for the follow up.

SARDs post IVIg therapy



Movies show patient before and 24h after systemic IVIg therapy. Recovery of the crude visual navigation behavior is evident. This patient died 10 months post treatment due to the kidney failure.

SARDs response to IVIg treatment



The most frequent response to the IVIg treatment is recovery of visual navigation skills in the bright light conditions.

SARDs patients are frequently completely night blind and do not recover menace response.

Visual maze testing in dim and bright light conditions is essential when making a diagnosis whether patient is blind or not (before and after treatment). This patient positively responded to the treatment, however developed pancreatitis 8 months after initial treatment which resulted in discontinuation of systemic immunosuppressive medications and development of blindness.

SARDs and IVIg treatment



- It is not unusual to observe the visual recovery, which is limited to objects with a good contrast to the background.
- This patient was treated with the intraocular IVIg, and has visual navigation behavior which is limited to objects with good contrast to the background in the bright light conditions. The white wall can not be well discriminated and patient can not avoid it, which is not the case with red cones.

IMR – lack of visual response after therapy



Even with the best effort and investment of time and resources, the blindness can be the final outcome of the IVIg therapy. This patient was treated with the systemic steroids and IVIg, but without positive results to the therapy.

IMR response to the systemic immunosuppressive therapy



Patient remains visual 24 months after the onset of systemic therapy. Currently is receiving 0.5mg/kg of prednisone twice per week. The complete withdrawal of steroids results in the complete blindness within 24-48h.



This patient's vision is maintained with the high dose of daily steroids. Careful monitoring of the liver and kidney function is a must for patients receiving high dose of systemic steroids.

How fast the response to therapy develops?

Before IVIg



6 days after IVIg



Majority of patients respond to the IVIg therapy within 14-21 days after the initiation of therapy, however we have seen cases where the response to therapy was delayed up to 2 months post the initiation of the therapy.



8 days after IVIg

Is IVIg therapy safe in patients with cancer?



Before intraocular IVIg



60 days after intraocular IVIg

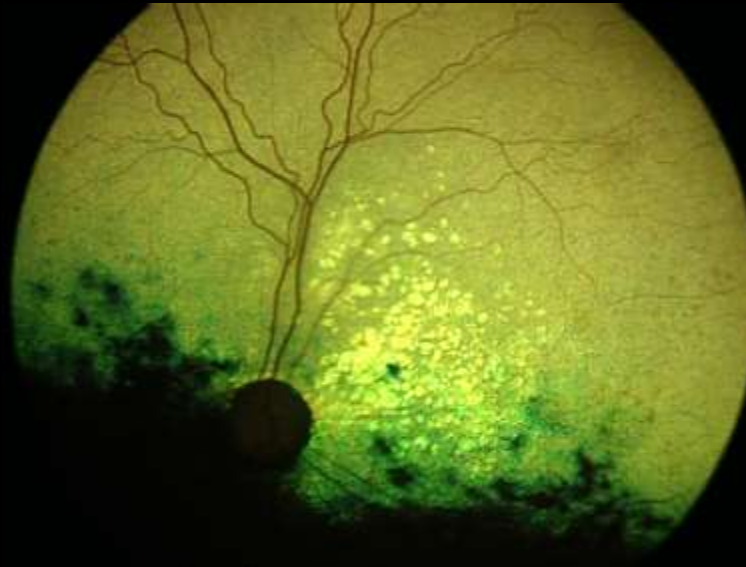
This patient was diagnosed with a malignant neoplasia 3 years after successful treatment with intraocular IVIg.

Considering that the autoimmune response against the eye can potentially target the cancer, at this time we do not recommend treating cancer patients with IVIg unless the goal is to improve the quality of life in patient with the end stage disease.



60 days after intraocular IVIg

My dog is very young and has been diagnosed by
SARDs/IMR – is that possible?



This is a fundus image from a 6 month old Golden Retriever, with a history of sudden onset of night blindness and almost complete day blindness and excessive thirst and urination 1 month prior.

My dog is diagnosed with SARDs/IMR. Is there anything that can be done?

- Regardless whether therapy for restoring vision will be pursued, SARDs/IMR patients should have rigorous evaluation of systemic organ function (liver, kidneys, endocrine glands) .
- All possible measures for the control of autoimmune disease should be put in place (initiation of hypoallergenic dietary regimen, careful planning on the vaccinations, etc...).
- In the case systemic organ abnormalities are detected, the appropriate medical care needs to be initiated.

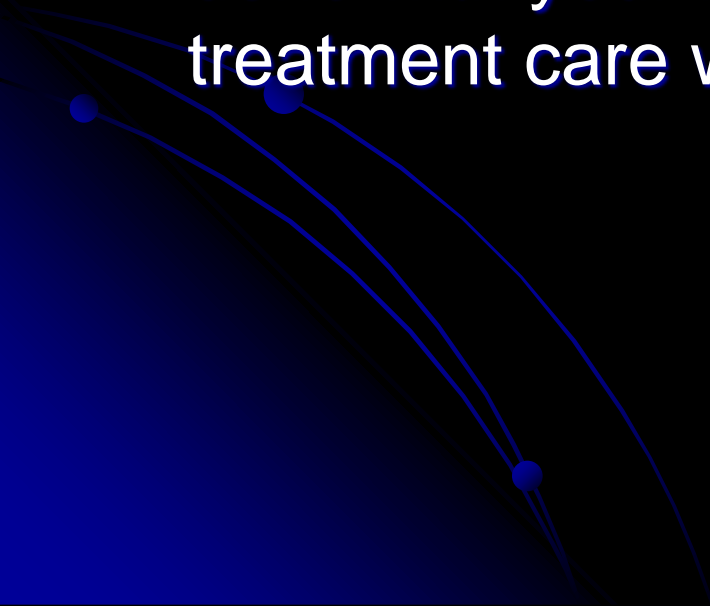
I would like to come to Iowa for the IVIg treatment.
How long it will take for the treatment to be done?

