Pompe Disease

CME Course 2023 -2024

Topic and Faculty

This CME course will discuss when to test for and how to diagnose Pompe disease in those with muscle weakness. The faculty members of the course are

- Tahseen Mozaffar, MD: neurologist and professor at the University of California, Irvine.
- Jordi Diaz Manera, MD PhD: neurologist and professor at Newcastle University, UK.

Discussion Question 1

What Are the Clues for Pompe Disease in Those with Limb-Girdle Muscle Weakness

Dr. Mozaffar: Now I am going to serve as the moderator and ask Dr. Diaz Manera to help out with three questions that I had thought of. One of them was when you see a patient with limb girdle pattern of muscle weakness, what are the diagnostic clues that will make you lean towards or direct the workup towards Pompe disease?

Dr. Diaz Manera: Gluteal muscle is always affected in Pompe, along with psoas muscle. Another important clue is the more severe involvement of the posterior muscles of the thighs than the quadriceps. Quadriceps tend to be fine until late in the disease course. Distal muscles in the lower limbs are spared in Pompe disease, in both early and late stage of the disease. So if we see, for example, an atrophy of the gastrocnemius of the calves, this is probably not Pompe disease. Axial involvement is very typical in Pompe disease. Patients can have difficulties to extend the trunk when lying flat in the bed. They also have respiratory involvement. So if we have a combination of respiratory insufficiency and gluteal muscle weakness, we always need to think Pompe disease.

I have mentioned the confirmatory tests and MRI findings. I would like to point out here that the EMG can also be helpful. If we have suspicion of Pompe disease and we do an EMG, especially when we explore the paraspinal muscle, and we see myotonic features, that is very suggestive of the disease. It's not a specific because it can also be seen in many other muscular diseases such as myotonic dystrophy. But I think it's something to add to the diagnosis of Pompe.

Dr. Mozaffar: I think there is another diagnostic clue that I have sometimes found useful. There is a 22% risk of developing cranial or other body vascular abnormalities in Pompe disease. So the presence of aneurysms or dilation of the aorta may be common in Pompe patients. If I have a patient that has a history of aneurysms or vascular dilatation and with all the typical features that Dr. Diaz Manera mentioned, I would think very highly of Pompe disease. So that's another clue there.

Discussion Question 2

What is the Best Way to Test for Pompe Disease (Dry Blood Spot or Genetic Sequencing)

Dr. Mozaffar: Dr. Diaz-Manera, I wanted to hear of your thoughts on the best way of testing for Pompe disease. At least as we talked about, the paradigm shifted in the US because of the availability of free genetic testing. Most of the cases of Pompe are being picked up on genetic testing. But how do you feel about the enzyme assay and is it still a valid way of testing versus whole genome sequencing? Nothing is perfect and let's say if you only find one mutation, what is your strategy to find the second mutation?

Dr. Diaz Manera: You're completely right. We need to decide if we go for a genetic test or for dried blood spot.

When I was in Spain, Dried Blood Spot test was the first choice. It was very useful because in most of the cases, not in all but in I would say more than 95% of the cases, you can detect the decrease in the activity. Sometimes it's borderline, it's not clearly pathogenic and it can happen in patients that are carrier who have just one mutation. This is when it becomes a bit tricky. But in many other occasions you can clearly see that the GAA enzyme activity is reduced. Then this leads to genetic testing that demonstrate the mutations, in our experience in around 90% of the cases. So this is the algorithm. I have a suspicion of Pompe and then this allowed me to diagnose the patient.

Here in UK, it is completely different because we do next generation sequencing (NGS) to all patients. So when a patient comes in and we suspect muscle dystrophy or a muscle disease, we do NGS. In most of the cases we can identify patients with Pompe disease. As you said, what can happen is that you have just one mutation.

If you have one mutation and you have not done the enzyme activity test, I would do it for sure., either this is the dry blood spot or analysis in lymphocytes. The guidelines recommend that the diagnosis can be made if you demonstrate the activity using two tissues. These two tissues mean blood, fibroblast, and/or muscle. I would advocate for muscle. So if you have doubts, do an MRI, for example, and identify a muscle that is not completely replaced by fat and take a muscle biopsy, because this will allow you to do the GAA enzyme activity test, to see if there is glycogen accumulation, and if are lysosomal vacuoles in the in the muscle fiber. So you will be able to find pathologic changes that are supportive of diagnosis.

Dr. Mozaffar: That's pretty much what we do as well. One point that I wanted to bring out, especially in the context of the enzymatic assay, is that in certain populations, especially the Japanese and the Southeast Asian population, there is a reasonably high incidence of what we call pseudo deficiency, where they have two genetic mutations in cis. They're not disease-causing mutation, but they interfere with the enzymatic assay and artificially lower the value. You just have to be mindful of that.

In our IPaNeMA study, 1% of the 900 patients had pseudo deficiency. The rate goes up when you're dealing with a population that has more Asian individuals. So just to be mindful that the diagnosis of Pompe disease should never be made on the basis of a low enzyme alone. It should always be confirmed with a second testing, be it muscle biopsy, be it mutation analysis, and that's going to be important.

Discussion Question 3

When to Initiate Enzyme Replacement Treatment in Pompe Disease

Dr. Mozaffar: Dr. Diaz Manera, I wanted to ask you the last question, which is somewhat controversial, especially now that in the US we are picking up cases at birth with most of these being late onset. What would be your threshold for starting enzyme replacement therapy in somebody who's pre-symptomatic or at risk genetically for Pompe disease? I have recognized that between Europe and the US there are already differences. I know, for instance, in France they would not start patients on enzyme replacement unless they have respiratory involvement. I wanted to hear your thoughts on what threshold would be for starting treatment.

Dr. Diaz Manera: In my opinion, when we think about this treatment, we sometimes are prompted to say that this is just an economic problem. I don't agree with that. I think that's of course one of the reasons why we discussed this is, the drug is expensive, but there are all the other things to take into account. When we are going to ask patients to start the treatment, that means that every two weeks they need to come to the hospital and spend almost half a day being infused with a treatment just because we think that they can develop symptoms. We think that this treatment can reduce the chances of the symptoms to present earlier. As of today, we don't really know if the treatment can delay the onset of symptoms. We think that's possible. But there is not any study that have demonstrated in late onset Pompe disease that starting the treatment in patients who are two years old can delay the onset of symptoms from 20 to 35.

Just to have an example, on the other hand, I think that what cannot happen (this is what is happening now) is that you have some patients that start very late. So for me, waiting until patients have respiratory involvement is not

correct. What I would do is that we need to follow the patient very carefully. This means that we need to see the patients at least twice a year in the clinics with muscle function test. I would include in the muscle function evaluation the time test, like for example, the 6-minute walking test, the time to walk 10 meters test, and functional analysis.

If we identify that there is a worsening of the muscle function or if we identify that there is fat replacement in, for example, the paraspinal muscle, gluteal adductor magnus, this is compatible with a disease that has started to destroy muscle. We are seeing that the muscle is suffering, the muscle is being replaced by fat. For me, that's the first moment when we should start treating patients. I don't think that we need to wait until patients come and say, I'm starting to have problems in my life. I think that we need to monitor these patients very closely. As soon as we see something either in muscle function test or MRI, we start the treatment.

Transcript edited for clarity.