Logbook

Nov. 29

- Decided on what I would like to do
    - What medication for Myasthenia Gravis would work best for you and your dog?

Dec. 2

- Started doing basic research
    - What the neuromuscular junction is
        - How it is related to myasthenia gravis

- The research
    - In myasthenia gravis
        - antibodies (immune proteins made by the immune system):
            - Block
            - Alter
            - destroy receptors for acetylcholine
                - at neuromuscular junction
                    - Prevents muscle from contracting
    - Neuromuscular Junction
        - Site of chemical communication between nerve fibre and muscle cell
            - Nerve fibre divides into lots of terminal branches
                - Each terminal branch ends on the end plate (region of muscle fibre)
                    - End plate has thousands of receptors (long protein molecule that forms channels through the membrane)
            - When the nerve impulse stimulates the terminal
                - Releases acetylcholine from synaptic vesicles
                    - Acetylcholine binds receptors
                        - Channels open
                            - Sodium ions go into the end plate
                                - Initiates end plate potential
                                - Leads to contraction of the muscle

Dec. 5

- Modified testable question:
  - What is the single best possible medication for all major forms of Myasthenia Gravis in humans?

- Researching forms of myasthenia gravis + grades of severity
  - Ocular MG
    - Muscles of the eye are affected, if only ocular muscles are affected it is called ocular MG (OMG)
    - OMG patients can have ptosis, strabismus or diplopia
      - Ptosis
        - Drooping of the upper eyelid
      - Strabismus
        - Eyes don't line up
      - Diplopia
        - Double vision
      - Weakness improves when rested (later in day, weakness is worse)
        - Patients may complain of
          - difficulty walking (not because of extreme muscle weakness but because of trouble seeing where they are walking)
    - OMG can affect 1 eye or both eyes
      - Rates of moving to generalized MG are 50-80%
        - Preadolescents(under age of 13) are less likely to shift than adolescents(over age of 13)
        - Sudden remission (getting better all of a sudden) with OMG is common
  - Generalized MG
    - Creates weakness in muscles in the body
      - More severe than ocular
        - Because it may cause respiratory distress
      - Weakness improves when rested
        - Develops in 50-80% of people with ocular MG
      - Patients might complain of
        - Difficulty speaking
        - Difficulty eating
        - Difficulty doing everyday things
          - Combing hair
          - Climbing stairs
    - Affects limbs, legs, facial expression, etc.
  - Transient neonatal MG

        - Cause: Maternal antibodies are passed to the newborn through the placenta
            - happens in 5-30% of infants of mothers with MG
        - Shows at/shortly after birth
            - Ocular MG or more generalized weakness may happen – weak cry, poor suck, generalized weakness, respiratory distress, etc
        - Diagnosis by detecting antibodies
            - Resolves when antibodies are gone
                - Because only the antibodies are transferred, not the cause of the antibodies
    - Unclear why this happens
        - Scientists believe this is because specific autoantibody characteristics that are different from person to person
- Congenital MG
    - Also called Congenital Myasthenic Syndrome (CMS)
        - Different from other forms of MG
            - Caused by genetic defect rather than abnormal immune system response
                - Results from changes in genes involving neuromuscular communication
                    - Usually inherited
                        - By an autosomal recessive pattern
                            - If a person only gets one copy they can be a carrier but not have the disease
                        - A specific form is slow-channel CMS
                            - Is an autosomal dominant pattern
                                - Means you only need one copy of the gene to get the disease
        - Types
            - Presynaptic CMS
                - Caused by a mutation that results in the nerve cells not releasing enough acetylcholine into the neuromuscular junction
                    - Makes bad signal strength
            - Post synaptic CMS
                - Caused by wide variety of genetic mutations
                    - Result in the muscle having not enough acetylcholine receptors/having defective receptors

                - Sometimes mutations result in defective acetylcholine receptors
                    - Don't stay open long enough
                        - Called fast-channel receptors
                - Different form
                    - Slow-channel CMS
                        - Receptors stay open for too long
        - Synaptic CMS
            - Lack of acetylcholinesterase
                - Too much acetylcholine
                    - Too much lingering in neuromuscular junction disrupts the signal
- Juvenile MG
    - Same cause as adult MG
        - Juvenile MG is when MG develops in someone under age of 18
            - Can have ocular or generalized weakness
                - Share symptoms with adult MG
            - When it occurs in a child that has reached puberty, weakness is more generalized
        - Symptoms get worse throughout the day
            - With more fatigue, more weakness
- Myasthenic crisis
    - 20% of people with Myasthenia Gravis will have at least 1 myasthenic crisis at some point
        - Women with myasthenia gravis are more likely than men to have a myasthenic crisis
            - Respiratory infections are a common cause
    - You will need to be intubated
        - Inserting a tube into your airways to assist breathing
            - Most people require intubation for about 2 weeks
                - If breathing and muscle strength improve, the doctor may slowly remove you from the ventilator until you can breathe on your own

