

RUBELLA and PARVOVIRUS B19

RUBELLA and PARVOVIRUS B19 are world-wide childhood illnesses caused by unrelated viruses:

Rubella virus and **parvovirus B19** cause similar, mild rash diseases, and arthritis is a common complication of both. Both may endanger the fetus if the mother is infected in pregnancy, but in very different ways.

Parvovirus B19 has other unique complications in children and adults because of its tropism (predilection or affinity) for immature red cells.

For both of these viral infections, man is the only natural host and reservoir, so that the viruses must keep circulating in human populations, and tend to occur in small epidemics. However, because of long-lasting immunity, these infections usually occur only once in one person's lifetime.

Note that the person is infectious for about a week before the onset of symptoms, and then for a few days from the onset of symptoms.

RUBELLA

Rubella virus is shed in oropharyngeal secretions and is spread by the respiratory route. After a 2 - 3 week incubation, a rash of pink macules appears on the face and behind the ears, and spreads downwards to the trunk and limbs. There is associated *low-grade fever and lymphadenopathy*, specifically of the posterior cervical and occipital nodes. These signs resolve in a few days. *Arthralgia / arthritis*, usually of the fingers and knees, can occur, especially in adult women.

It is relatively common for rubella infection to occur without a rash, so called "*subclinical*" infection.

Post-infectious encephalitis or thrombocytopenia are very rare complications.

Congenital rubella syndrome

Primary rubella infection of the mother in the first 12 weeks of pregnancy is very likely to infect the fetus, with a high risk (80%) of **congenital abnormalities**. As in other congenital infections, the baby at birth may be of low weight, and have a thrombocytopenic rash and hepatomegaly with jaundice.

Specific features of **congenital rubella syndrome** are: cataracts, microphthalmia, heart defects, sensorineural deafness, and mental retardation. Infection between about the 13th and the 17th week of pregnancy may result in deafness alone, but infection beyond the 17th week is no longer a hazard.

A confirmed laboratory diagnosis of rubella in a pregnant woman is thus very important, as termination should be offered for 1st trimester infections.

Rubella IgM by ELISA becomes detectable a few days after the rash appears. The presence of IgM antibodies indicates an acute infection, and will be detectable for approximately 8 weeks. (Rubella IgG will appear almost as early as the IgM, but then persists for life).

Suspected congenital rubella in a neonate is also diagnosed by IgM in the baby's blood, or by culture of the virus from urine.

Note that maternal **IgG class antibodies** can cross the placenta, but not **IgM**, and so the presence of IgM in the baby indicates production of its own antibodies in response to its own infection. Congenitally infected babies may shed virus for many months, and staff and family contacts should be aware that the baby is infectious for this time.

PREVENTION:

Rubella vaccine is a live attenuated strain called RA27/3. In some countries it is given as the combined **MMR** (measles, mumps, rubella - all live, attenuated) vaccine to all children at 15 months of age, with a second dose at school entry. Some countries have tried a policy of rubella vaccine alone given to girls at high school entry age (+/-13 years) specifically to try to prevent congenital rubella. In practice, good herd immunity of both boys and girls is necessary to prevent circulation of the virus and protect vulnerable pregnant women.

Women should be screened for immunity to rubella (indicated by IgG antibodies) prior to pregnancy so that they can be vaccinated if necessary.

*(Note that **live virus vaccines should not be given during pregnancy, but inadvertent rubella vaccination during pregnancy is not grounds for termination as there have been no cases of congenital abnormalities associated with the vaccine.**)*

Often women are only screened during their first pregnancy, but they can at least be vaccinated prior to the next pregnancy if they are non-immune.

PARVOVIRUS B19

This virus was only discovered in the 1970's, although the disease it causes, *erythema infectiosum*, has long been described. It is also sometimes called "**fifth disease**" from an historical enumeration of the rash diseases of childhood, or "slapped cheek disease" because of the facial rash. Its name "B19" refers to the batch number of a serum in the bloodbank in which the virus was discovered.

The respiratory route also spreads parvo B19, and the rash appears after about 17 days. It's distinctive feature is the red cheeks, with circumoral pallor. On the rest of the body it is a lacy, pink macular rash that fades quickly, but may reappear after a warm bath. Arthralgia or frank arthritis, in fingers and knees most commonly, is more frequent and troublesome than in rubella. The arthritis can in some cases persist for months, and can even imitate juvenile rheumatoid arthritis.

Parvo B19's site of replication is red cell precursors in the bone marrow. It utilises as its receptor the P antigen (a red cell surface glycoprotein) which determines the P blood

group phenotype.

The infection will cause a temporary shut-down in red cell production until the virus is eliminated by the immune system, usually within 10 days. In a normal child this causes an insignificant drop in haemoglobin of around 1g/dl. However, people with hereditary red cell disorders (eg sickle cell anaemia, hereditary spherocytosis, thalassaemia) have either red cell under-production or rapid red cell destruction by haemolysis. In this context, the brief cessation of red cell supply caused by parvo B19 infection will precipitate an "**aplastic crisis**" ie. severe anaemia. These patients present with extreme pallor, lethargy and sometimes in cardiac failure, and require blood transfusion. A parvo B19 vaccine will soon be available and will benefit this vulnerable group.

