2022 Neuroimmune Foundation Inflammatory Brain Disorders Conference Day 2 Q&A

Q: I have seen a study [1] that showed positive GAS infection with a lack of a titer rise, but have not seen any published number on the frequency of this, though people quote 10-15% or even as high as 30%. Have you seen this clinically? Do you know of any study about the frequency of this? Is it possible due to infection from a non-group A strep? [https://doi.org/10.1086/650167
A: Dr. Mark Paternack: The Hysmith paper in J Pediatr Infect Dis Soce 2017;6:187 speaks to this with regard to GAS serologic limitations. I am really not aware of non-group A strep playing a role in this syndrome.

Q: Could you please comment if one sees erythema on/around the vaginal area and including the skin of the labia minora…and not seeing the perianal involved…suspicion for GAS…do we swab the area or clinically treat?
A: Dr. Mark Paternack: In a child referred for PANS/PANDAS with vaginal erythema I would certainly swab the area and would initiate treatment regardless of the test result using the clinical response (erythema, effect on PANDAS symptoms) and culture to guide further therapy.

Q: How do we change the belief that young kids don't get strep?
A: Dr. Mark Paternack: Hi! I think a compilation of a current case series of children under the age of 3 would be helpful.

Q: I have numerous post-strep urticaria [patients]
A: Dr. Mark Paternack: This is less common but not surprising. Hopefully antibiotic therapy is effective in controlling this presentation, and prophylaxis effective in preventing recurrences.

Q: I have seen PANS in individuals with vector borne illness such as bartonella and borrelia, and even positive Mycoplasma titers…could you please comment?
A: Dr. Mark Pasternack: I have seen post Lyme PANS and certainly seen Mycoplasma-associated PANS. I have not seen Bartonella-associated PANS. I always distinguish between routine laboratory Bartonella serology testing and various specialty lab tests which often are discrepant from the commercial assays and are of uncertain significance to me.

Q: Would it be useful to use Benzathine Benzylpenicllin?
A: Dr. Mark Paternack: Several of my colleagues have successfully used IM Benzathine in this clinical setting when compliance with oral therapy is poor. I worry about failure due to pharyngeal beta-lactamase production but clinical responses have been favorable.

Q: It seems the exotoxin symptoms seem consistent with dopaminergic stimulus. Are children with PANDAS history more sensitive to increased reaction to other dopaminergic stimuators, e.g. paranoia with THS? (i.e. should kids with PANDAS be specifically warned about marijuana risks?)
A: Dr. Mark Paternack: I am afraid I am not expert in this area of psychopharmacology but I will try to explore thai with my colleagues.

Q: With urticaria post-strep…also see elevated anti-TPO and anti-thyrogobulin
A: answered live

Comment: Dr. Theresa Willett: Regarding ANA, I would also add the highest ANAs that I have seen have been post strep infection.

Q: Is thera a role for probiotics and/or botanical treatment to help eradicate perianal strep infections? Looking for something beside long-term antibiotic treatment.
A: Dr. Mark Pasternack: Of course, we would all love non-antibiotic approaches to this problem but I am not aware of any probiotic or non medicinal therapies that would address this problem. I am not aware that topical therapies such as mupirocin have a role in this disorder.

Q: Please comment re: tonsillectomy for pts with PANS/PANDAS
A: Dr. Mark Paternack: The role of tonsillectomy is somewhat controversial; the guidelines recommend tonsillectomy when there are standard indications (sleep apnea, recurrent GAS infection) but there are centers where tonsillectomy is pursued early in the management of these patients. Parents have told me this was terrific in improving symptoms, and other parents told me this was the worst thing that could have happened. There are anecdotal reports of GAS sequestered in the intratonsillar abscesses, supporting tonsillectomy. In the current COVID era, where I can't easily access the tonsils, I have had a high threshold to recommend tonsillectomy.

Q: Could you speak to the use of Augmentin with kids with PANDAS?
A: Dr. Mark Paternack: I love Augmentin. I generally offer cephalexin initially but frequently switch to Augmentin if I encounter a suboptimal response to cephalexin.

Q: What is your treatment recommendation for a patient with perianal strep (without PANDAS)? Similar questions but how would that treatment recommendation change if the perianal strep has a sibling WITH PANDAS?
A: Dr. Mark Pasternack: In an otherwise asymptomatic child, I would offer a 3-4 week of amoxicillin therapy and observe their response. If a sibling has PANDAS, I would probably offer 4 weeks of cephalexin and monitor the patient closely after completing therapy.

Q: How often in your practice do you see Lyme and PANS coincidentally?
A: Dr. Mark Pasternack: Rarely but not never…I have seen perhaps 2-3 cases over the years.

Q: Do you use double antibiotics - zithro and keflex together?
A: Dr. Mark Pasternack: I have done this very occasionally, typically based on illnesses with positive throat cultures for GAS and positive strep and M. pneumoniae serologies who fail to improve with cephalexin or amoxicillin/clavulanic acid given for GAS. I always worry about C. diff in patients on combined macrolide/beta lactam therapy.

Q: What is the genetics/passing tendency on to children or grandchildren of index patient? I had chorea when I was 7 and am 76.

A: Dr. Mark Pasternack: We certainly have concerns regarding heritable risks for nonsuppurative complications of GAS. Genomic investigation of this population is an area of very active research now and hopefully this information will reach publication level conclusions in the near-mid future.

