DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

Autoimmune Autonomic Ganglionopathy
Live Facebook Chat – January 14, 2015

The following is a transcript of a live Facebook chat hosted by Dysautonomia International, with special guest Dr. Steven Vernino. The names of all participants have been removed to protect patient privacy. All of the answers below are provided by Dr. Vernino. This information should not be considered medical advice and is provided for general educational purposes only. Please consult your own physician for medical advice.

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Let's begin with some definitions from Dr. Vernino:

AAG is Autoimmune Autonomic Ganglionopathy. The main symptoms of AAG are orthostatic hypotension (a significant drop in blood pressure when standing up), constipation, and bladder problems (typically urinary retention). AAG is caused by autonomic failure (the autonomic reflexes don't work) because of problems in the autonomic ganglia (a relay center for the autonomic signals from the brain to the body).

Some patients with AAG have antibodies against the ganglionic acetycholine receptor (g-AChR). This the antibody-mediated form of AAG. AAG can also occur without these antibodies. Sometimes the immune system can attack the autonomic ganglia in other ways. This can occur in the setting of other autoimmune diseases like Sjogren syndrome. There are also cases of AAG that are seronegative - these tend to be a little different from the AAG cases with the ganglionic antibody.

AAG is very different from POTS. In AAG, when you stand up your blood pressure drops and the heart rate doesn't change. In POTS, when you stand up, the heart rate goes very high and the BP doesn't change.

Autoimmunity = when the body's immune system attacks normal tissues. This can occur with the immune system makes an antibody against a normal nerve receptor, as in AAG.

