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➔ The sheet was written according to the record of section 2.

So last lecture we started talking about some of the lysosomal storage diseases, now we'll finish the rest, and of course not all of them, just some examples.

1- Gaucher disease

One of the Sphingolipidosis, it means the accumulation of glucocerebrosides (which are made of ceramide + glucose). It's an AR disease, that results from a mutation in glucocerebrosidase, not necessarily one mutation, there are multiple types of mutations that result in this disease and all of them are AR. These mutations result in the accumulation of glucocerebrosides in the phagocytes, which are so called "Gaucher cells". If you look at these cells under the microscope, they will look like somebody has wrapped up a tissue paper and thrown them in the middle of a cell, this is pathognomonic for Gaucher disease.

This enzyme is a lysosomal enzyme, glucocerebrosides aren't being digested and they're accumulating inside the lysosome, so should you look at the lysosomes under the microscope (in the case of the picture in the slide it's an EM) you'll also find distended lysosomes. However, just accumulation of glucocerebrosides in the lysosomes doesn't seem to be the whole story. We're talking about accumulation of these glucocerebrosides in the phagocytes (macrophages), which produce all sorts of cytokines (IL1, IL6, TNF). When you inappropriately activate your immune system, it comes at a price. So the features of Gaucher disease don't just result from accumulation of glucocerebrosides, but also from inappropriate immuno-activation, production of these interleukins from macrophages, and macrophages will accumulate and become activated in the liver, spleen, lymph nodes and bone morrow, and you'll have multiple effects because macrophages aren't just there, they're found everywhere.

Where do these glucocerebrosides come from?

From senescent red blood cells, when they die, we recycle everything (the iron, the haemoglobin and the cell membranes). Those are the cells that will be dying most frequently, that means most of glucocerebrosides are coming from the senescent RBCs.

Originally Gaucher disease was divided into three types (1, 2, 3), the line between these 3 types isn't clear cut, the disease is a continuum (in the terms of symptoms). Anywhere from just asymptomatic, skeletal disease, some organ involvement, all the way to hydropsfetalis and neurologic manifestations.

Originally type 1 was termed the chronic non- neurological form,

Type 2 was the acute infantile neurological form and

Type 3 was the chronic neurological form. But these divisions don't exist anymore because the disease is a continuum (a combination of symptoms in all 3 types).

The clinical findings that apply to all types of Gaucher disease:

1- Bone involvement (Acro-osteolysis)

2- Reduction in blood elements, since you have accumulation of macrophages also in the bone morrow, pushing out the normal bone morrow cells.

3- Hepatosplenomegaly, because of the accumulation of these macrophages in the liver and spleen.

4- CNS involvement.

For most patients with Gaucher disease, the treatment is to replace the defective enzyme (glucocerebrosidase). In severe cases bone marrow transplantation (BMT) can also help, and you try to inhibit the synthesis of these particular subsets of cell membranes (glucocerebrosides) so you actually inhibit other enzymes not related to this disease to prevent synthesis of these sphingolipids.

2- Tay sachs disease

Another disease of Sphingolipidosis. It is the accumulation of gangliosides, present on the cell surface specially in the nervous system. They're important in cell-cell communication and in immunity, therefore you expect symptoms to result from problems in these areas (cell-cell interaction, immunity and the nervous system).

There are more than a hundred mutations that result in various problems, most importantly affecting the Beta subunit of hexosaminidase A, that result in its misfolding.

What happens when a protein is misfolded?

The cell tries to fix its misfolding by increasing the production of chaperons and reducing the production of the protein. This is called "**the misfolded protein response**" which tries to fix those misfolded proteins. We've seen this response in atrophy and we've said that if adaptation fails and atrophy goes on for too long, the cell ends up with apoptosis.

Atrophy in the nervous system isn't a good thing. Apoptosis in the nervous system is definitely not a good thing! So it's not just the accumulation of gangliosides, it's the misfolded protein response and the failure of adaptation that leads to atrophy and apoptosis of not just central, but peripheral nervous system cells and the ANS as well.