The 5 grades of severity as defined by the task force of the medical advisory board of the Myasthenia gravis foundation of america:

- Grade 1

        - Ocular weakness only
            - All other muscle strength is normal
- Grade 2
    - Mild generalized weakness
        - May still have ocular symptoms
            - Grade 2a
                - Affecting limb, axial muscle, or both
            - Grade 2b
                - Affecting respiratory, oropharyngeal muscles, or both
- Grade 3
    - Moderate generalized weakness
        - May still have ocular symptoms
            - Grade 3a
                - Affecting limb, axial muscle, or both
            - Grade 3b
                - Affecting respiratory, oropharyngeal muscles, or both
- Grade 4
    - Severe generalized weakness
        - May still have ocular symptoms
            - Grade 4a
                - Affecting limb, axial muscle, or both
            - Grade 4b
                - Affecting respiratory, oropharyngeal muscles, or both
                    - Use of feeding tube may be needed
- Grade 5
    - Intubation required
        - With or without mechanical ventilator
            - If the patient uses feeding tube without ventilation
                - Places them in 4b

Dec. 6

- Researched medications + made a hypothesis
    - **acetylcholinesterase inhibitors**
        - Medications such as pyridostigmine enhance communication between nerves and muscles
            - These medications aren't a cure
                - can improve muscle contraction and muscle strength

        - Possible side effects:
            - gastrointestinal upset, diarrhea, nausea, and excessive salivation and sweating.
    - Price: 16-80$
- **Corticosteroids**
    - such as prednisone inhibits the immune system
        - limiting antibody production
            - Possible side effects:
                - bone thinning, weight gain, diabetes and increased risk of some infections
- Price: 10-30$
- **3,4 diaminopyridine**
    - Blocks potassium channels in nerve terminals
        - Increases the amount of acetylcholine released from synaptic vesicles
            - By making the duration of release longer
                - Creates more acetylcholine to enter the neuromuscular junction
                    - Possible side effects:
                        - Tingling in fingers + toes
                            - Only lasts for an hour
                        - blurred vision
                        - Diarrhea
                        - Excess saliva
- Price: 32-435$
- **Fluoxetine**
    - Used for certain forms of CMS
        - Blocks the acetylcholine receptors
            - Reduces the time they are open
                - Especially useful in slow-channel CMS
                    - Where the channels are open for too long
                - Possible side effects:
                    - Dry mouth

- Diarrhea
- Nausea
- Heartburn

    - Price: 8-27$

- Hypothesis: If the patient has any form of Myasthenia Gravis, then the medication pyridostigmine should be able to treat most of them because all those cases could benefit from more acetylcholine in the neuromuscular junction, as juvenile, ocular, and generalized MG has attacking antibodies (with more acetylcholine, more would make it to the receptors), congenital MG has a form where it produces too little acetylcholine, and Transient neonatal MG would be the same as Juvenile MG, but it goes away on its own.

Jan. 14

- Emailed 3 experts
    - Used email template
        - Ms/Mr. (Surname)

          My name is Julia Kang, and I am a grade 7 student at Louis Riel School in Calgary, Canada. I am in the process of conducting a science fair research project looking into what the 'best' treatment option would be for a patient with Myasthenia Gravis. I noticed that one of your clinical interests is Myasthenia gravis and I was wondering if you could assist me, or advise me towards a researcher that could help.
          Based on your research, what treatment option would you recommend to a patient with Ocular/Generalized, Transient Neonatal, Congenital, or Juvenile Myasthenia Gravis? What treatments or medications would you strongly advise not to take?

          Thank you for taking the time to read this email. I recognize that you may be very busy and I really appreciate any help you can give me in pursuing this research.

          - Julia Kang

Jan. 15

- One expert got back to me
    - Dr. Michael W Nicolle
        - The reply:

Julia

Neonatal MG occurs when the fetus receives antibodies, usually against the acetylcholine receptor, made in the mother. The antibodies, but not the cells that produce the antibodies, cross the placenta and produce temporary weakness in the baby. Once the antibodies wear off (usually several weeks) the baby improves and will not have problems later in life. The treatment is usually supportive (helping them feed and breath) although sometimes acetylcholinesterase inhibitors (like pyridostigmine for instance) are used until the baby improves.

Congenital myasthenia syndrome (CMS) is a very rare hereditary non-immune form of MG. It's caused by a genetic mutation in one of the proteins involved in 'neuromuscular transmission'. There are many different subtypes, depending on where the mutation is. The treatment of CMS is highly variable but medications used include pyridostigmine, ephedrine, 3,4-diaminopyridine, fluoxetine, salbutamol etc. Because it's not caused by an autoimmune response, there is no role for immunosuppression.