Autonomic Vocabulary

Autonomic failure

- Autonomic reflexes don't work

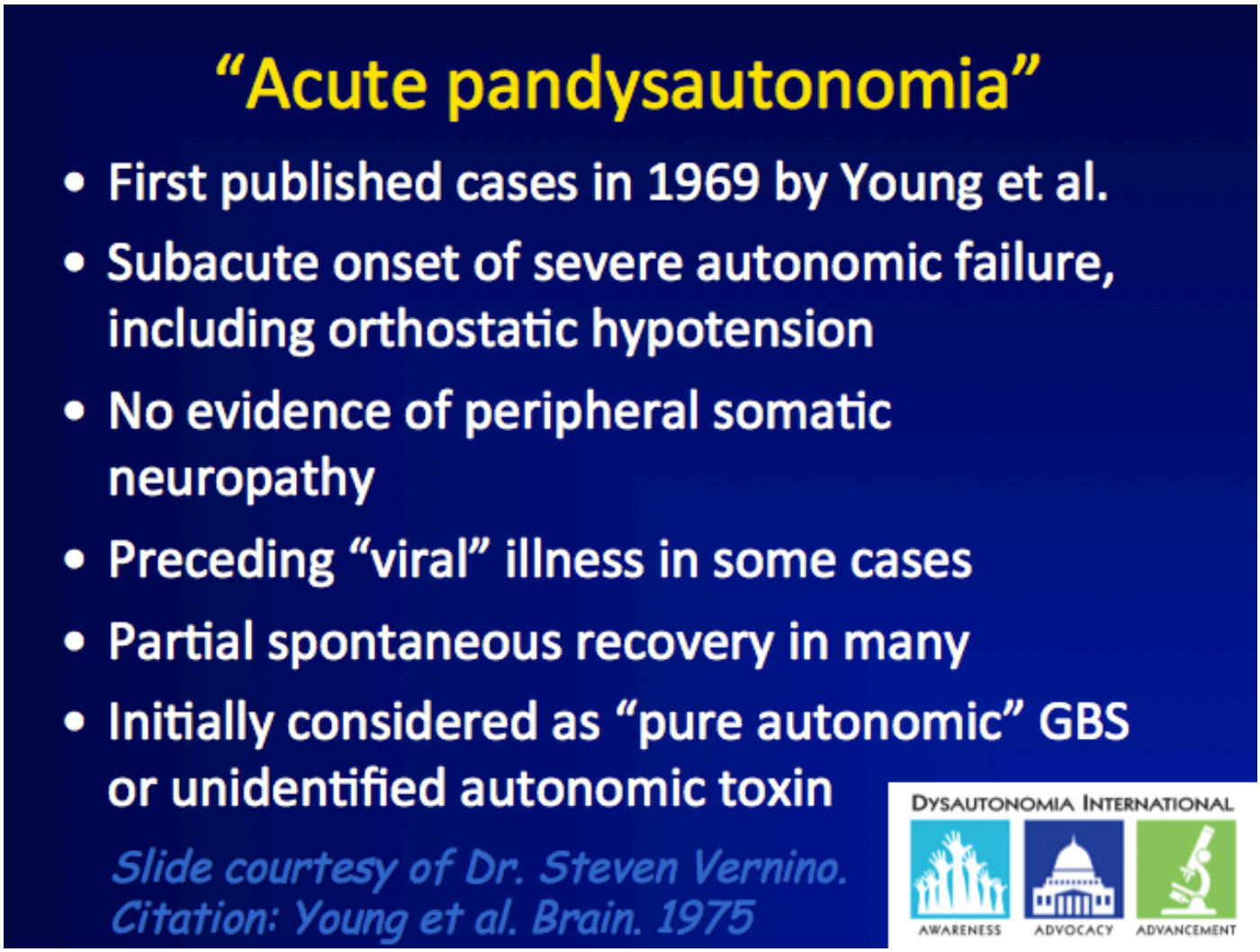
Autonomic neuropathy

- A problem with autonomic nerves
- Usually longest nerves affected most

Dysautonomia

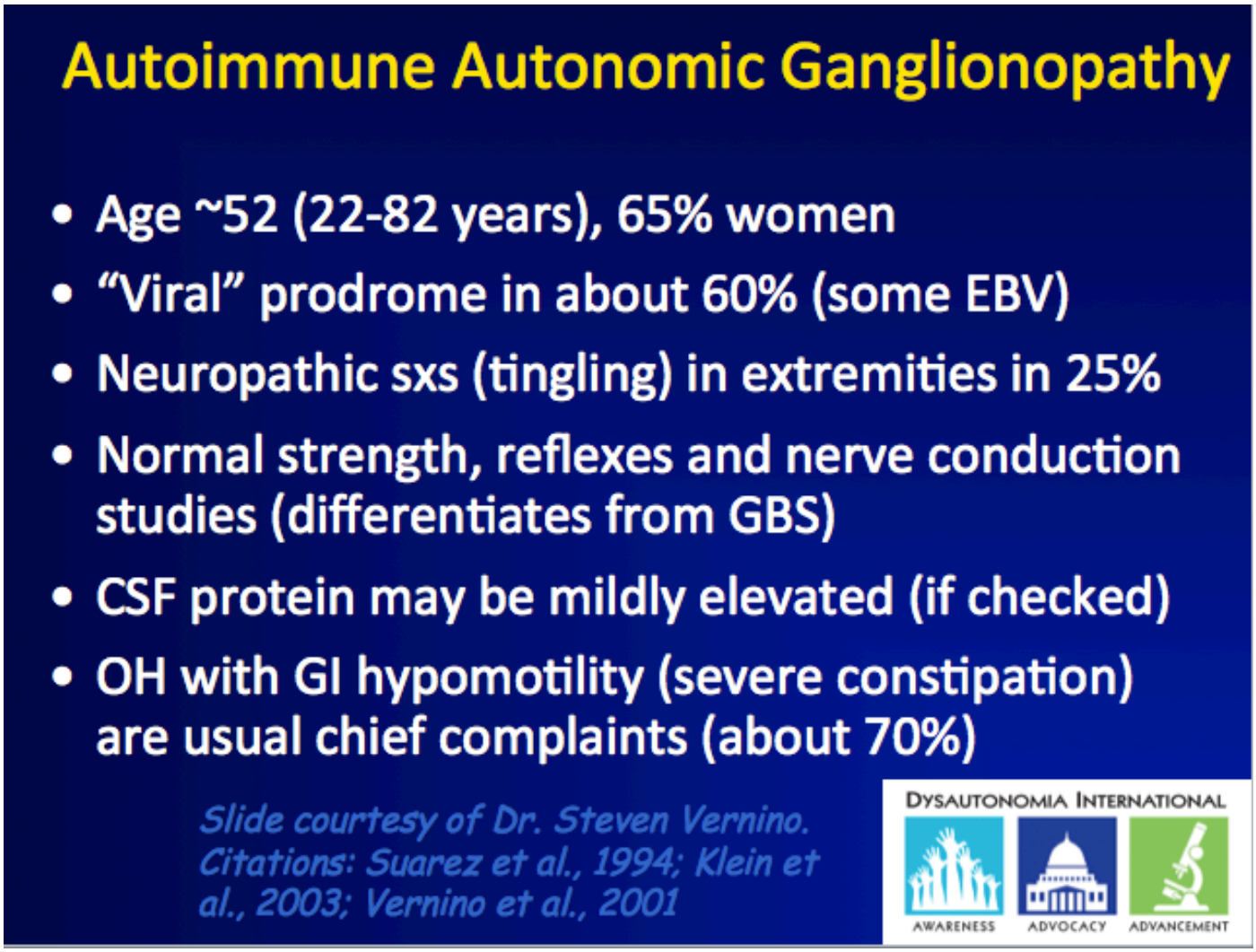
- A somewhat vague term
- Autonomic reflexes work but not correctly
- An imbalance in the autonomic tone
- Many causes and symptoms

Slide courtesy of Dr. Steven Vernino.



Older terms for AAG included pandysautonomia, autoimmune autonomic neuropathy (AAN) or autonomic variant of Guilain-Barre.

Q: Can AAG in any way mimic Guillain-Barre or Miller Fisher Syndrome?
A: No. These two conditions are autoimmune disorders that affect the motor nerves and cause weakness. AAG affects the autonomic nerves (not motor nerves) and therefore does NOT cause weakness. There should not be any confusion. However, in the early descriptions of AAG (in the 1970s) - AAG was sometimes called the autonomic variant of Guillain Barre syndrome. This is inaccurate.



Q: How does one know if being seronegative that they truly have AAG? I have all clinical symptoms that coincide hence why I was diagnosed as seronegative-AAG but I am still apprehensive going thru treatments (was on IVIG) if there's no definitive answer that I do have it. Do you have any suggestions or recommendations?
A: This is a great question to start with since it is a big challenge. Firstly, if one has the clinical symptoms of autonomic failure (OH, GI motility problems, bladder problems etc) then one could consider AAG. The next step is to characterize the autonomic problem using clinical testing (usually in an established autonomic laboratory). The testing helps to differentiate AAG from autonomic neuropathy (like can occur in diabetes) and from POTS. If the clinical picture looks like AAG and other causes are excluded, then a trial of treatment is reasonable. IVIG or steroids can be tried. Our experience in a few patients is that seronegative AAG may respond better to a large dose of iv steroids as opposed to IVIG. If the patient responds, then the likelihood of an autoimmune cause is supported. IVIG and steroids are not great long term options but we don't yet know the best long term treatment for AAG.

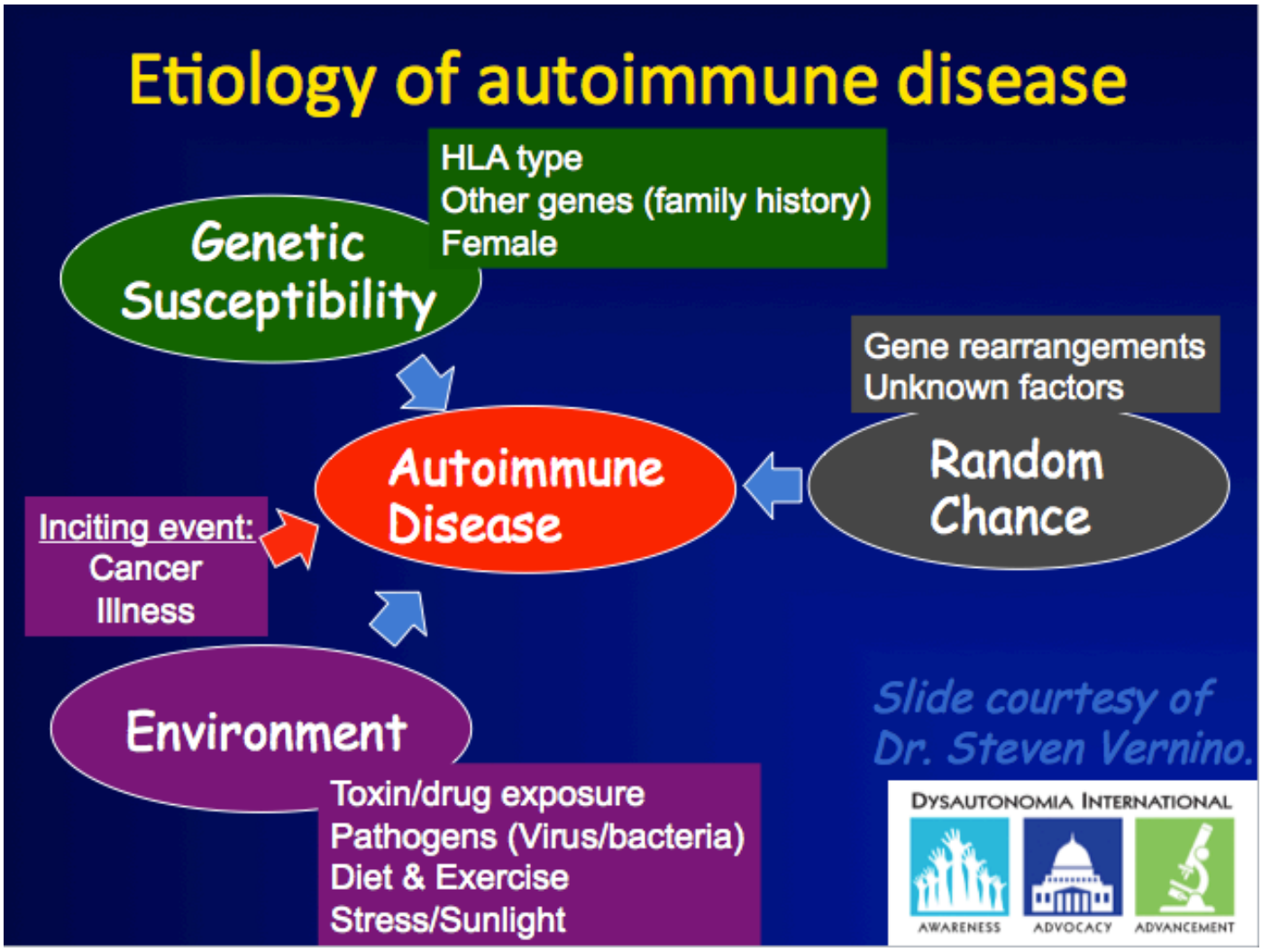
Q: Can you have symptoms of your fingers and toes going numb with AAG? Can AAG damage the nerves? Then why do so many AAG patients live with chronic amplified pain?
A: If there is a lot of numbness and/or pain, then a different diagnosis needs to be considered. Those are not common symptoms of AAG.