Q: Your thoughts on anti-inflammatory properties of the antibiotics you use?
A: Dr. Mark Pasternack: I am aware of, and impressed by, the publications documenting the anti-inflammatory properties of both beta-lactam and macrolide therapy. I can only speculate as to whether these antibiotic features are playing a clinically significant role in this patient population. That said, I seem to see better responses with beta-lactams than with azithromycin even though the latter is thought to be more prominently anti-inflammatory.

Q: Do you use any immunomodulatory agents to treat PANDAS/PANS?
A: Dr. Mark Pasternack: Yes – I was constrained by time to give a more encyclopedic approach to the management of children with PANS/PANDAS. I routinely offer NSAIDS as an initial adjunctive measure, and use short course steroids in the setting of antibiotic/NSAID failure and/or symptoms flares. I offer IVIG in selected patients (?10%) who fail to improve with milder Rx. Plasmapheresis is not easily available in my hospital for my patients. I have largely stopped using rituximab during the COVID pandemic; COVID in rituximab treated patients can be fatal.

Q: If a child has low IgG does that account for the failure of ASO or the other one to rise with strep infection?
A: Dr. Mark Pasteranack: This is an important consideration, which is one of the reasons we measure IgG and subclass levels in our patients. I would also lower the threshold to consider IVIG therapy in children with refractory symptoms.

Q: So if a child had past 2-3 strep infections but presented with sudden OCD after some time and responded well to antibiotics and SSRI, would you still treat as PANDAS and continue antibiotics for 6 months?
A: Dr. Mark Pasteranack: For mild-moderate symptoms, I might consider 3-4 months of therapy, but for more severe illness I would treat longer.

Q: What is your antibiotic of choice for prophylaxis in GAS induced PANS?
A: Dr. Mark Pasternack: I primarily use cephalexin. Some children are doing well on amoxicillin at the time of my initial evaluation and I simply maintain this therapy.

Q: I'm curious about your thoughts on use of a trial of antibiotics in PANS children during flare when underlying etiology has not yet been identified (negative cultures and serology). Patients usually present to my office months after initial onset.
A: Dr. Mark Pasternack: This is the common situation, and I offer empiric therapy all the time, especially in the COVID setting where many of my visits are telemedicine-based.

Q: My PANDAS son had an ASO over 1200 and anti-DNAse over 800 for over 2 years. He was on Zithromax prophylactic treatment during this time. 1 year ago removed the tonsils but they found no strep in the tonsils. But after the operation, they found the titers finally went down to ASO 500 and Anti-DNAse 300. How can you explain this when they did not find any strep in the tonsils? They did find staphylococcus and aerobic bacteria.
A: Dr. Mark Pasternack: I am glad to hear that tonsillectomy was helpful. The failure to find GAS on culture is perhaps not sufficiently sensitive in this context. It is possible that the staph infection provoked nonspecific inflammation that augmented the specific GAS antibody responses and that tonsillectomy reduced the background inflammation. This is why many PANDAS centers recommend early tonsillectomy.

Q: Do you usually give probiotics with long-term cephalexin?
A: Dr. Mark Pasternack: I don't have a rigid policy. Some children have diarrhea and other GI symptoms and I certainly offer probiotics then. Others have minimal -no symptoms and the thought of an additional "medicine" complicates compliance with antibiotic therapy. Many parents offer probiotics on their own.

Q: Perhaps I am mistaken, but I can't imagine a single rheumatologist or neurologist in my town ever doing this workup or thinking these are symptoms of rheumatologic disease. Truly. How is anyone getting these complicated work ups done outside of studies to actually help patients? I am honestly asking. I can order complicated blood work in integrative primary care but certain brain scans or CSF tests I cannot. Accessing this work up is integral so I am not guessing.
A: Dr. Janet Cunningham: The division of professionals is a huge problem and it has not been easy at stages due to budget restriction (and pandemics). In Uppsala, we started with a collection of cases with very severe symptoms and high healthcare use and worked our way out from there. Success with even a single case that other professionals witness, does wonders for the curiosity of the medical community. This level of investigation is more suited for university associated clinics. This must be done with very high structure to be able to extract and learn from the data.

Q: Re: probiotics, have you seen any positive or negative issues with oral strep (e.g. BlisK12) used for dental strep competition
A: Dr. Mark Pasternack: Great question - I do not have experience with this product.

Q: Dr. Cunningham, in the first case, how long had the patient tried Rituximab? Could it be she just needed longer treatment with the Rituximab to get rid of the other psychiatric symptoms, in addition to finding the thiamin deficiency? Is she back to normal with just the thiamine?
A: Dr. Janet Cunningham: She was still on Ritux when she presented with the cognitive symptoms. The cognitive symptoms varied over time. They got worse when the diarrhea started. The almost complete resolution of symptoms after thiamine treatment is a strong indication this was the problem. She has been sick for nearly 2 decades and this has its own impact on long term function but she has much much higher function and independence now than she did a decade ago.

Comment: There is an article on NDNR on management of streptococcal infection with botanicals you may find helpful.

Q: Dr. Cunningham - do you ever consult with patients in the US? Do you recommend someone that does what you do here in the US? Difficult to find physicians who treat adult with PANS-like situation.
A: Dr. Janet Cunningham: We have a plan to try and build for this but we don't have the capacity yet.

Q: Has anyone in your immunopsychiatry clinic undergone an FDG-PET scan of the brain? Do you think this imaging modality may be worth investigating further for the type of patients you see?
A: Dr. Janet Cunningham: Yes. We see lots of things that don't look normal. BUT there is a lack of controls. Hard to know that the findings mean. We do use it in cases with severe symptoms and where we are on the fence and need more to spike the diagnosis.