Juvenile MG is when immune-mediated MG develops in someone less than 18 years old. Most cases are due to antibodies against the acetylcholine receptor on the muscle surface. Treatment can be symptomatic (i.e. only treats symptoms and not the underlying immune problem) with pyridostigmine or immunosuppression (prednisone, azathioprine, mycophenolate etc). Thymectomy (the surgical removal of the thymus gland) may also be suggested in some patients with juvenile MG.

There are a bunch of medications that might worsen neuromuscular transmission and therefore worsen the weakness in MG. These can cause problems because of effects on the nerve ("pre-synaptic"), junction between the nerve and muscle (the neuromuscular junction) or effects on the muscle (post-synaptic). When combined with the impaired neuromuscular transmission in MG, they can result in worsening weakness in a patient with MG. The

medications that most commonly cause problems are some antibiotics, including those in the aminoglycoside (e.g. gentamycin) family, fluroquinolones (e.g. ciprofloxacin) and macrolides (e.g zithromycin). There are many drugs on various lists of medications 'to avoid' in MG but most don't cause significant problems.

I've attached a medical article that I wrote on MG that covers some of these issues. It's in medical language – sorry!

This is a very brief response. If you have further questions, email me.

Good luck with your project.

Mike

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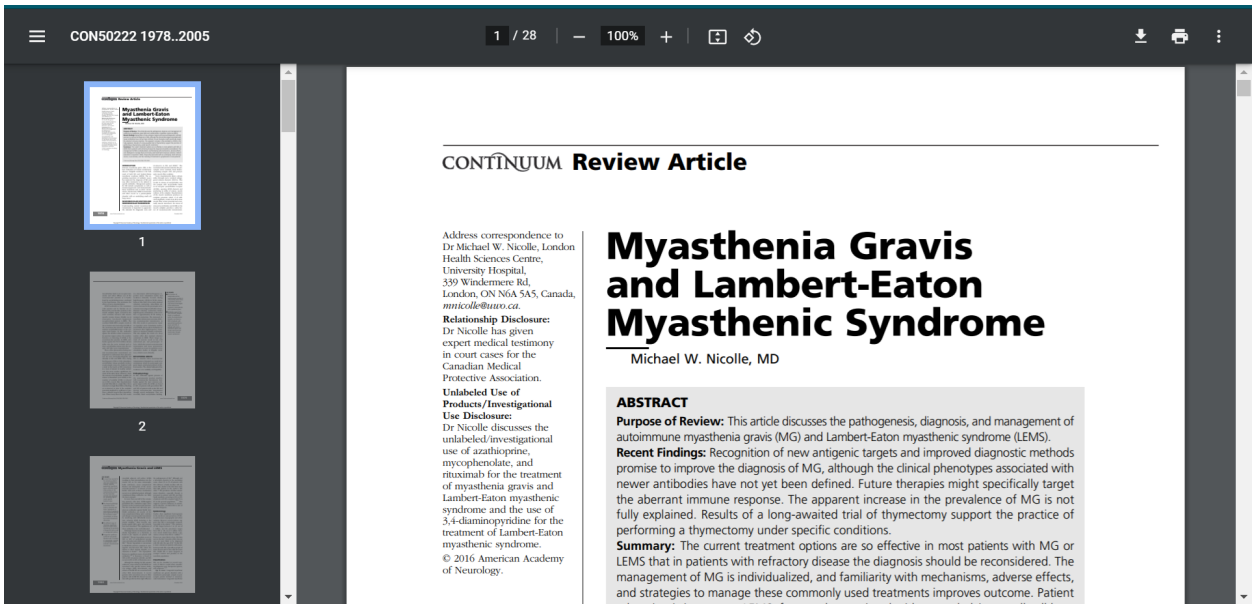
- Attached a pdf:



- Emailed 3 more experts

- Came to a conclusion:
    - My hypothesis was correct because when comparing the medications and their prices, the results I found showed that the medication Pyridostigmine, which is an acetylcholinesterase inhibitor, was the best option for Myasthenia Gravis as a whole. Even though it may make some forms of Myasthenia Gravis worse, it is usually the first medication the doctor will prescribe if you have any other form. The price was also not as expensive as some, and generally affordable. The side effects caused by Pyridostigmine are not as severe as others, for example, instead of having long-lasting side effects such as diabetes, it causes some diarrhea, sweating, etc. Although this is not completely ideal, it is much better than the alternatives.

Jan. 24

- Worked on the powerpoint

Jan. 25

- Still working on the powerpoint

Jan. 27

- Finishing up PowerPoint and starting script

Jan. 28

- Finished powerpoint and finished script

Feb. 5

- Found out that I got into CYSF

Feb. 6

- Another expert got back to me
    - James F Howard Jr

Dear Julia,

Thank you for you email and more importantly thank you for you interest in science. This is great.