Q: Does AAG cause extreme gait imbalance?
A: No

Q: You mentioned that peripheral neuropathy is not associated with AAG. If a person has peripheral neuropathy over an entire side of their body has a diagnosis of AAG, should they look at alternative diagnoses?
A: That is correct. if there is sensory neuropathy (or motor neuropathy) along with autonomic failure - consider a different diagnosis, such as sensory and autonomic neuropathy which can also be immune-mediated.

Q: Can AAG come with sensory or motor neuropathy, or is it purely autonomic?
A: By definition, there is no neuropathy. There are immune-mediated forms of sensory and autonomic neuropathy, but this is not AAG

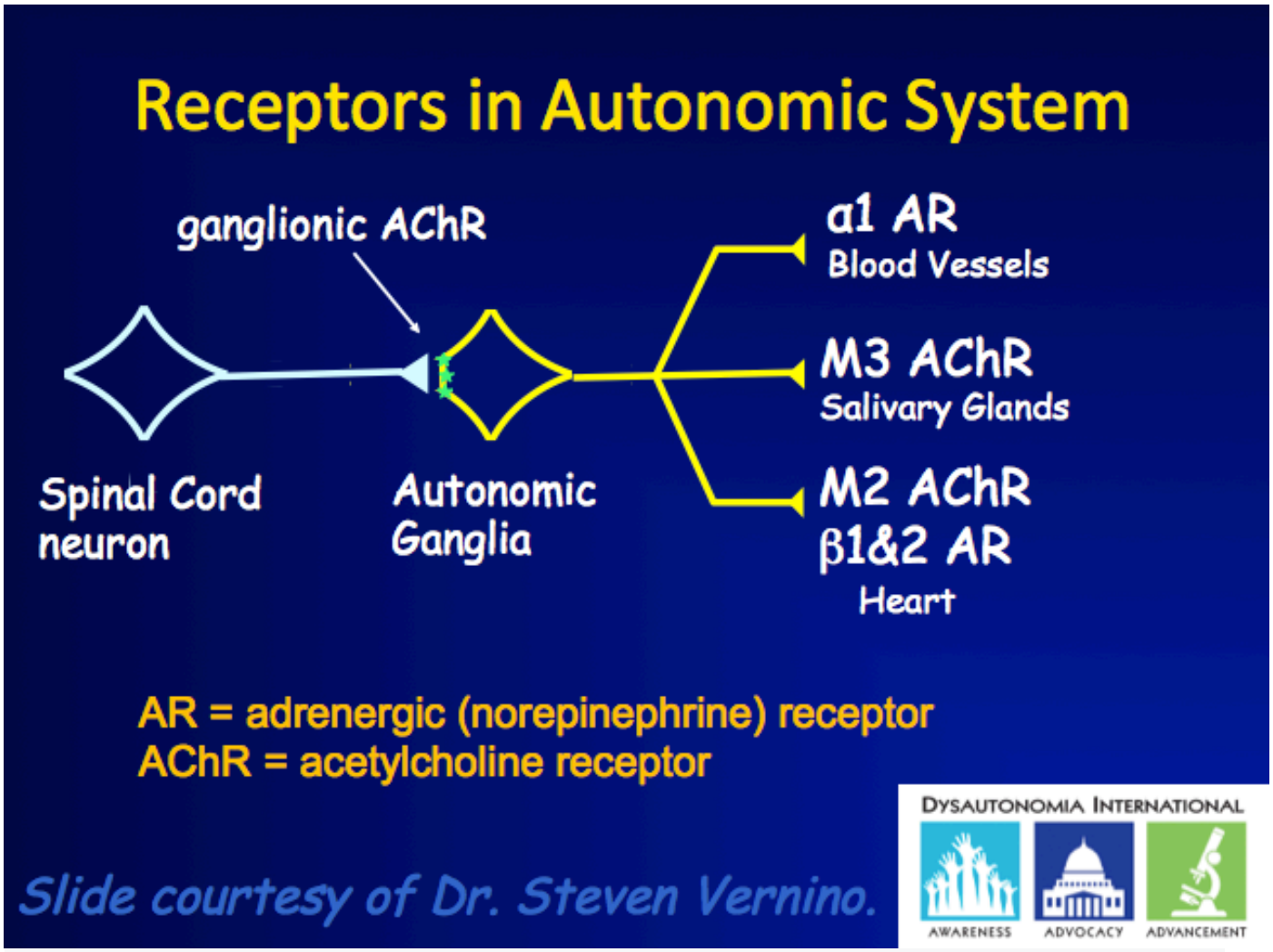
Q: Does untreated AAG lead to neuropathy, small or large fiber?
A: It is unclear. Some patients with AAG do have impairment of the QSART responses indicating some damage to the autonomic (small fiber) nerves. There really is no reason that the sensory or motor nerves should be damaged, but if the autoimmune attack on the ganglia goes unchecked for long enough, the autonomic nerve may get permanent damage.