Q: Children with neuropsychological lupus lose IQ points over the years and clinically their cognitive function declines. Does this not occur in your patients? Our patients seem to be otherwise controlled.
A: Dr. Janet Cunningham: I see this too. I think the neurological complications are very underdiagnosed. We have been able to break cognitive decline with more aggressive therapy (cyclophophamide, ritux). In the cases with thiamine deficiencies, thiamine supplementation really does help - and very low risk to try. In some of our older cases we see a disproportionate level of WMC's on MRI. Adding NFL to the CSF workup has helped us identify cases with more aggressive ongoing damage.

Q: I have a young teen patient with severe depression, almost catatonic in her early years, cognitive malfunction, separation anxiety, etc. Onset was rather sudden but not overnight like PANS. Also thyroid antibodies postive. She has had a complete work up with Duke who ruled out autoimmune encephalitis over 2 years ago but she is not getting much better and I 100% don't think it's just psychiatric. Can you recommend where else to refer her to in the US, preferably East Coast?
A: Dr. Janet Cunningham: Perhaps others in the panel can suggest a clinic? Otherwise the patient associations may be able to help guide you. Hashimoto's encephalitis is included in the Guidelines for "Autoimmune psykos" https://pubmed.ncbi.nlm.nih.gov/31669058/ I have seen a few cases with thyroiditis and catatonia features respond to steroid but also one that responded to T4 treatment (was euthyroid at treatment initiation). I have seen one respond to clozapine.

Q: How helpful has the Cunningham Panel been in evaluating your patients, even if adults, if you use this? I think it is helpful, but many do not give it enough credit, especially conventional adult neuroimmunology neurologists, I find.
A: Dr. Janet Cunningham: I agree. We have some data that we are trying to validate. In the preliminary data we have, it looks like the panel is catching different conditions and not one cohesive diagnostic group. The controls are not appropriate for adults. Slightly elevated levels

are not specific - especially in adults. The DRD1, 2, IgM abs may be interesting but we need to validate with other systems. The CAMKII% data had pretty high variability in the test-retest in our hands which may be due to several technical issues that we were not able to resolve but we don't put much weight in these. We are no longer able to order clinically in Sweden and don't have the budget to pay with research funds so we have not had the possibility to continue evaluating.

Q: Or it means that they feel validated since they got a treatment. Not sure which is more valid.
A: Dr. Janet Cunningham: Absolutely. This is why we need the high quality trial. The dramatic and sustained improvement speaks against validation - placebo, but I will only know when we put this to the test.

Q: How do you feel about Rituximab treatment vs. IVIG vs. Plasmapheresis? Do you find the risks of using Rituximab are low vs. the benefits you have seen? For how long do your patient have to be treated, usually?
A: Dr. Janet Cunningham: We gave 4-6 doses and ceased therapy afterwards. 3 patients that reached stability, remained stable. One relapsed. This was in association with a high stress situation. We don't have enough data to know anything for sure.

Q: Is there any data on low-dose naltrexone for autoimmune encephalitis? This has been studied a bit for MS and I would be interested in your thoughts on a possible role for LDN for autoimmune OCD.
A: Dr. Janet Cunningham: I have never tested it. I would be interested if anyone else has tried it with success.

Q: What dosing regimen do you use in your adult patients using Rituximab?
A: Dr. Janet Cunningham: We have given 500-1000mg every 6 months. Maybe close dosing for the first 2 doses is needed? For the trial 4 months between dose 1 and dose 2 (to reduce the trial time and increase feasibility).

Q: Any thoughts on Rituximab for PANDAS/PANS?
A: Dr. Janet Cunningham: PANS is not one thing. The response will completely depend on what the underlying mechanisms are. I am sure there are cases that will respond but we need the trial to start sorting this out in a structured manner.

Q: May you repeat the protocol for your rituximab treatment study?
A: Dr. Janet Cunningham: A more complete description here:
https://clinicaltrials.gov/ct2/show/NCT04323566

Q: I believe you mentioned that your rituximab study participants will receive the infusion every 4 months. In the autoimmune encephalitis world, standard convention is every 6 months (though it seems I'm noticing more clinicians starting to shorten the timeframe between infusions). Can you speak to how the 4 months was chosen?

A: Dr. Janet Cunningham: We see clearer response after the 2nd treatment. I do not know what the optimal timing is. Perhaps nobody does? We chose 2 doses with 4 months interval for practical reasons to maximize our chance of catching the potential improvement while keeping the timeline more feasible. After 2 doses, if a patient responds but regresses when B cells come back, 6 month intervals will be our standard.

Q: Do you know of any physicians or institutions in the US or otherwise in Europe, including Sweden, that care for adult PANS patients? I find it difficult to find believing adult medicine doctors in the US that believe this condition or treat it. Frustrating.
A: Dr. Janet Cunningham: There are a growing number of individual doctors recognizing these cases but very few clinics. Our clinic does evaluate and in selected cases treat adult patients with "PANS" after a multidisciplinary team evaluation. I am also aware of a clinic at UNIVERSITATSKLINIKUM FREIBURG Klinik fur Psychiatrie und Psychotherapie. There may be others. The patient associations can sometimes help patients navigate the local health system. I can also recommend the recently published Guidelines for "Autoimmune OCD" that provide a summary of the data we have so far to feed your arguments for more extensive investigations. https://www.nature.com/articles/s41398-021-01700-4

Q: Dr. Cunningham - is your RCT study accepting patients from outside Sweden?
A: Dr. Janet Cunningham: Not for the moment. We are interested in expanding it to multicenter and are looking for funding.