When you look at these cell under the microscope, you'll find a foamy appearance, like most lysosomal storage diseases. But when you look at them under the EM, you'll see the lysosomes having a very characteristic concentric ring appearance (looks like an onion), which is very characteristic for Tay sachs disease. Brain is mostly affected but you'll find pathological changes throughout the CNS, PNS and ANS.

The retina and ganglions in the retina are also involved, when the ganglions become "edematous" or "swollen" with the gangliosides they appear pale. Now the macula is where the nerve bundles enter the retina. The macula in contrast looks rather red. Actually the macula isn't involved, it's just the peripheral "paleness" that makes the macula looks that particularly red. So should you be looking at a young patient who has some neurological abnormalities, who's not developing as normally as they should, and you happen to look at their retina and you see that **cherry-red spot,** it raises the flag of Tay sachs disease.

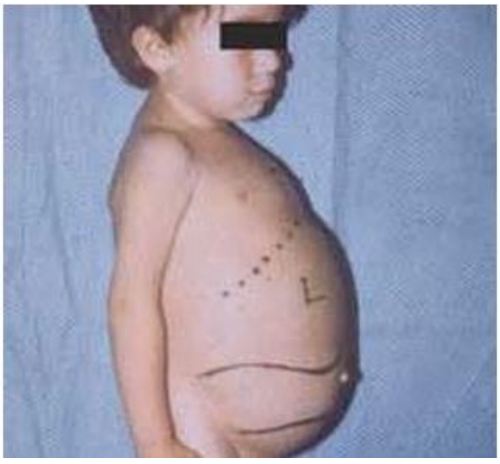
There are multiple variants or presentations of this disease, the most common presentation that the patients start being normal at birth, then they start having motor weakness in about 3-6 months, followed by blindness, and they usually die within 2-3 years, unless we treat them.

3- Niemann pick disease

3 types (A, B, C), although type C is no longer really considered one of the three types, because it has a very different mechanism.

For types A + B, the cause is a deficiency in acid sphingomyelinase and accumulation of sphingomyelin in phagocytes in spleen, liver, bone morrow, lymph nodes, lungs and neurons. So you're noticing that the mechanisms and the layers of accumulation are very similar and very difficult to distinguish, with the exception of certain signs and symptoms that are unique to each one. For Tay sachs it was that cherry-red spot.

For Niemann pick, types A+B are characterized by massive organomegally, less severe in type B than in type A. In the picture, the "L" and the lines represent the liver, all the way from their umbilicus to their rib cage.



Normally, you can barely feel the liver when you stick your hand under your rib cage and you take a deep breath, then you may feel the tip of your liver. If you can feel your liver without even making an effort then it's definitely enlarged, and this case (down to the umbilicus) it's definitely abnormally enlarged.

With type A, you do have severe neuro-manifestations and death can occur within 3 years. Type B has a milder course, less organomegally and no neurologic involvement.

Type C involves not just accumulation of gangliosides, but also cholesterol (remember: **Smith–Lemli–Opitz (SLO) syndrome** also involves accumulation of cholesterol). So type C shares some phenotypes with it.

This is not strictly a lysosomal enzyme disease it's actually a transport disease. NPC1 and NPC2 are responsible for transporting cholesterol and other things from the lysosome to the cytosol. So when they accumulate in lysosomes you start getting these manifestations.

The clinical presentation is heterogeneous, they present in childhood,

-They have ataxia (motor discoordination).

-They have gaze palsy (like SLO syndrome).

-Dystonia and dysarthria (dys- means abnormal, tonia refers to the muscle tone and arthria means speech), so they have an abnormal muscle tone and speech problems.