Q: Is there any theories of why the immune system starts making AChR antibodies as a mistake? What is it structurally similar to?
A: I wish we knew. Probably there are some proteins made by viruses (like the Ebstein-Barr virus, EBV) or cancer cells that are similar to the AChR and trigger the immune response. This has been researched for other autoimmune diseases for decades and we still don't have a clear answer.

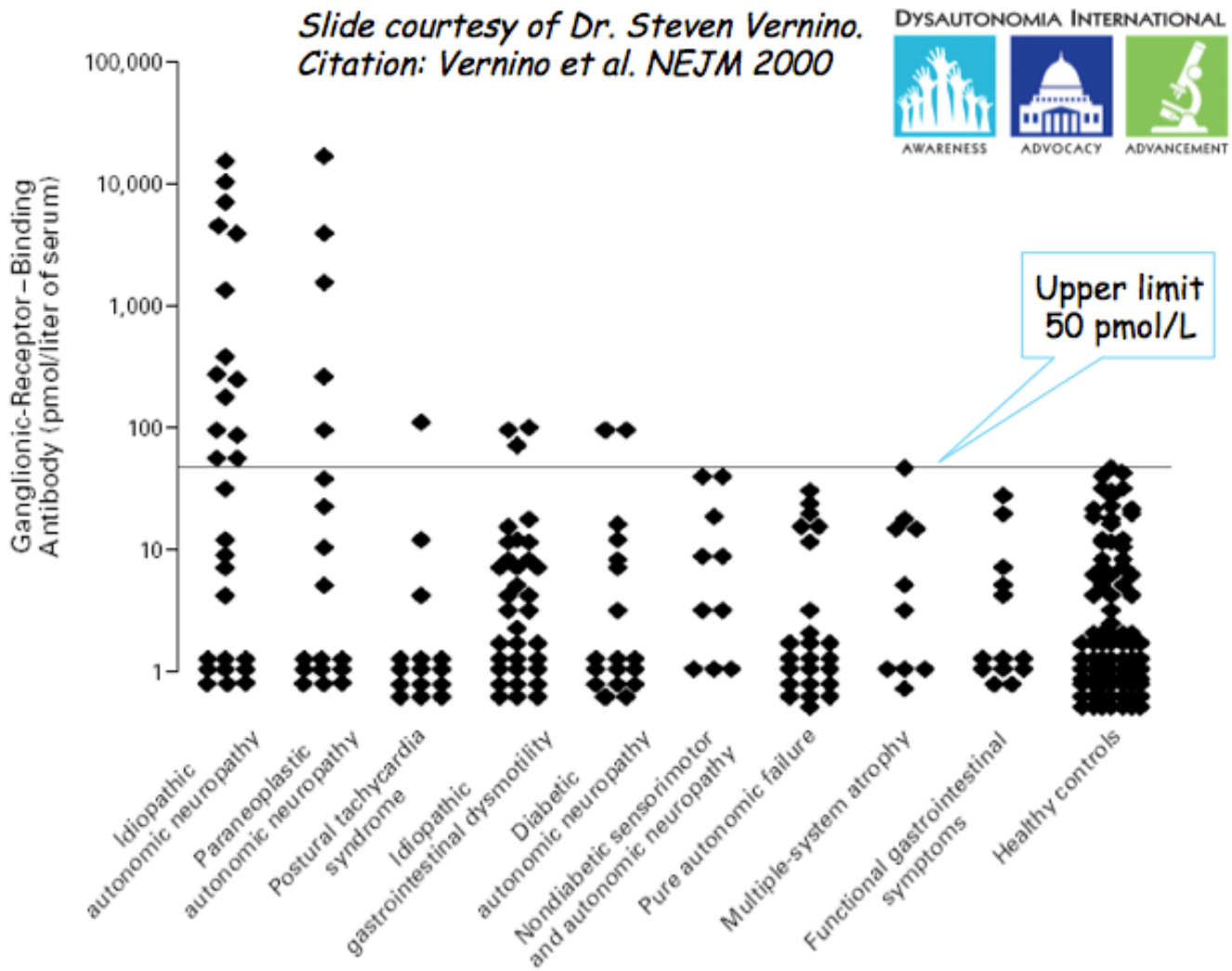
Q: I know each case is very individual but is there any know causes for AAG? Thank you!!!
A: Some patients have a trigger, like EBV or a surgery.

Q: What is HLA type?
A: Human leukocyte antigen type. HLA genes are one of the many factors that can increase or decrease your risk of developing autoimmune diseases, but there are no HLA genes known to be associated with AAG.



This diagram shows where the ganglionic receptor sits in the autonomic ganglia. The ganglia is the relay center for autonomic signals. If the antibody blocks the signals, the central nervous system can't send messages to the blood vessels, heart etc. The yellow lines are the autonomic nerves - which is where the problem happens in patients with autonomic neuropathy

Q: Any correlation between AAG and other channelopathies?
A: Not really. Although there are a few cases of overlapping MG and AAG known.