Comment: It would be so helpful to get a list of academic institutions who are studying CSF autoimmunity in PANS/PANDAS. This would help the primary care providers get the diagnosis and treat for our sickest patients.

Q: Unfortunately just depending on evidence-based medicine is limiting our ability to innovate and learn more and avance, as was possible in the past in medicine. We can't learn or innovate or progress if our ability to care for patients is stunted or restricted by bureaucrats or politicians! This could be the curse that kills our own progress and our own health in the future if we have rare disease or difficult to understand disease.
A: Dr. Janet Cunningham: It is likely that many PANS are just rare variants that will never be represented in the mainstream group level data. Precision medicine may be the way forward here.

Q: Do you also use ECT in your autoimmune cases with catatonic features? Have you found this to be a beneficial adjunct?
A: Dr. Janet Cunningham: Yeah. In a couple cases it has been helpful. In some cases the symptoms recur and repeated ECT is needed. In some cases it has helped with the depression symptoms but not the motor symptoms.

Q: How are you thinking about CD20 depletion during the pandemic?

A: Dr. Janet Cunningham: Definitely. We put the breaks on the trial and weaned our ongoing cases. We have not had any complications for those who were treated pre-pandemic. We have now started the trial but vaccinate for covid pre-inclusion.

Q: How often do you use Rituximab clinically?
A: Dr. Janet Cunningham: Rarely. Now as soon as the funds are available, we want to put everyone who qualifies into the trial. In severe cases, it may be considered as an off label option when other immunotherapies are considered in a patient with severe symptoms. Multidisciplinary team decision is needed as well as a clear evaluation of risks and gains. The guideline papers provide some support. Guidelines for "Autoimmune OCD" https://www.nature.com/articles/s41398-021-01700-4 Guidelines for "Autoimmune Psykos" https://pubmed.ncbi.nlm.nih.gov/31669058/

Q: Problems to solve slide: The DSM needs to change with regards to meeting requirement of medical evidence and going beyond evidence based medicine for these very sick patients
A: Dr. Janet Cuningham: Doing this makes a huge mess to solve with allocation of budget, resources, health care structures and so much more. So I get there is a huge resistance but for the patients with psychiatric phenotypes we have no other options. And psychiatry is not doing everything wrong. I think there are many psychiatric treatments that have immunological and other actions that we could target with better precision.

Q: How long does it take to de-construct psychological compensatory mechanisms developed during the acute psychosis?
A: Dr. Janet Cunningham: In acute psychosis, I would never attempt it.

Q: The COMT gene may be something to look for with mania/psychosis. PANS male hospitalized 2 weeks for mania at age 16 which resolved within 24 hours with antibiotics. 3 years later was exposed to THS and had <24 hours mania which completely resolved. His sister had mania lasting 1 week when she had 1 week of daily THC during COVID - required benzos/lithium. Could just be dopaminergic sensitivity, but could have some genetic overlay?
A: Dr. Janet Cunningham: Absolutely! We have a patient with catch 22 where I think the COMT gene is involved in the phenotype. There are a long list of genes we are planning to sift through.

Q: What do you specify in the prior authorization for Rituximab? Autoimmune encephalitis?
A: Dr. Janet Cunningham: Not a problem in Sweden so I do not know what would work in your setting. Autoimmune encephalopathy I think this is a more appropriate term for what we are seeing.

Q: We have published on unmasking of primary immunodeficiency with Ritux…do you pre-evaluate?
A: Dr. Janet Cunningham: In cases where we suspect immunodeficiency (such as case 2) we do, often without findings. The cases with immunodeficiency are then treated according to guidelines.

Q: Would love the contact infor for Dr. Cunningham if possible.
A: Dr. Janet Cunningham: janet.cunningham@neuro.uu.se

Q: What if a patient is already on IVIG or has a known infection? Would you continue treatment for both with Rituximab?
A: Dr. Janet Cunningham: IVIG is not a problem. The goal would be to taper. I would not give Rituximab with an ongoing infection.

Comment: Dr. Cunningham - appreciated your effort in combining psych with neuro. Wish all neurologists have an open mind and try to connect psychiatric symptoms with neuro/autoimmune diagnosis.

Q: As a psychiatrist, do you give Rituximab IV yourself or do you have to convince a rheumatologist to do the treatment?
A: Dr. Janet Cunningham: We use the ECT unit for both lumbar punctures (I do these myself, atraumatic needles are the best) and we administer Rituximab there as well. Would like to add that we are VERY restrictive with Rituximab. It is always a multidisciplinary decision and a severely ill patient with a careful risk and consequence analysis. Otherwise, I hope the trial, once funded, will help us broaden the group we can test the treatment on.

Q: Dr. Cunningham - would you see a 25 year old patient from Ireland suffering for many years? It is impossible to get a diagnosis of PANS/PANDAS here.
A: Dr. Janet Cunningham: We are working to establish international services. We don't have the capacity yet.

Q: Wonderful presentation! So glad you brought up the phenomenon of accompanying psychophysiologic disorders PPD/TMS/MBS in these disorders.
A: Dr. Janet Cunningham: We see it a lot. It can manifest as a meta-OCD as well "are these OCD thoughts or not?" "Is it back?" Patient need help feeling secure in the time after symptom reduction.