-Psychomotor regression (regression means backward), babies normally start their lives with being pretty helpless, then they start moving their heads, then they start sitting, then they start standing, then they take a step or two, then the say their first words, then they start putting sentences together, this happens as they grow. Also babies at first they don't smile, then they start smiling, then they start laughing, so there are the psychological and motor milestones as children grow. In case of psychomotor regression things go backwards and these milestones start getting worse! They used to be able to walk and now they can't, they used to be able to put a sentence together and now they only say a word or two, they used to be able to say word like "mama, baba" and now they only make sounds like " Ma, or A' ". That's psychomotor regression, which is very characteristic for this particular disease (Niemann pick type C).

Urea Cycle Disorders:

What does the urea cycle do? It gets rid of ammonia. So if you have a urea cycle disorder, accumulation of ammonia will happen, you'll have hyperammonemia, toxicity will happen and this leads to mental problems because ammonia has a toxic effect on the brain.

Which other symptoms are present with hyperammonemia?

Liver diseases like Reye's syndrome.

Whether you have a defect in any of these 5 enzymes (CPS, OTC, ASA, AS, Arginase) the end results and the symptoms are essentially the same and you're going to try to replace that enzyme or try to get rid of ammonia. If it's severe then you dialyze the patient in order to reduce the toxic effect on the brain.

All of the defects are AR, with the exception of OTC deficiency which is X-linked.

So all you need to know about urea cycle disorders is that hyperammonemia causes **mental disorders,** and the differential diagnosis is liver disease especially in children, just like the case in Reye's syndrome.

Energy Production Defects:

What do we use to get energy? Glucose, glycogen, electron transport chain, fatty acid oxidation, etc.

So basically any of the previously described problems is an energy production defect. So MCAD deficiency, LCHAD deficiency, etc..

So what are the ones that we didn't talk about? Oxidative phosphorylation defects. As we all know oxidative phosphorylation occurs in the mitochondria, and the genes responsible for it are present in the mitochondria and the nucleus. So this means that these diseases have two modes of inheritance: one related to nuclear chromosomes, and mitochondrial inheritance.

Now if it's severe, this means it's going to be amniotic lethal, you're not going to see it. There should be enough function left, that you're not really properly doing oxidative phosphorylation and you're shunting down some different pathways, losing a lot of ATP on the way and sometimes because you can't use pyruvate in oxidative phosphorylation, instead it will be converted to lactic acid, and there will be lactic academia (metabolic acidosis). The most common AR defect is in the pyruvate dehydrogenase complex, that's made up of 5 different enzymes. You're not required to know what they are, but do realize that lactic academia is a characteristic and the patient will be constantly tired because he can't have acetyl coA from pyruvate to enter the oxidative phosphorylation pathway (He can get Acetyl coA from lipids but it needs time, it's just like the patient is fasting).

Also you need to realize that this is not the only example, because as we said we've already talked about a lot of energy production defects.

Transport System Abnormalities:

The most common one is **cystinuria**, a transport problem in moving cystine (not the amino acid, but the dipeptide of the amino acid cysteine) between the cell and the ECM. Cystine is highly insoluble and causes renal stones and all their complications. So if you have a young person who's complaining of renal stones and their complications, the 1st thing you should think about is cystinuria; because renal stones don't typically occur in very young people, they occur in older people, where there has been enough time and enough damage for renal stones to occur.

What are the complications of renal stones?

1- Kidney failure (in extreme cases) which might also result in hypertension.

2- Pain on urination (if the stone has moved from the kidney into the ureter).

3- Infections (UTI) and this causes an increase in the frequency of urination (not the volume of urine).

A more rare disease but also related to system transport is **cystonosis,** a transport problem between the lysosome and the cytoplasm. In this case there will be accumulation of cystine crystals all over the body, in the cornea, the bone, kidneys, pancreas, gonads and muscles. This results in hypogonadism, renal failure, pancreatic insufficiency, **Rickets** and diabetes. Cystonosis is more severe and more rare than cystinuria.

The treatment for cystinuria is to flush it out. Lots of fluids intake (4-6L) per day. Also, alkalinizing the urine to make sure that the crystals have an unfavourable environment and they remain soluble rather than deposit.