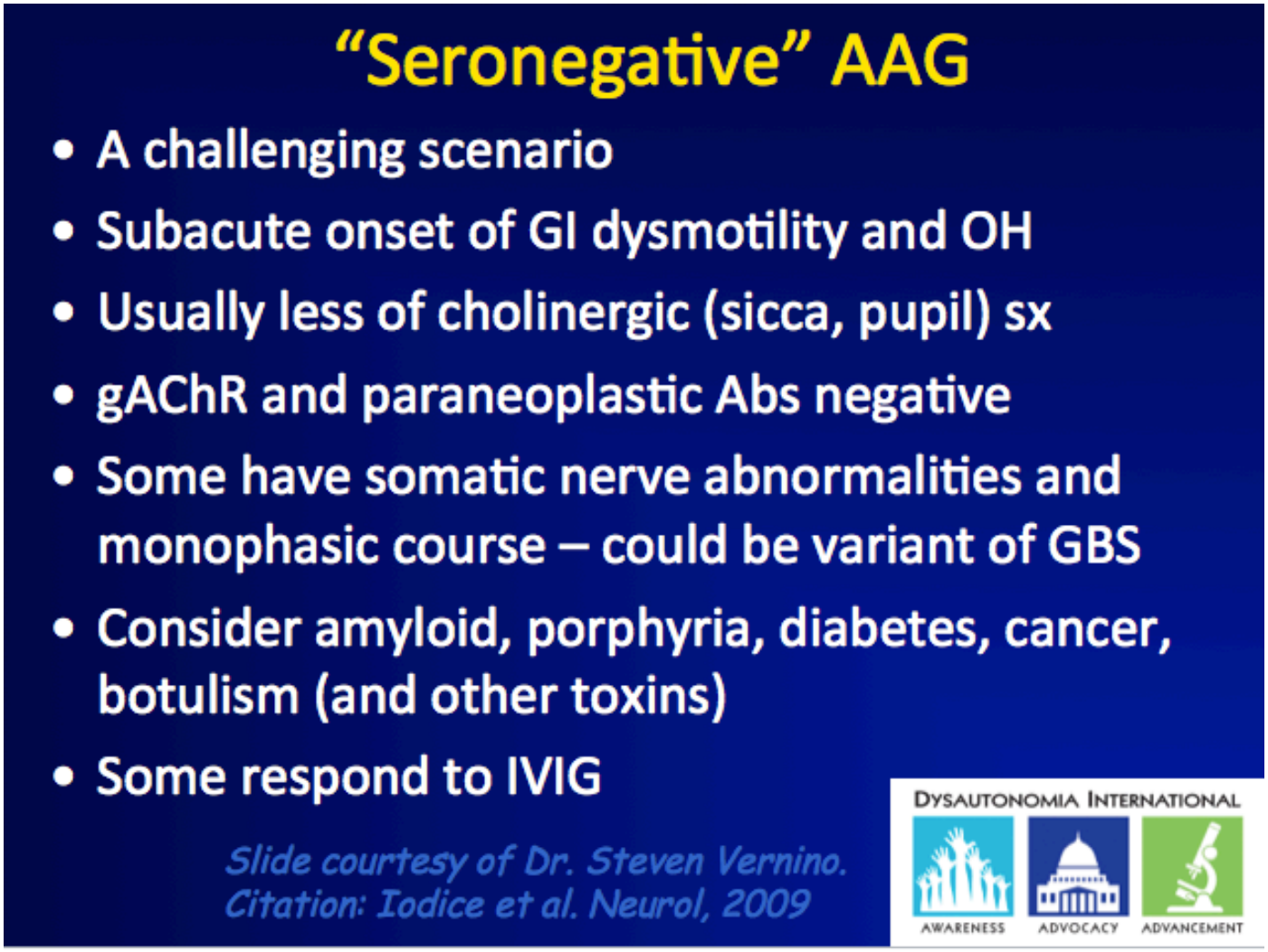
This is a graph from the 2000 New England Journal of Medicine article. In the past 15 years, we have gotten more experience. We now know that some normal people can have these antibodies. In recent studies, it was found that 0.5% (1 out of 200) of healthy controls had positive antibodies (but these were very healthy young medical student types). Among unselected normal people that may have other medical conditions, the antibodies can be found at low levels in up to 3%. In patients with positive low level antibodies, about 40% have no neurological disorder. In this graph, you will see that only one POTS patient was positive (7%). In bigger studies, the positive rate in POTS is about the same (5-10%). Not everyone with ganglionic AChR antibodies has AAG. This antibody can be found in cancer patients that don't have any neurologic problems for example.

Q: Can one have AAG without the common symptoms?
A: Not likely (since the clinical symptoms are part of the diagnosis). We do recognize that there may be a restricted partial form of AAG that just causes gastrointestinal dysmotility (nausea, vomiting, constipation due to slow bowel function). You can see on the antibody graph that there are a few dysmotility patients that had the ganglionic AChR antibody. However, when we test more carefully, there are always other signs of autonomic problems in other systems if it is AAG.

Q: What's the prevalence of the antibody in asymptomatic people?
A: 0.5% in healthy controls. Up to 3% in unselected normals (using the cutoff of 0.05). Higher in patients with cancer or other autoimmune disorders. In those with antibody level < 0.25, more than half have no neurological problem.

Q: What percentage of POTS patients have a positive g-AChR antibody?
A: 5% in our recent study from Dysautonomia International's conference. Higher in some prior studies. This number was not significantly different from the control patients (3%)

Q: Is it possible to have AAG and POTS?
A: I don't think so. We should think of these as two different disorders. However, some POTS patients have autoimmunity which may contribute to their symptoms.



Q: How many patients in the world truly have AAG?
A: I know of 150 seropositive patients. There are at least as many seronegative patients. There are probably some patients I have not heard about, and there are probably others undiagnosed. But all in all, it is a very rare disorder.

Q: Is that 150 with high titres only or does that include us with low positive titers
A: Low positive antibody titers do not equal AAG. Most patients with low antibody titers have something other than AAG. As discussed in this forum, some people with low antibody titers have no neurological disorder, some have POTS, some have other autoimmune disorders. The presence of a low positive antibody is a useful thing to know but you and your doctor need to figure out what it means in the context of the symptoms and other data.

Q: What do you consider low positive antibody ?
A: Here's my current thinking, Low titer is 0.05 - 0.25. High titer is greater than 1.0. Levels of 0.25 to 1.0 are considered intermediate of moderate antibody titers. When antibody levels are high (greater than 1.0), then 85% of those patients will have typical AAG. Notice that the number is not 100% even for high antibody levels.

Q: If my understanding is correct AAG and POTS can't coexist. How about the g-AChR antibodies causing POTS like symptoms in a patient?
A: POTS and AAG are different disorders. In AAG, the autonomic responses are impaired (broken) while in POTS, the autonomic responses are out of balance and in some sense exaggerated. With respect to antibodies, we find that about 5% (or as high as 10% depending on the study) of POTS patients have ganglionic AChR antibodies at low levels. We don't yet know what these antibodies are doing in POTS. Probably, the antibodies in POTS just reflect some activation of the immune system and are not the cause of POTS. At this point, we don't recommend treatments to treat the antibodies unless there are features of AAG. Also, in studies of ganglionic AChR antibodies, among patients with antibody levels less than 0.25, about half of those patients had no neurological problems and very few of them had AAG. However, among patients with ganglionic AChR antibodies higher than 1.0, 85% had AAG.

Q: Someone told me that Sjogrens and AAG are the same? I don't have dry mouth, but I do have dry eyes. I have not tested positive for Sjogrens via blood work. Are they the same?
A: Sjogren's syndrome and AAG are not the same thing, although there can be a lot of overlap in the autonomic symptoms of Sjogren syndrome and the autonomic symptoms of AAG. Dry mouth and dry eyes can occur in both conditions for example. Autonomic failure (orthostatic hypotension for example) is typically much more prominent in AAG. In rare cases, Sjogren's can cause an autonomic ganglionopathy. Dry eyes are often reported more often than dry mouth in Sjogren's, because the eyes are more sensitive. Sjogren's cannot be ruled out with blood tests. Some people with Sjogren's do not test positive on the Sjogren's blood tests. Minor salivary gland biopsies (sometimes called lip biopsies) are also used to diagnose Sjogren's. If you have autonomic symptoms similar to AAG, but don't have a higher titer of g-AChR antibodies, it would be helpful to look for Sjogren's with blood tests and a lip biopsy. This is even more important if you have any non-autonomic symptoms, like sensory nerve pain, numbness, increased sensitivity to painful stimuli, or joint or skin inflammation.