Q: Is there any data or experience specifically in the treatment of OCD associated PANS?
A: Dr. Janet Cunningham: Everything I know so far is here: Guidelines for "Autoimmune OCD" https://www.nature.com/articles/s41398-021-01700-4

Q: Will there be any discussion of how to find specialists who have interest/training in this area? I am Family Med with a strong interest in autoimmune disease. When I'm seeing patients with the combinations of illnesses or symptom patterns discussed, i have no idea where to refer. Our local psychiatrists and neurologists do not appear to have any interest or training in this area. I would be glad to provide them with the slides from this presentation, videos, or articles when referring but I'm not sure where to find the best research. Dr. Cunningham's lecture would be particularly useful as a starting point for many of them. Thank you for this fascinating and well presented course. I have many non-physician/PA/NP friends in allied health positions who would benefit also from this information.

A: Dr. Chandra Menendez: There are studies showing 86-90% accuracy in the correlation of anti-neuronal antibodies with neuropsychiatric symptoms, and resolution with treatment. Thus, there may be clinical utility for using these autoantibodies as markers to monitor treatment efficacy in addition to help confirm a PANDAS or PANS diagnosis. More studies will be needed to clinically validate. I'm also hoping that our work may help guide more specific therapies in the future for individuals with specific pathogenic antibodies.

Q: Have you seen a close association between antibody titre and severity of clinical symptoms? Are the reference ranges considered to be the same for adults and children?
A: Dr. Chandra Menendez: See last answer. I am on the basic science research side, so I cannot answer the reference ranges. But adults can have anti-neuronal antibodies. We need to perform more longitudinal studies to determine differences in chronic vs. remitting cases, since we know that the antibodies are elevated during symptom exacerbation.

Q: Have you been able to test for these antibodies in the CSF?
A: Dr. Chandra Menendez: Both antibodies to the dopamine receptor 1 and 2 are detected in CSF. The challenge with CSF studies and why I have not tested CSF for the dopamine receptor signaling assays is that we do not have healthy controls to properly control our experiments and determine if we see an elevation of signaling above normal levels.

Q: Are the antibody markers (anti D1R, CAMKII, etc) only noticeable during a period of flare in a PANS/PANDAS child? I.e does the test need to be completed within a certain time frame?
A: Dr. Chandra Menendez: The anti-neuronal autoantibody markers do correlate with the manifestation of symptoms and decrease after effective treatments. We suspect that they will be elevated during flares. We are in the process and need to do additional longitudinal studies to investigate how they may change to understand their role during flares and remissions.

Q: If there are antibodies stimulating dopamine receptors and dopamine production, should we see psychosis or mania in patients?
A: Dr. Chandra Menendez: This is a great question and I don't necessarily have an answer as I'm a basic scientist with background training in neuroimmunology. We believe that dopamine receptor autoantibodies may change the sensitization and kinetics of receptor signaling and internalization, so are potentially causing aberrant responses of dopaminergic neurons. This requires additional experiments. Keep in mind that a lot of children also have antibodies to both D1 and D2 that may further disrupt circuitry signaling. It likely depends on the quantity and strength of signal and duration. Considering basal ganglia disorders can have symptom overlap as PANDAS/PANS, we speculate that the antibodies contribute to the symptoms observed during acute onset and flares if they are abnormally elevated and getting into the brain. Especially considering their resolution following effective treatment.

Q: Do you think blocking D1 activity in children with PANS could blunt OCD symptoms?
A: Dr. Chandra Menendez: My immediate response would be to try to limit the production of the antibodies with immunomodulatory therapies (and eliminate any infectious trigger), but future

studies are needed to see if readily available psychoactive therapies could reduce any potential dysregulated dopamine receptor signaling.

Q: Have you looked at these antibodies in other conditions such as autism?
A: Dr. Chandra Menendez: Yes! We are working on a manuscript about antineuronal autoantibodies in ASD. There also was a study in collaboration with Dr. Richard Frye on IVIG therapy for autoimmune encephalopathy in autism. IVIG for the treatment of Autoimmune Encephalopathy in Children with Autism. Connery, K., et al, Translational Psychiatry 148 (2018)

Q: Would you expect to see high or low dopamine with PANDAS/PANS?
A: Dr. Chandra Menendez: Dopamine is honestly a pain to measure from samples and why we like the idea of measuring something more stable like antibodies that may provide clues to disease pathogenesis. My guess is that the levels would be abnormal as the body tries to compensate for the over or underproduction. Perhaps this may explain the combination and acute onset and overlap of so many different clinical manifestations during disease (at least with children that have the D1 or D2 autoantibodies).

Q: I have done a number of Cunningham panels on PANDAS kids. Many of them have very high tubular antibodies. Often also D1, but the tubular is extremely high. Are there any correlations your lab has made with this and with symptoms?
A: Dr. Chandra Menendez: Thanks for your comments! My work mostly focused on D1 in PANDAS, but I should go back and look at tubulin. We are interested in D1 because of the potential pathophysiological role. I'm not sure if tubulin would be more of a biomarker rather than the tubulin auto-antibodies being pathogenic. However, this is another great point as children may have different auto-antibodies than others (and some that we may not have identified yet, or may have other inflammatory causes altogether) which is why the antibody panels are investigated together as a group for diagnosis. I will look more into the tubulin, thanks!

Q: Amazing work Dr. Menendez and Dr. Cunningham. Would like to know if most people find utility in sending Cunningham panel? Since it isn't covered by insurance, I have patients that are worried about cost and how much it will help. Thoughts?
A: Dr. Chandra Menendez: Thank you! Biomarkers aren't as accepted as they should or could be in these disorders. Which is another reason why my work has also focused on the functionality of specific auto-antibody biomarkers and how they may be more useful. The panel is a guide to a clinician's diagnosis of autoimmune encephalitis and basal ganglia encephalitis of which PANDAS/PANS would be considered. It may also be useful in guiding more targeted therapies. Dr. Cunningham will also discuss more on the panel during her webinar with the Neuroimmune Foundation on Jul 26, 2022.