In persons with AIDS, or other immunodeficiency states eg. children with leukaemia on chemotherapy, inability to clear the virus can cause chronic anaemia.

Normal immunoglobulin preparations for intra-muscular injection contain parvo B19 antibodies and will usually successfully eliminate the infection in immuno-compromised patients.

Maternal infection with parvo B19 in pregnancy can cause foetal infection, and foetal anaemia. In the worst cases (rare, usually second trimester infection) this may manifest as foetal hydrops. The mechanism here is severe foetal anaemia causing cardiac failure with oedema. This may end in intra-uterine death, but it has been possible to treat severely affected foetuses by intra-uterine transfusion, given the right technology. The milder cases tend to resolve spontaneously.

Note that parvovirus B19, unlike rubella, is not teratogenic, and outcome of infections in pregnancy is usually good.

Because the rash and mild illness cause by parvo B19 is very similar to rubella, it is essential in pregnant women to distinguish between the two virus infections by laboratory diagnosis.

Laboratory diagnosis of acute parvo B19 is also based on the presence of IgM antibodies. The virus cannot be cultivated in routine cell culture lines, but direct detection of the viral DNA may be achieved by PCR.

Some extra information which is just for interest

The 2 viruses described above are not related to one another.

Rubella is a togavirus. Toga means coat. All the other togaviruses that can affect humans are mosquito-borne viruses.

However, since rubella is a lone togavirus that does not have an insect vector, and spreads directly from person to person, it has been put in a genus on its own within the togavirus family.

Parvovirus B19 is a parvovirus - these are the smallest virus particles known.

Parvovirus B19 is the only parvovirus that causes disease in man. Its name doesn't mean

anything, the virus was found in unit of blood in a bloodbank, and B19 was just the batch no. for that blood.

There are important animal parvoviruses, eg. feline parvovirus and canine parvovirus. These cause leukopaenia (ie. depletion of white cells) and enteritis (ie. bowel inflammation with diarrhoea) in kittens and puppies. When your pets have their routine vaccinations, you should ask the vet what they are being vaccinated for. You'll find that the routine domestic animal vaccinations include these parvoviruses, because they are lethal for young animals.

Both viruses cause really trivial childhood infections, BUT they all have interesting complications.

We'll start with rubella, also called **German measles** because it was described by a German physician in the 18th Century. This virus causes a rash, some lymphadenopathy (all the lymph nodes at the back of the head and neck for some reason - post auricular, posterior cervical & occipital) and quite often arthritis in adults, especially women.

But generally it is a very mild illness, and seemingly of no consequence...

However back in 1940 there was an astute Australian ophthalmologist called Gregg. He saw 78 cases of cataracts in babies in one year, one after the other, and often these babies had other serious congenital abnormalities, especially cardiac. He linked these cases to a directly preceding epidemic of rubella in Australia, and suggested that the babies' defects were a consequence of rubella during pregnancy. He published his observations in the *Transactions of the Ophthalmological Society of Australia*, and there was huge scepticism - everyone said, rubella is a common and trivial disease, how could we have missed this consequence up till now? But because of the awareness he had raised, others started to confirm his observation in other populations. Gregg was the first to introduce the concept of viruses as **teratogens**. A teratogen is an agent that causes MALFORMATION in the developing fetus.

In 1964 there was a major epidemic of rubella in the USA. An estimated 20,000 babies suffered permanent damage from *in utero* rubella infection - CONGENITAL RUBELLA SYNDROME.

The risks of rubella in pregnancy have now been carefully studied and it's clear there is only a risk to the fetus in the early part of pregnancy.

So what are the defects that these babies get?

The virus specifically damages the HEART, commonly causing a patent ductus arteriosus, sometimes pulmonary artery stenosis, the EYES (typically causing cataracts, but also other abnormalities) and the NERVOUS SYSTEM causing mental retardation predominantly. Deafness is the commonest sequelae of congenital rubella and should actually be included here as it is a nerve type of deafness. What has also been observed is that the majority of major defects occur in the earliest weeks, up to week 12.

It is worth mentioning that an interesting late manifestation in children who survive congenital rubella, is DIABETES which becomes evident only in young adulthood.

After the epidemic in the USA, the general public became well aware of the risk of rubella in pregnancy, and apparently there was a phenomenon of "rubella parties" - if a child in the neighborhood got rubella, all the little girls would be invited round to try to get them infected with rubella so that they would be immune in adulthood before they ever fell pregnant.

However, in the late 60's a live attenuated vaccine became available commercially and was put into use for all children in the USA - today in the USA they use the combined measles-mumps-rubella vaccine, and children must have this vaccine before they start school. Rubella, and especially congenital rubella syndrome, is now extremely rare in the USA. For the last few years they have had about 4 cases of congenital rubella per year, and that is in a population of 260 million.