Q: Have you seen any cases of AAG with Sjogren's Syndrome?
A: Yes, I have seen a few cases where there is enough evidence to diagnose both conditions.

Q: How do you distinguish AAG and Sjogren's autonomic ganglionopathy, particularly for those who have seronegative AAG or seronegative Sjogren's?
A: Very challenging since AAG can be associated with dry eyes and dry mouth. Patients with SS may have joint/skin or sensory nerve problems.

Q: Most common differential dx(s) in your clinical experience?
A: Sjogren syndrome related autonomic neuropathy, diabetic autonomic neuropathy, POTS, amyloidosis, pure autonomic failure (this is a neurodegenerative disorder that is related to Parkinson disease).

Q: Dry eyes and mouth very difficult to treat any recommendations
A: Mestinon (pyridostigmine) can help in some cases (this is not an approved use of this medication). Also Biotene drops for dry mouth and artificial tears of course. Avoid artificial tears that have preservatives in them. Avoid "anti-cholinergic" medications including some antidepressants (like Elavil) and medicines for bladder spasms (like Flomax) which can make things drier. Restasis may help the dry eye, but this has not been studied in AAG.

Q: Have you found the same antibody that causes Myasthenia is the same that causes AAG? Or could it be a different antibody as the culprit?
A: No, it's a different antibody. They are both acetycholine receptor antibodies, but the MG antibody is specific for the muscle acetycholine receptor and the AAG one is the ganglionic acetylcholine receptor. Some labs don't make this very clear on the lab reports, so it can be confusing.

Q: Is there any correlation between AAG & any types of heart abnormalities? Arrhythmias, Tachy/Brady Syndrome, murmurs, etc.
A: There is a case report on one Mayo Clinic patient who had a prolonged QT interval and high titer AAG. Nothing else reported in the literature on this. AAG patients tend to have a fixed heart rate that doesn't change much. I have seen some older patients who have bradycardia (slow heart rate).

Q: What are the chances of remission in AAG? How many/how often do you see true remission in AAG patients? If a patient has achieved remission, what was their treatment regimen?
A: Remission can happen. I would say that about 20% of my patients are in remission and no longer require any treatment. Many other patients stabilize with treatment and then do not need further immune treatment but still have some autonomic problems that can be treated symptomatically. There are several approaches to treating AAG and we do not yet have research data to indicate which are the most effective. Treatments that have been used are plasma exchange, IVIG, rituximab, mycophenolate (CellCept), imuran (azathioprine) and steroids. One of my patients that had remission had been treated with rituximab and another one with mycophenolate. Usually, the immune treatment must be used for 1-2 years before we can be sure about remission.

Q: My Autoimmune Dysautonomia test through Mayo Clinic came back would support neurological auto-immunity. What is the difference between this and AAG? Thank you.
A: AAG is only one of many different autoimmune diseases that can impact the autonomic nervous system, and is it associated with the ganglionic-AChR antibody. If you had other antibodies come back positive, it would depend on the antibody or antibodies that were present, how much of the antibody you have, plus your symptoms and autonomic test results. The doctor who ordered your test should help you interpret the results and their meaning as it pertains to your diagnosis.

Q: My titer was low, but I had all the AAG symptoms and they were severe (not Pots). So, is it possible that the titer test needs to be tweaked so to speak. I am doing better since I have been on IVIGs. 2. Also, if you are on treatments, is there a reason to get the titer looked at again to see if there is progress, I don't think my titer level has moved?
A: We continue to work on making the antibody tests more accurate and reliable and also to look for other antibody tests that may be helpful. Diagnosis requires a doctor with good clinical skills. Antibody tests are not a substitute for seeing a doctor who knows about autonomic disorders. Rechecking the titer is usually not necessary but in some cases it retesting is reasonable if symptoms have changed. In general, antibody levels tend to go down with effective treatment. However, since IVIG is an infusion of a large amount of antibodies, antibody testing within 3 weeks of an IVIG infusion will not be very accurate. Inaccurate high or low results can happen.

Q: Executive dysfunction and cognitive dysfunction (diagnosed by a neuropyschologist) with positive antibodies. Is this a common symptom? If so is it typical AAG? I have low titers. I also have alot of AAG symptoms.
A: We have seen some cognitive problems that occur in patients with AAG (not all). We don't really understand why some people have these and some don't. It could be that these patients also have another antibody affecting cognitive function, OR it may be that cognitive function is affected when there is chronic repeated episodes of low blood pressure

Q: For those already on IVIG with continuing symptoms ie. neurogenic bladder, what adjunct therapies do you recommend?
A: Bladder symptoms are challenging. Many people are stuck using intermittent catheterization to manage the bladder symptoms (we try to avoid chronic catheters). There have been some trials using bladder stimulators ("pacemaker" for the bladder)

Q: Do you see many siblings with dysautonomia?
A: Yes, in other forms of dysautonomia like POTS, but not in AAG. There are also some rare genetic disorders that affect autonomic function and often happen in several family members.

Q: What are your thoughts about stem cell treatment for AAG?
A: I don't think there is any role of pluripotential stem cell therapy. If you are talking about autologous stem cell transplant - this has been used successfully for some severe autoimmune diseases (like MS or MG). The idea is that you take some stem cells and then give the patient heavy duty chemotherapy to kill all the immune system cells, and then give back the patient's own (autologous) stem cells to resurrect the immune system. Hopefully, the immune system comes back without the autoimmunity. This treatment has really worked in some cases to reset the immune system. The downside is that the process of autologous stem cell transplant is risky and includes a risk of death.

Q: Is it possible for AAG to misdiagnosed as encephalitis/meningoencephalitis?
A: That would be unlikely.

Q: What has he found to be most helpful with nausea related to this disease?
A: It's very difficult to treat nausea in AAG. There is some research going on to look at treatment of nausea in other types of dysautonomia – stay tuned.

Q: Does a patient's blood need to be sent overnight for the AAG test to be accurate?
A: Your doctor should follow the instructions from the lab. Each lab may have its own protocol. Antibodies in the blood sample are usually stable; however exposure to heat can damage the sample. Since my lab is in Texas, I recommend that samples sent to me are sent overnight so that the samples don’t spend time a lot of time in a hot warehouse or delivery truck.