Q: Can you please put the last slide up on how to contact Dr. Harris?
A:Dr. Brent Harris:
Marina Selenica - POND Coordinator
ms4739@georgetown.edu

Brent Harris - POND Brain Bank Director
bth@georgetown.edu

More information about POND and the Georgetown Brain Bank
https://thealexmanfullfund.org
https://neurology.georgetown.edu/patientcare/goergetownbrainbank/

Q: Is there a PANDAS CME series on Jul 26, 2022 ?
A: Neuroimmune Foundation: We will be doing a non-CME event with Dr. Madeleine Cunningham on that day.

Comment: https://www.sciencedirect.com/science/article/pii/S0165572819303522

Comment: I am wondering if we shouldn't be treating more and more with antiviral valtrex in patients who get EBV or CMV infections instead of the approach of "everyone gets EBV eventually." We have underestimated this virus and its effects on individuals (I trained in peds 1992-1995 at Georgetown). In certain patients I have used Valtrex to minimize the effect.

Comment: I have observed improvement in cognitive based processing speed as tested by school teams in patients who have been on longer term valacyclovir for elevated titers to some of the herpes viruses in patients who have been diagnosed as autistic, as you mention. As PANS researchers almost universally agree, titers are far from optimal, but the paucity of accurate, reliable, available commercial markers makes this a viable therapeutic option. The final decision is, of course, individually based.

Q: Dr. Harris - Thank you for your presentation. I see that you sit on the expert panel of the VICP and you briefly mentioned vaccine induced encephalitis in your presentation. I'm curious if you have identified any themes or underlying predisposing factors in these children. What may make a child susceptible to vaccine encephalopathy? I understand some practitioners test for measles, mumps, rubella, and varicella antibodies in PANS work up. I'm trying to understand the relevance of these titers in vaccinated children, if any?
A: Dr. Brent Harris: Not any direct themes, and I've not seen any testing results for MMR titers in the 20 or so cases I've consulted on. There is a nice review of neuropath findings from the neuropathologist who covered these cases prior to me.
https://pubmed.ncbi.nlm.nih.gov/21854821/

Q: Is there something particular in patients of European ancestry with PANS?
A: Dr. Agnieszka Kalinowski: We haven't examined this. Our clinical cohort is enriched for patients with European ancestry.

Q: For PANS patients, is the specific target known for what auto-antibodies bind onto the cholinergic interneurons in the striatum? If so, is ti the D1 or D1 dopamine receptor, or something else?

A: Dr. Agnieszka Kalinowski: This has not been determined yet, though I believe the Pittinger group (Yale) is working on it.

Comment: Dr. Madeleine Cunningham: In asking about psychoses - in a case of psychosis where the presence of D2R antibodies were elevated and in a case with hallucinations, patient responded to treatment with haloperidol and IVIG.

Q: How would we explain the lack of autoimmune disease and likely PANS in indigenous populations? I would think genetics would be similar or effect must be environmental and would think exposure to pathogens would be greater in idigenous populations?
A: Dr. Agnieszka Kalinowski: Interesting question. I don't know, perhaps a role for immune system training?

Q: Is the cross reactivity with cholinergic interneurons ONLY in the brain or does this cross reactivity involve the peripheral nervous system as well?
A: Dr. Agnieszka Kalinowski: I don't think this was examined. The sera was only exposed in brain slices.

Q: Is C4 altered in the serum of the patients with copy number deficiency?
A: Dr. Agnieszka Kalinowski: I examined this on a subset of patients because serum C4 was not performed routinely on everyone. There does appear to be a correlation between C4 gene copy number and the serum C4 protein in patients.

Q: Have you seen a correlation between Ehlers Danlos Syndrome as a genetic factor?
A: Dr. Agnieszka Kalinowski: We haven't looked at this.

Q: Question regarding the complement system. Mannose binding lectin deficiency affects up to 8% of patients of western European descent and MBL plays a role in tissue defense and clearance of drying material. Has this protein been evaluated in your PANS cohort?
A: Dr. Agnieszka Kalinowski: Good point! We haven't measured this in our cohort. Would be great to do.

Q: Activation products C3a and C4a are available commercially.
A: Dr. Agnieszka Kalinowski: Yes, thank you! Dr. Frankovich generally sends the samples to National Jewish for activation product RIA.

Comment: Dr. Theresa Willett: Re: Ethnic background bias. I am still suspicious that for underserved minorities, the suspicion for behavioral issues being biologically mediated may be lower. Or the first line providers may be looking for different issues and PANS is not high on the differential diagnosis.

Comment: https://www.cdc.gov/tuskegee/timeline.htm

Comment: I know 2 African American boys in the LA area with PANS. One was adopted by a Caucasian family, onset in preschool. The other a teen with baseline mild autism. Both with limitations of MediCal insurance. Both very quickly labeled “psych” or “prenatal drug exposure” or “worsening autism.” Extremely difficult to overcome this to find diagnosis, also to get to good providers with severe insurance limitations.

Comment: Dr. Theresa Willett: Regarding ethnic backgrounds and bias, I think the recent appreciation that race-based lab values under-appreciate the systemic socioeconomic factors in health is a good example of how we might miss the bias in our own populations: https://www.statnews.com/2021/09/23/expert-panel-recommends-against-use-of-race-based-tool-in-assessment-of-kidney-function/

Comment: Dr. Theresa Willett: Regarding C4a clinical labs, our experience was that sample handling was variable and could impact results, e.g. prolonged room temp sample would have falsely elevated C4a read. I think Quest or Labcorp use a different process, but they may be just as fussy.