Those countries where they tried to vaccinate JUST HIGH-SCHOOL GIRLS have been less successful in controlling rubella and congenital rubella. This is because with this strategy you will still allow the virus to circulate in younger children and males, and at the same time it is impossible to achieve vaccine immunity in 100% of women - so these 2 factors together will allow cases of congenital rubella to occur.

Let's look at the sequence of events in rubella infection, and especially the immune response to rubella. In fact this is very similar to events in parvovirus B19 infection, and in principle this scheme applies to almost any type of viral infection.

If you take as the reference point the rash, the things to note are:

1. the virus has been incubating in the person for at least 2 weeks, and
2. they have been shedding virus from the throat (and therefore potentially infecting others) for a week already;
3. the lymph nodes swell up before the rash and stay swollen after the rash (the rash itself is quite brief).
4. the joint involvement starts at the end of the rash, towards the end of the illness;
5. the IgM becomes positive a day or 2 into the rash, and the IgG simultaneously or shortly afterwards;
6. the IgM only lasts for about 8 weeks, but the IgG persists for life.

Now we'll move on to parvovirus B19.

This virus also causes a rash disease with arthritis - the rash is rather typical. Arthritis, again especially in adults and especially in adult women, is common and can be quite severe. It usually affects the finger joints, and also some of the bigger joints such as the knees, wrists, ankles. The symptoms of arthritis are swelling and pain and sometimes redness.

But the key to understanding this virus's life-threatening complications is knowing that it is erythrotropic, in other words it really replicates best in red cells, specifically young red cells which haven't even left the bone marrow. It is directed into these red cells via the P antigen which is its cellular receptor- Like the ABO blood group, and the Rhesus blood group and the Kell and Duffy systems, there is a P blood group which is determined by whether you have a gene (big P) for the P antigen or not. In fact almost everyone in the world is P positive ie they have at least one big P gene (big P being a dominant gene).

The gene frequency of small p is very low. There are literally a handful of people who have two small p genes and are P blood group negative, and studies of these people have clearly shown that they are resistant to parvovirus B19 infection - they cannot get infected because the virus can't get access to their red cells where it replicates.

The consequence of parvovirus B19 replicating in your bone marrow is that you can't make any red cells until you get rid of the virus. Now for you and me this doesn't really matter - our red cells last for 120 days on average, and 10 days without new red cells is not a problem. But there are people who need to keep up red cell production all the time, and they are people with congenital red cell abnormalities - whether of the red cell membrane, red cell enzymes or haemoglobin - they either have poor production of red cells or the red cells are so abnormal that they are rapidly broken down. These people cannot afford to stop producing new red cells, and if parvovirus infects them they go into severe anaemia; or what is known as **aplastic crisis**. For years, no one knew what caused aplastic crisis in these patients, but when parvovirus was discovered in the 1970's it was soon recognized as a cause. Fortunately parvovirus infections are normally self-limiting, but these patients will need transfusions of red cells to tide them over.

Another type of person who cannot afford to stop producing red cells is the rapidly growing fetus, who needs a rapidly expanding blood volume. Maternal infection with parvovirus B19 can result in fetal infection which can, in turn, result in a varying degree of fetal anemia. Most fetuses seem to get through the anemic patch, but some don't and become very anemic. The consequence of a severe anemia is cardiac failure, and a major manifestation of cardiac failure is edema - these fetuses become extremely edematous, a condition which is called **fetal hydrops** (this translates as "water on the fetus") and is visible on ultrasound. Parvovirus is just one cause of foetal hydrops.

Now, parvovirus is NOT a teratogen. It doesn't cause irreversible malformations, so if the baby survives a parvo infection, and most of them do, it won't have congenital abnormalities, and its outlook is good.

We know therefore that the outlook for rubella infections *in utero* is very bad in the first trimester, but the outlook for parvovirus infections at any stage in pregnancy is quite good. With rubella there is a strong case for termination of pregnancy, NOT for parvovirus.

The infections in the mother look very similar, so lab test is used to distinguish the two.

DIAGNOSIS of these infections is quite simple today - an acute infection is diagnosed by an IgM assay. And you should all know know that this is because IgM is the first class of antibody that is made in response to an infection, and it is transient; so if it is detectable, it means that the infection is current or very recent.

Finding IgG alone means that the person has been infected or vaccinated sometime in the past.

Diagnosing infection in newborn BABIES - congenital rubella babies are usually IgM positive at birth, and IgM stays positive for quite a long time. You can also culture virus from them at birth and for a long time afterwards; their immune response is deranged and ineffectual because they were infected at such an early, immature stage.

In congenital parvovirus babies, IgM is not reliably positive at birth, but if you suspect this congenital infection it can be confirmed by PCR to detect the viral nucleic acid itself.

These babies also tend to be persistently infected for some time after birth because of an immature immune system.