Attached are some articles that you may find helpful. Should you have questions do not hesitate to reach out to me.

Myasthenia gravis is not a single disease but rather, I believe, a syndrome of multiple diseases. While they "look" they look the same, there are differences in their cause, pattern of weakness and treatment.

Let me try and answer you question at the 100,000 foot view as we say – it will be a starting point for you.

1. Transient Neonatal MG – this results from a mom who has MG and her antibody crosses the placental barrier (as do all mom antibodies; this is how the newborn is protected from some infections until is can get its immune system working vigorously. There is no specific treatment for TNMG; Often, the cases are mild and we simply let the transferred maternal antibody self clear from the infant and they get better. In some cases, if the weakness is severe, we will use a class of drugs called cholinesterase inhibitors (example is Mestinon/pyridostigmine). This class of medication slows the breakdown of the chemical transmitter that is necessary for nerve-muscle communication and allow it to work longer. This would be similar to knocking on the front door of your friend's house and if no answer, you have time to go around to the side or back door. Very rarely, we will use a procedure called plasma exchange or apheresis to "wash" the infants blood and remove the offending antibodies.

2. Juvenile MG: is treated much like we do with adult autoimmune MG using the same immune suppressing drugs and surgery (thymectomy). Which drugs we use and whether they get surgery depends upon which antibody they have. For instance, we know that patients who have the MuSK antibody often do not respond to cholinesterase inhibitors or surgical thymectomy but do respond to our other medications
3. Congenital MG is a different issue. This is not an immune disorder but rather think of it as an architectural problem – the nerve-muscle junction was not built correctly. There are multiple forms depending upon which gene messed up. There are no antibodies like the autoimmune form of the disease. Many do respond to cholinesterase inhibitors (example is Mestinon/pyridostigmine) but do not respond to immune suppression medications or surgical thymectomy. Depending upon the gene abnormality we may consider other drugs that were actually developed for asthma; albuterol, salmeterol and an interesting drug called 3,4-diaminopyridine

As you can see it is a very complex group of disorders and that is what makes it a fascinating area to spend a career in. We have been vigorously developing new classes of treatment for the autoimmune form of the disease over the last several years. They are proving to have tremendous benefit as they work more quickly than our current treatments and have much less side effects.

Another resource is the national foundation, Myasthenia Gravis Foundation of America - https://myasthenia.org/
They have many educational pamphlets that might be of interest

I hope this is of help to you and should you have questions do not hesitate to reach out.
Best of luck on your project

Regards,

jfh

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- Attached 3 files

Feb. 7

- Asked a few more questions to Mr. Howard
    - Mr. Howard,

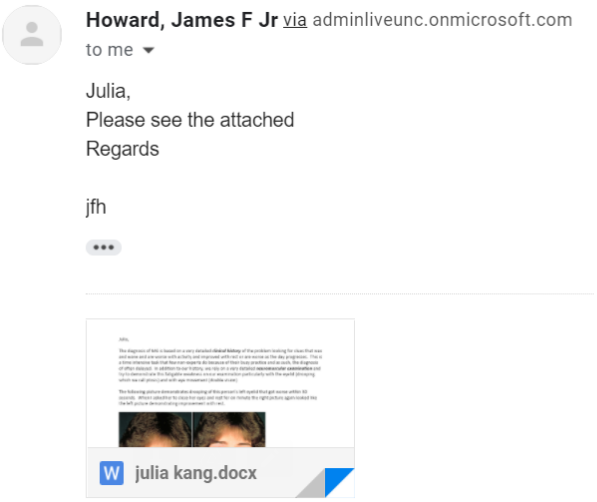
      Thank you so much for your information, it has helped a lot. I have a few other questions if you want to help me with them. If not, that's fine, but if you could, it would really benefit my project.

What would be the steps you would take to diagnose and prescribe medication for a patient? What is the process you use to figure out what dosage to prescribe? If a patient had any of these forms, what would be the first medication you suggest for each?

Again, if you don't want to help me, that's ok, as I recognize that you may be very busy, and if you do not respond, that would also be fine. But if you can answer, I feel that it would really push my project forward.

- Julia Kang

- The reply:



Feb. 9

- Research on main autoantibodies in MG
    - Anti-AChR
        - Antibodies that block the acetylcholine receptors from receiving acetylcholine
            - Can be tested through a blood test
                - Most common autoantibodies in MG
                    - Binds onto receptors
                        - Making acetylcholine unable to bind
                            - Creates weaker muscle signal
    - Anti-MuSK
        - Antibodies that target the Muscle specific kinase protein
            - MuSK protein is essential to the binding of acetylcholine to receptors
                - When anti-MuSK binds onto MuSK
                    - Agrin(another protein) cannot signal to allow acetylcholine to bind