For cystonosis, renal transplant is frequently required. Plus, cysteamine to make sure to prevent crystals formation all over the body.

Transport system abnormalities are also related to **heavy metals**.

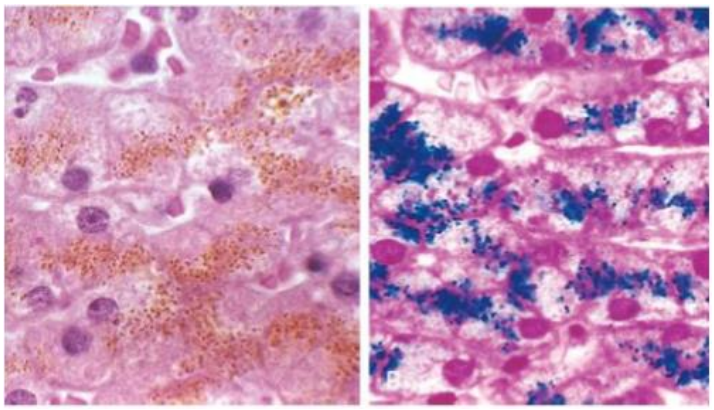
Do we use heavy metals in our bodies? Yes we do. We use Copper for cytochromes, Zinc for metalloproteases, Iron in haemoglobin, etc..

So we need heavy metals, but we frequently hear about heavy metal poisoning, that means we need to tightly regulate the amount of heavy metals in our bodies, and constantly get rid of any excess.

So should you have a transport problem, whether in absorbing or excreting heavy metals, that means you're going to be affected with a toxic accumulation of heavy metals.

1- Iron

We've already talked about the accumulated pigment which is called "hemosiderin", and its accumulation is hereditary it's called "**hereditary hemochromatosis**".



This is an AR disease, however despite of being AR it also has "incomplete penetrance" which is more common for AD diseases, so here's an exception to the rule.

Why does it have incomplete penetrance?

Males typically present having this disease during their 40's, while females present during their 60's, mainly due to menstruation, pregnancy, delivery and lactation, so that's a lot of iron leaving females' bodies. As for males, they don't menstruate, they don't lactate and they don't give birth so that's why they show up 20 years earlier. But still showing up in 40's is a long time, so what's happening is that since the liver is a massively regenerative organ, if you accumulate iron in your liver it's going to take a long time for the symptoms to show up. These symptoms include: fatigue, joint pain (because iron accumulates in joints), diminished libido, diabetes (because of the accumulation in the pancreas), darkened skin (because of the accumulation in the skin), cardiomyopathy, liver enlargement and cirrhosis.

They'll have abnormal serum iron. When you do a histochemical staining for hemosiderin you find a lot of iron in your tissues, and if you stain it will turn iron deposits blue.

Now what's the problem here? The common mutation is in a protein called HFE, it senses how much iron you have and it tells the intestines to stop absorbing iron by the induction of production of another signalling molecules that turn on or off the absorption of iron from the intestines. So when you have enough iron, rather than stopping its absorption and pulling in the transporter, the transporter remains in its place and you continue to absorb iron regardless of how much iron you have.

Treatment: serial phlebotomy (phlebotomy means to draw blood) so serial phlebotomy means to get these patients to keep donating blood. Don't mix this condition with "Polycythaemia" where the patient also has an increased chance of coagulation and excess RBC's, and may have more circulating iron than the general population, so you also get them to donate.

And you can also use iron chelating agents like deferoxamine.

2- Copper

A- **Menkes disease:**

Lack of copper, the protein involved is **ATP7A**, this protein has several transmembrane coils and it helps in the absorption of copper. It's found in the Golgi and cell membrane of **the intestines**. If you have enough copper it remains in Golgi. If we don't have enough copper, it goes to the cell membrane and increases the absorption of copper. So if you have an abnormality in it you develop Menkes disease.

It's characterized by:

- Intellectual disabilities.

- Seizures.

-pilli torti, they will have pale curly hair, because copper is also important in melanin production, but they won't be as pale as PKU patients.