Q: With provider education in Arizona, we are starting to see a more diverse patient population with the demographics in our state. But our initial patients were all of European descent.
A: Dr. Agnieszka Kalinowski: Interesting. Did you mainly target pediatricians and child psychiatrists?
A: ED physicians, school nurses, pediatricians, psychiatrists, and psychologists

Q: In chronic or post infection Borrelia neurologic disease, is this due to post-infectious immune response or persistent infectious forms of borrelia?
A: Dr. Shannon Delaney: My best guess is a combination of both as the best clinical responses are from antibiotics (including IV) and IVIG.

Q: If a kid sort of fits Lyme as a possibility a decade ago, but is treated for PANS with antibiotics and gets better to about 90% or greater mark over the past 3 years, does that likely negate that Lyme is/was at play? More simply, if you do not treat with Lyme specific treatment and the child improves, is that enough to say Lyme was not a factor?
A: Dr. Shannon Delaney: Difficult to say as many antibiotics to treat PANS overlap with those used to treat Lyme disease.

Q: What tests did you use to diagnose Lyme?
A: Neuroimmune Foundation: Many of the questions being asked here are also covered in an interview we did with Dr. Delaney recently that can be found here: https://neuroimmune.org/dr-shannon-delaney-interview/

Q: Where do you send the tick-borne illness labs and was species do you test for (lyme, bartonella, babesia)? Also can we send C6 to commercial labs?
A: Dr. Shannon Delaney: We use Stonybrook for Western Blot, Medical Diagnostics Lab for Lyme C6 peptide ELISA and as well as Anaplasma, Bartonella, Babesia microti. We use

Sonoma County Public Health lab for Babesia duncani and Quest for miyamotoi and other co-infections.

Q: Dr. Delaney - do you see adults for lyme?
A: Dr. Shannon Delaney: Yes

Comment: MayoClinicLabs.com also have B.miyamotoi assays as well as co-infection antibody and PCR assays.

Q: How accurate is TickReport? I have had patients with negative testing who ultimately developed Lyme.
A: Dr. Shannon Delaney: Not sure–I do see a lot of positive results but not sure about false negatives.

Q: Have you ever used Vibrant America's tick borne illness testing? If so, can you give an opinion of accuracy or benefit?
A: Dr. Shannon Delaney: We don't use Vibrant labs but I know practitioners who do.

Q: What are your treatment approaches to target B. Miyamotoi in a patient with relapsing fever?
A: Dr. Shannon Delaney: The treatment approach to miyamotoi is the same as Lyme disease. I have observed the same chronic symptoms and difficulty in treating.

Comment: Most Departments of Natural Resources will test ticks. You can find your state results by contacting them. Most in the Midwest now show positive.

Q: I notice you mention IL-6 as a biomarker found in your psychosis patients in the interview linked. Have you ever used Actemra in any of these patients? Results?
A: Dr. Shannon Delaney: I have never used Actemra in these patients, but it's an interesting idea.

Comment: ELISA Multi Peptide Assays also have some literature behind them to show efficacy. TO Osp (s) and other epitopes. Good pick up and comparative Western blot performance personally with this platform.

Q: Do you see patients with Bartonella infection present with neck rigidity and muscle spasms?
A: Dr. Shannon Delaney: I see considerable clinical overlap between all these tick borne illnesses.

Q: Does treatment with steroids worsen PANS symptoms, in your experience?
A: Dr. Shannon Delaney: We usually don't give steroids to patients with a history of Lyme disease.

Q: How does complement get into the brain?

A: Dr. Emily Severance: Complement is produced in the brain likely by neurons, microglia, and astrocytes.

Q: In cardiac studies, endothelial inflammation and damage is associated with increased heart disease. Have your gut endothelial findings been considered for this since people with schizophrenia not only have cardiac issues secondary to meds, weight gain, etc, but part of the higher early morbidity rates.
A: Dr. Emily Severance: That is a great idea and we do have some data on cardiac comorbidities in schizophrenia. Taking into consideration the physiology of the whole body is so important. Dr. Dickerson at Sheppard Pratt has reported on the increased mortality rates in schizophrenia.

Comment: Food reactions and yeast appear to be involved in the rising tide of evidence for increased zonulin and claudin-5. These are implicated in possible increased gut and BBB permeabilities, respectively, with schizophrenia. These may offer encouraging testing and therapeutic potential for such patients. This also interfaces with the translational research and treatments in autism.

Q: Please clarify - are you seeing increases in C1q protein, auto-antibodies to C1q or both?
A: Dr. Emily Severance: Astute observation. In our early studies of C1q, we looked at C1q protein, C1q as part of an immune complex, and C1q autoantibodies. Our C4 measures (in humans) are all protein-based.

Q: S-100b presence in the gut - is there an indication of increased gut permeability or ENS disruption?
A: Dr. Emily Severance: I am convinced that the S100B comes from ENS disruption (but I have not pursued this study yet).

Q: From my reading, it seems there might never be found a specific marker for BBB vs. gut hyperpermeability. My understanding is leaky gut = leaky brain. Comment?
A: Dr. Emily Severance: I agree. Many people from different disciplines talk about brain specific markers and have difficulty answering how these markers would rule out gut associations. I think that most brain specific markers are at best neuron-specific, or glial-specific. I am open to suggestions though, because it would be great if there was a truly brain specific marker.