Q: As autoimmune diseases often bring their friends along to the party, have you ever seen a case of a channelopathy (like Neuromyotonia/Isaac's Syndrome) presenting alongside someone with a long term history of AAG?
A: I don't think I have seen Isaacs sydrome with AAG, but we have seen cases of AAG along with myasthenia.

Q: What are the specific antibodies usually found in paraneoplastic autonomic ganglionpathy?
A: Anti-Hu is also called ANNA-1 and is found in patients with small cell lung cancer. This is the one most commonly found in paraneoplastic autonomic ganglionopathy. However, many cancer patients with gastroparesis or autonomic neuropathy have a negative antibody panel. Striated muscle antibodies can be found in some patients with thymoma. However, the striated muscle antibody is very NON-specific. Many older people have this antibody. This antibody is not really associated with autonomic ganglionopathy. A recent study from Mayo indicated that striated muscle antibodies that are lower than 1:7680 titer probably do not have ANY clinical value.

Q: I'm curious to obtain more information pertaining to the mechanism of action of rituximab for treating autoimmune diseases. From what I understand, this drug would aid in the destruction of B cells, thus hindering further antibody production. This would be beneficial in terms of reducing harmful autoantibodies from being produced, but what about the "good" antibodies that our bodies require to fight off pathogens? Is it not dangerous to immunosuppress oneself in this way?

A: It's a risk/benefit analysis you have to do with your doctor. The risks that come with immunosuppression vs the risks of not suppressing the B-cells are different in each patient.

Q: Is there any correlation between GAD65 antibodies and AAG?
A: I haven't seen any correlation. GAD65 is a fairly non-specific antibody at low levels.

Q: If somebody tests positive for the Anti-Hu antibodies but further tests are negative, should they periodically be tested again?
A: Yes, anti-Hu is associated with paraneoplastic (cancer-related) disorders. Period testing for cancer should be done even if the first cancer screening is negative. This is not AAG

Q: In chronic seropositive patients is there a known rate of progression?
Most AAG patients get the majority of their symptoms within the first 6-12 months and then stay about the same or even get a bit better.
A: In patients with AAG, what do you see as some of the most common precipitating or preceding factors in AAG? or do you see that most patients do not have an identifiable trigger?
Most don't have a trigger that they can remember, but there is pretty good data that some cases start after a trigger like a viral illness (many viruses, but EBV has been reported a few times). Autoimmune diseases like this can also come on after surgical procedure or other physiological stress.

Q: Does it cause uncontrollable shaking? My daughters having chest pains and can't stop shaking.
A: Uncontrollable shaking is not a symptom seen in AAG, but you should talk to your daughter's doctor about this. Some people get shaky when they have low blood pressure, and some POTS patients get shaky when they are standing and have rapid heart rate.

Q: Can AAG be fatal?
A: Not directly, but people can die of syncope with head injury, or prolonged hypotension, or from complications of bowel or bladder problems.

Q: Do people ever fully recover or go into remission from AAG?
A: Yes

Q: If we are diagnosed as acute/sub-acute onset, does this dx eventually change to chronic if our disease does not resolve?
A: Many cases improve incompletely and then enter a chronic phase.

Q: Is measurable and specific muscle weakness that is not due to decreased nerve conduction a feature of AAG?
A: Not really. You may be talking about fatigue which is pretty common in autonomic disorders

Q: How many cases of AAG actually turn into cancer?
A: I differentiate AAG from paraneoplastic autonomic ganglionopathy (which usually has different antibodies).

Q: Two cancers seem to be linked to AAG. Lung cancer (SCLC) and thymus (Thyoma.) What is the correlation between AAG and these two particular cancers. Why those specific cancers?
A: These two cancers are known to stimulate the immune system to attack the nervous system. As noted above, when there is a cancer involved, the term paraneoplastic autonomic ganglionopathy is more appropriate than AAG.

Q: Can thymic hyperplasia also stimulate the immune system to attack the nervous system?
A: Yes, but this is more often associated with myasthenia gravis.

Q: My son was diagnosed with AAG and is producing paraneoplastic antibodies as well. What does this mean for him? They are scheduling him in for a PET scan to look and see if any cancerous tumors are the cause, but coincidentally he has a 6 cm Osteochondroma bone tumor growing on his upper arm. Can a benign bone tumor cause them?
A: Benign bone tumors are usually NOT associated with autoimmune diseases. However, any sort of cancer is likely to stimulate the immune system.

Q: Can AAG be diagnosed solely from a tilt table/autonomic test results?
A: No

Q: Two odd symptoms that I have now is convergence issues with my eyes. My eyes dilate constantly. When I stopped the IVIGs to go to Mayo, I got severe vertigo attacks. They went away when I resumed the IVIGs. Could the convergence issues and vertigo issues be related to AAG since it is brain related?
A: Eye movement problems are not a feature of AAG. Abnormalities of the pupil can be seen in AAG (like pupils that don't react well to light or pupils that are unequal in the two eyes). With convergence problems and vertigo, you probably have a different neurological disorder.

Q: For those on IVIG treatments, how long do you recommend the treatment to continue? Months, years... what are some criteria to determine if/when the treatment should stop, continue, or continue but add more treatment options?
A: For long term treatment, I try to switch AAG patients to other therapies if possible, and save IVIG for flares/relapses. Each patient will have to do an individualized risk/benefit analysis with their doctor.

Q: For those with antibodies and little symptoms, would you recommend cancer screenings to rule out? If so, how often.
A: For AAG, the likelihood that there is an undiagnosed cancer lurking is small. It is reasonable to do a cancer screening one time at the time of initial diagnosis. For people with cancer risk factors (smoker) or with suspicious things on their first screening tests, a second cancer screening in 6-12 months is reasonable. But that is all. PET scans etc are generally not needed in the setting of ganglionic AChR antibodies. However, rare patients may have symptoms of AAG and have the anti-Hu (or ANNA-1 antibody). This antibody is strongly predictive of cancer and more aggressive cancer screening is needed.

Q: Should we be concerned with what lab our blood is being test for AAG?
A: Yes, there are differences in the labs. Right now, the two commercial labs that do the test well are Mayo Medical Labs and Athena diagnostics (a division of Quest labs). The two research labs that do the test are my lab (Vernino lab at UT Southwestern in Dallas) and Dr. Vincent's lab at Oxford in England. There is a company that sells an antibody kit but it is not a good idea to use this kit for diagnostic testing.

Q: Any recommendations - doctor's names, labs etc for those who are not in the US? Say Canada, UK, Europe in general, Australia etc?
A: In Canada try Dr. Satish Raj at the Univeristy of Calgary, Dr. Steve Baker at McMaster, or Dr. Ronald Schondorf. In Germany, Prof. Jens Jordan. In the Netherlands, Prof. Wouter Weitling.