- Loose skin because lysyl oxidase is Cu dependent and it's responsible for the cross-linking of collagen to elastin. It's also a precursor for lysyl hydroxylase (Vitamin C dependent) which is responsible for collagen cross-linking.

Treatment: restore Cu level, give them Cu (you can't give them oral supplements because they can't absorb it, you have to give them subcutaneous injections).

B- **Wilson's disease**

Too much copper, AR, due to impaired excretion, the defective protein is called **ATP7B,** it has several transmembrane coils, and it goes between Golgi and the cell membrane in the **LIVER**. When we have too much copper, the protein goes to the membrane and it increases the excretion of copper into the bile. A defective protein → no excretion, and you end up accumulating copper.

How did they find ATP7 protein? Wilson's disease was known first but they didn't know it's molecular abnormality till they found out the abnormality for Menkes disease. (This part was written according to the record of section 3).The way that they figured out that the two proteins are homologous (similar), and the ATP7 which is responsible for Menkes disease is also responsible for Wilson's disease (ATP7B), and it's also present between Golgi and the cell membrane and on a different chromosome. They looked for the sequence of Menkes disease ATP7 mutation and started looking for a similar sequence throughout the rest of the genome, and that's a lot of nucleotides to look through! So the way they narrowed it down is by using "**The Linkage Analysis**" Remember when we talked about polymorphisms? Certain polymorphisms may be linked to a disease, i.e. they're so close to the gene that no homologous recombination can occur between them, so if a particular disease happens, that means certain polymorphisms are going to be always associated with that disease. They found out the certain polymorphisms are associated with Wilson's disease on chromosome 13, so instead of looking throughout the whole genome they only looked specifically at that chromosome and they found a gene that's VERY similar to the gene of Menkes disease. Also, we don't only

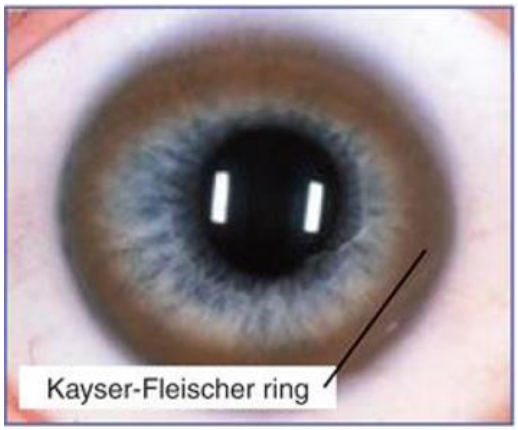
use genes from inside the human genome, we use genes from outside the human genome. You may be disgusted to find out that the cilia in your trachea are essentially the same as the hairs on a fly, so the proteins that make up the cilia are incredibly similar to the ones in the fly. There are some parts of your enzymatic pathways that are so conserve that they go all the way back to yeast.

Signs and symptoms for Wilson's disease:

Progressive liver disease, dysarthria and diminished coordination, arthropathy, cardiomyopathy, kidney damage, and hypoparathyroidism.

Treatment: reduce copper levels, using chelating agents like **penicillamine and trientin,** and once reduced you maintain these patients using zinc salts.

Also Kayser Fleischer ring, which means accumulation of Copper in the cornea, is very characteristic for this disease, but might not be easily observed in brown eyes, more easier to see in people with pale-colored eyes.



3- Zinc

Zinc is important in immunity.

If you don't have enough zinc, you end up with Acrodermatitis. Abnormality in its absorption is AR and is called **Acrodermatitis enteropathica.**

Signs and symptoms: growth retardation, diarrhea, immune dysfunction, and severe dermatitis.

Treatment: stuff them with zinc, here we have two sets, either the mutation leaves some residual activity to the absorbing protein so they can take oral supplementation of zinc. Or there's another protein that they haven't identified yet that also absorbs Zn.

"Chance favors the prepared mind"

Shout out to Dana Rida :D