Q: Is NMDAR found in the neurons of the myenteric plexus?
A: Dr. Emily Severance: I am 99% sure that there are, but I would need to look up the references.

Q: Have you found any associations with Beta microglobulin with acute psychosis? I've reviewed some of the literature but not found it clinically.
A: Dr. Emily Severance: I have not looked at beta microglobulin, but really should. It used to be used as a housekeeping gene in RNA expression studies; then people found out that there were case-control differences in its expression.

Q: Is the NMDAR antibody tested specific for receptor subtypes? R1? R2?
A: Dr. Emily Severance: The NMDAR ELISA we use is supposed to be specific to NR2.

Q: Any research into potential treatments for T. Gondii infection in schizophrenia?
A: Dr. Emily Severance: It is an active research area. One problem is that many of the best treatments for T. gondii infection are also those that are used to treat malaria, and there is the fear that overuse of these treatments will lead to treatment resistance. One of my colleagues, Lori Brando, has shown that some of the different antipsychotics have anti-toxo activity.

Q: Although several presenters mentioned that C4a is not yet ready for routine use as a diagnostic marker for several reasons, are you able to clarify whether or not you would expect to see elevated levels in patients with neuropsychiatric symptoms secondary to neuroinflammation? In my patient base, I have been using this marker for several years and have noted definite correlation between patient symptoms and C4a levels. In my patients the C4a levels almost always track with Prostaglandin E2 level.
A: Dr. Emily Severance: Your observation is very interesting. My initial tests of peripheral C4 (not C41, and not the genotypes) did not show a correlation with symptoms. But yes, I would expect that some portion of C4a activation is the result of neuroinflammation regardless of the source.

Comment: I have had the same experience up in the SF Bay Area in my work with the Alameda County Social Services and local school districts. Symptomatology of PANS is there, but no real physical or financial access to diagnostic care or treatment. Language barriers (even amongst monolingual English speakers), along with cultural perceptions held by both providers and patient/parent also pose major obstacles to obtaining appropriate diagnosis/treatment.

Comment: Dr. Standing, your experience working on your own PANS patients, and your mention of the courage and difficulty it takes to approach this problem, mirrors my own experience.

Q: Are there any dosing guidelines for using Rifampin for strep? I am familiar with using 4 days with PCN for carrier state but have not used it by itself as monotherapy.
A: Neuroimmune Foundation: I believe it may be in the appendix of the JCAP treatment guidelines. Otherwise, please join us for Dr. Pasternack's CME even this summer.

Comment: I have found using Ketotifen compounded beginning at 0.5mg and going up helps with mast cell stabilization and anti-histamine component.

Comment: It is being posited that gluten ingestion may be implicated in clinical changes not just because of the immune ramifications of gluten itself but possibly the "spectrum" of increased permeability which is now observed in "asymptomatic" individuals.

Q: Dr. Standing - how long are you keeping patients on the antibiotics?

A: Neuroimmune Foundation: Thank you so much for your question. We are sorry we could not get to your question, but Dr. Standing co-moderates our physician community meetings that meet one Monday per month. The details are on the website under the clinicians/providers tab.

Q: I have heard several presenters who mention both antibiotic choice and use of NSAIDS for their anti-inflammatory effects. Is anyone using or studying other, more natural, choices that are not known to cause intestinal dysbiosis and impairment of the gut and brain? Like Curcumin, for example. Clinically, much better in other conditions.
A: Neuroimmune Foundation: I'm not aware of any research in this area.

Q: Dr. Thienemann - how could I get a copy of this manualized intervention for parents, please?
A: Dr. Margo Thienemann: I will have to find out! It is not published yet and we continue to adjust hoping to improve it

Q: Are there resources for those of us who have young adults who are still battling with flares?
A: Dr. Margo Thienemann: This is a very difficult problem. When patients/families approach adult providers saying PANS, etc, usually they say I don't know about that, I don't do that. What we are trying is to have them to go to particular specialists for particular symptoms: rheum for joint issues, psych for OCD, depression, etc, endocrinology for thyroid, etc.

Q: Other sources of trauma in families and children with PANS: Lack of access to appropriate care and support for PANS patients and families, inappropriately psychologizing PANS or incorrectly misattributing the etiology to the parents (e.g. "mother's anxiety is transferred to child" as the cause of motor tics and/or OCD, "poor parenting" or nonexistent "abuse" and more), misunderstandings which can follow families within a health care system and community, causes trauma and is a barrier to care.
A: Dr. Margo Thienemann: You are right. It is terribly hard to be blamed, turned away, labeled, etc. And the resources are too scarce.

Q: We have found that those adult specialists won't take on the responsibility of these issues that have been going on for years. We have run out of professionals who will do continued testing to figure out more information. Is there anything different out there now, in terms of testing within PANS, that may have evolved, that we are missing?
A: Dr. Margo Thienemann: My best answer is: if they had some sort of inflammatory indicator (e.g. complement abnormalities, etc) in the past, that might be an indicator of ongoing inflammation. Careful physical exam for occult infection, allergy. I think that depression and OCD are recurrent issues; adult psychiatrists should be used to long-standing issues.

Q: Is the referenced book "PANDAS and PANS in School Settings" by Doran?
A: Dr. Margo Thienemann: I know that is a good one and there is more than one.

Q: What are parents to do when their child is almost age 18 and the parent is no longer in the driver's seat for their child's care and the child is not really capable of this responsibility?

A: Dr. Margo Thienemann: Parents Helping Parents is a good resource.
Guardianship/conservatorship is one option.