Q: Is there a correlation between AAG and small fiber neuropathy?
A: Not really. AAG is a problem with the autonomic ganglia where small fiber neuropathy is a problem with the nerves. When the small fiber nerves are affected, patients can have autonomic

symptoms and sensory symptoms (pain, tingling, numbness). When there are a lot of sensory symptoms happening along with the autonomic problems, a diagnosis of small fiber neuropathy is more likely than AAG.

Q: What causes EXTREME stomach distention in AAG patients?
A: Gastroparesis or intestinal pseudoobstruction.

Q: How prevalent is gastric dismotility and extreme stomach distention in AAG? Thank you!!!
A: Slow gastric and intestinal motility happens pretty often in AAG. Severe constipation is also common (about 70%)

Q: Where does most AAG research funding come from?
A: Research funding is a big challenge. There is a rare disease research consortium for the study of autonomic disorders (a small NIH grant). Dr. Vernino's lab also has support from research grants.

Q: How much funding does AAG research receive per year?
A: Very little

Q: Is the Autonomic Disorders Consortium AAG/IVIG study still recruiting?
A: No. I believe that this study is now closed.

Q: What are your thoughts on an exercise training program in patients with AAG?
A: Exercise can be helpful for AAG. It should always be done seated or in a recumbent position. Exercise is always good to improve autonomic function.

Q: How effective is IVIG vs rituximab or a combination of both in treating AAG? What is your normal recommended course of treatment with these two drugs? Thank you!
A: I'm sorry that we don't have data which can allow me to give a "normal recommended" treatment. The treatment selection depends on a lot of factors. In patients that have severe, disabling, life-threating symptoms, we typically use plasma exchange, IVIG or rituximab. For long term management, a combination of steroids and an immunosuppressant oral medication. The way I use treatment at this point is individualized to each patient.

Q: For AAG patients with little or no bladder function despite increase in IVIG, are bladder stimulators useful?
A: They may be in selected cases. Often intermittent catheterization is required.

Q: Are there any long-term side effects of IVIG and PE?
A: Any time you use IVIG, there is a small risk of kidney problems, aseptic meningitis or blood clots. There are also milder, more common side effects like headache, fever and chills, and muscle aches. There isn't much research that looks at the long term use of IVIG, but one 10 year study in multiple sclerosis patients found no increased risk of side effects with long term use. The biggest risk of long-term PLEX is line infections or coagulation problems.

Q: Is IVIG or PE more effective in combating this disease; does this determination include those of us with multiple autoimmune diseases; what adjunct therapies work best with IVIG or PE.
A: We don't know for sure, but my personal opinion is that PLEX is more effective. Other immunosuppressants include mycophenolate and rituximab.

Q: For those of us who are on IVIG, what is the longest period of time you would recommend using the max dose of treatment (2grams/kg) - what factors do you look at to see if this dose is contraindicated - i.e. age. Does long term high dose IVIG impact kidney function?
A: There are different treatment protocols. Some doctors use 2gm/kg every month. I think this is too high. I use an initial dose of 2gm/kg and if additional treatment is required, I use 0.4-0.5gm/kg every 2-4 weeks.

Q: Since immune modulating treatments like Rituxan can be the causation of some cancers, do you recommend regular cancer screenings: if so, what screenings, and at what frequency. In relation to this, if a patient has a history of other cancer causing habits such as smoking, does this influence your recommendation for screenings?
A: The risk of cancer and unusual infections is real but the risk is low. I recommend the usual cancer screening (colonoscopy, chest XRay). Important to monitor blood counts to avoid excessive immunosuppression.

Q: Any risks associated with the long term use of some of the meds prescribed for symptoms management? Mestinon, domperidone, linzess, etc.
A: Domperidone was actually removed from the market because of cardiac complications. Mestinon is usually very safe to use long term

Q: Is IVIG, PE or other immune modulating treatment recommended for those with a low positive titer but not typical AAG symptoms (someone with POTS for ex)?
A: No.

Q: What are some ways to gauge the efficiency of the treatment aside from a reduction in symptoms? (blood tests, other tests)
A: Autonomic testing. Standing blood pressure. Urological tests for bladder function.

Q: In a seropositive AAG patient, how does IVIG work?
A: IVIG can reduce the antibody titer, but it generally doesn't eliminate the antibodies and it doesn't stop the white blood cells from producing new antibodies. No one really knows how IVIG works. One explanation is that IVIG floods the system with high levels of normal antibodies which tricks the immune system into making less antibodies.

Q: Can AAG and Myasthenia Gravis be found together in one patient?
A: Yes, it's uncommon. There are about a dozen patients in total that have been reported. Many of those patients had a thymoma, but not all.

Q: How many approx. cases are diagnosed each year? What is the ratio of seronegative to seropositive?
About 25, less than 50% are seropositive

Q: How many pediatric AAG cases are there, and are kids more or less likely to be seropositive?
A: A few cases have been reported. Kids are very unlikely to be seropositive and so the diagnosis of AAG can be difficult. In the kids I have seen, most of them have a sensory and autonomic neuropathy – a bit different than AAG.

Q: If severity of symptoms is correlated with titer level, then how is severe idiopathic dysautonomia even possible?
A: Severity only correlates with titer when there are antibodies.

Q: What are the typical autonomic testing findings in patients with AAG and how does this differ from other types of dysautonomia?
A: Orthostatic drop in blood pressure, impaired HRV, pupil abnormalities.

Q: How often do you recommend checking titers?
A: No need to recheck in most cases, but we do it in the research clinic. It may occasionally be useful to recheck the antibody levels to guide treatment.

Q: Is there a certain level or antibodies you have to be at to receive IVIG treatments?
A: No

Q: Is there a proven correlation between the severity of symptoms and the titer of the antibody at low titer levels?
A: The correlation at low antibody levels is not as strong

Q: Can AAG cause a limited ganglionopathy, only targeting certain autonomic ganglia?
A: Yes, at low titers. This includes GI dysmotility

Q: Do the autonomic ganglia develop structural changes after the chronic presence of g-AChR?
A: Apparently not. We looked at this in the rabbit model of chronic AAG and did not find any structural damage to the ganglia. As mentioned above, it is certainly possible that some permanent damage will happen if the autoimmune attack on the ganglia goes on for many years.

Q: Is there any literature or evidence that Lyme disease can cause a positive g-AChR titer?
A: Not to my knowledge

Q: Are there other autoimmune diseases that are more likely to be seen in AAG patients?
A: Sjogren, myasthenia gravis

Q: When other autoimmune diseases are present, are there separate treatments for each condition?
A: Generally, we try to pick a treatment program (immunotherapy) that works for both. The “two birds with one stone” approach. But in other cases, each condition needs its own treatment.