- Intraocular IVIg treatment is an outpatient procedure. Patients usually have to come to the Iowa Veterinary Referral Center (IVRC) in the morning (9 am), and all diagnostics and treatment will be done by 5 pm same day. Patients are evaluated and treated every Monday, Tuesday and Saturday.
- Systemic IVIg treatment requires 4 day hospitalization at the IVRC

How will I know whether my dog will need intraocular or systemic IVIg treatment?

- Please contact the IVRC and send us following data:
 - Complete cell blood count
 - Serum chemistry
 - Urine analysis (including urine microalbumin levels)
 - Blood pressure values
 - Thoracic and abdominal radiographs
 - - Copy of ophthalmology examination with detailed description of the retina and optic nerve
 - Copy of the electroretinography testing
 - Filled SARDs/IMR history form (can be downloaded from our web site)

My veterinarian can't perform all required tests. What are the options?

- All required testing can be performed at the Iowa Veterinary Referral Center in Des Moines
 - We generally encourage that initial testing is done with your local veterinarian, since all post-treatment care will be done locally
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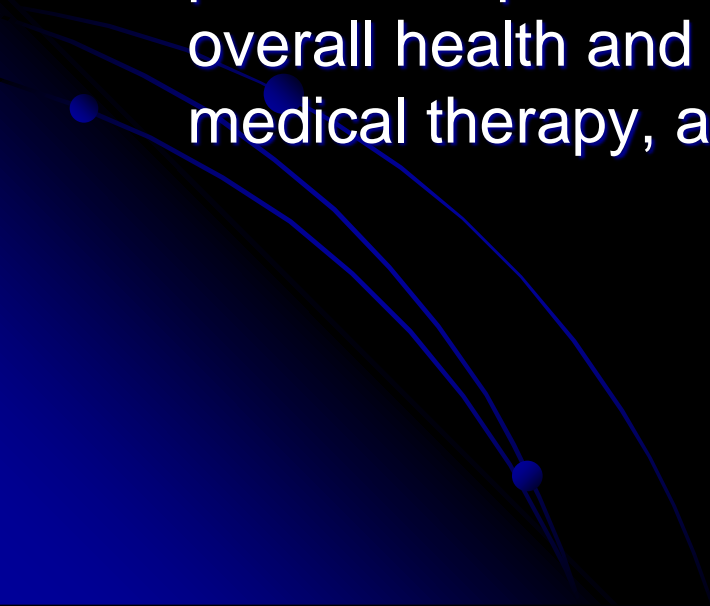
How long we can wait before pursuing the treatment?

- SARDs and IMR can have very rapid progression once when the complete blindness develops.
- Even patients with only 3 day long history of sudden onset of blindness may have very advanced retinal degenerative changes, while some patients still have good retinal preservation even 6-8 weeks after the onset of blindness.
- The general recommendation is that the medical treatment is pursued rather sooner than later.

Do I need to come to Iowa for repeated treatments?

- No – the purpose of the visit to the IVRC is to do a detailed examination of the patient, pursue systemic and intraocular treatment and initiate the proper course of therapy for the future.
- All follow up care is usually done locally by your veterinarian and ophthalmologist with our active assistance.
- We do charge a \$45 fee for the follow up review of laboratory work and medical findings from your local veterinarian.

Is it worth treating if chance of the success for preserving the vision is only 35-40%?

- The general principles of the medical treatment is not to address visual problems only, but also to address any possible systemic organ issues.
 - Even if the return of vision is not established, many patients experience significant improvement in the overall health and quality of life after initiating systemic medical therapy, and changing the diet.
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Appointment scheduling

- Please call Iowa Veterinary Referral Center in Des Moines at:

Iowa Veterinary Referral Center
4631 Merle Hay Rd
Des Moines, IA 50322
Call: (515) 727-4872

Please fax all laboratory results to:
1-877-516-6277 Attn: Dr Grozdanic

The nearest airport is Des Moines International Airport (<http://www.dsmaairport.com/>), which is located approximately 30 minutes drive from our facility

Travelling Arrangements

- The nearest airport is Des Moines International Airport (<http://www.dsmaairport.com/>), which is located approximately 30 minutes drive from our hospital.

- **Econo Lodge Inn & Suites**

4755 Merle Hay Rd. , Des Moines, IA, US, 50322

Phone: (515) 278-8858

Fax: (515) 974-5098

http://www.econolodge.com/hotel-des_moines-iowa-IA151?source=gglocalai

This hotel is located 5 minutes of walk from our hospital.

Locations to visit while in Des Moines, IA

- Attractions:

http://www.tripadvisor.com/Attractions-g37835-Activities-Des_Moines_Iowa.html

- Restaurants:

<http://data.desmoinesregister.com/mmx/top-100-des-moines-restaurants/>