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BABIES, PAROXETIN, COAGULATION AND BONE FORMATION

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Case report of two siblings born after Paroxetin use of the mother in her pregnancies.

The obstetric anamnesis of the mother mentioned one daughter born after amenorrhoe (Am.) of 41.3 wks birthweight: 3540 g. Second daughter born after an Am.42 wks and birthweight: 3600 gr. Both vaginal deliveries were in occiput presentation. The girls developed normal. After these two children she started to use Paroxetin because of a depression so severe that it was continued during her third pregnancy with 20 mg a day. Prenatal control at Am. 20 weeks a small head circumference was found by ECHOscopy.But later on in pregnancy the head circumference normalized and the brain structure was normal. At Am. 41.5 wks delivery started spontaneously with the child in face position. Because of this abnormal position the delivery was difficult, and the baby was slightly depressed and hypotonic and needed some hours of extra oxygen.The baby was hospitalized for a few days, but didn't developed severe signs of Pulmonary Hypertension and was given to the mother. The baby behaved not completely normal and the mother complained to the nurses about strange movements of the eyes. But no measures were taken, no control of blood sugar and the mother and baby were sent home. The first weeks after birth the baby looked fine, but had sometimes the abnormal eye movements. But at the age of 5 weeks he developed cerebral problems. Old and new subdural hemorrhages were detected and he was treated. His motoric and mental development was very retarded and he developed microcephaly and spastic tetraplegia and was at 7 years of age severely brain damaged. He had on both feet an indication of a club foot. A genetic reason was not found. And the cause of the subdural bleedings was not found, but could be related to the difficult delivery in face position.
Four years after this baby the mother became pregnant, her 4th pregnancy, again using Paroxetin 20 mg / day. In this pregnancy like in the third one at 20 weeks a small head circumference was found, but this became normal during pregnancy and also brain structure was normal. Because of the difficult delivery of the third baby and the face position of this baby it was decided to do a C-section at Am. 39.2 wks. Immediately after birth the baby did fine and went with the mother to the maternal department in the hospital for longer observation. During these days the mother realized that the baby had the same strange eye movements as her 3rd baby and she asked the nurses about it. But again the baby was considered to behave normal and no blood sugar was controlled. The mother was concerned about this 4th baby that he might develop the same symptoms like his brother. But at control by a pediatrician 3 weeks after birth he looks fine. However 4 weeks after birth the father fall down while holding the baby and he could protect the baby, but afterwards his left eye became swollen. The mother went to the hospital with the baby. He was alert and doesn't seem to have any problem, but he was hospitalized for observation. The next day he developed convulsions and also in this baby older subdural hematoma's were found. He was transported to a pediatric intensive care department. The ophthalmologist detected bleeding in the left eye, but not in the right eye. The neurosurgeon diagnosed chronic subdural hematoma's. And to lower the pressure of the subdural hematoma a punction was done and showed old blood with yellow color.The subdural hematoma's were responsible for a continuous mechanical trauma to the brain. After a difficult period the condition of the baby improved and was sent back to the regional hospital. There skeletal X-rays were done. Fractures were found, an older one in the right distal tibia (in his right heel the heelprick was done) and in the distal right humerus with subperiostal new bone formation and osteopenia of the left femur. This 4th baby like the 3rd one developed severe brain damage with a hydrocephaly and spastic tetraplegia. He too had indications of club feet and a sinus pilonidalis. Both children are mentally retarded. No genetic reason was found.

In summary: after two healthy daughters, two boys were born. Both with a problem of the head circumference at Am. 20 weeks, both in face position, both developing cerebral problems resp. at 5 and 4 weeks after birth, both several old and new subdural hemorrhages in both causing chronic severe mechanical brain damage. Both brothers developed mental retardation with a spastic tetraplegia and one with a microcephaly and the other with a hydrocephaly. Both had indications of club feet.

Explanation and discussion.

The interaction of the genetic profile of the fetus with Paroxetin medication used during pregnancy is analysed.

Serotonin.
Paroxetin belongs to the group of Selective Serotonin Reuptake Inhibitor's (SSRI's).Serotonin is an amino-acid that can function as a neurotransmitter. It is present in the gastro-intestinal tract, blood platelets and central nervous system. In the CNS it is present in presynaptic nerve termini and excreted in the synaps. There is a serotonin reuptake in the presynaptic cells. Serotonin is indispensable by the transport of the nervous stimulus in the synaps from one neuron to the other and in the connection with organs as muscles (hypotonia) etc. Serotonin is important to improve the mood and shortness of serotonin in the brain is thought to be the cause of depression. It is called the hormone of happiness. Serotonin is also very important in blood coagulation (since it results in aggregation and vasoconstriction upon its release from platelets) and in the bone formation (preosteoblast) 1.
The SERT protein is the transporter over the membrane and in the cell. It is generally accepted that the SERT protein expressed in platelets is identical to the one found in neurons displaying similar functional properties in these tissues.
SCL6A4 is the name of the gene encoding the SERT membrane transporter. Certain genotypes are related to the activity of this transporter. The SCL6A4-gene has two polymorphisms a long "L" and a Short "S" allel. And in the promotor area there is also a single nucleotide polymorfisme = SNP with G or A base, so for the SCL6A4 gene there are 4 combinations: La , Lg, Sa and Sg. Because these combinations are inherited from your father or mother every combination is possible. It is known that the La is associated with a more active transporter, more serotonin goes into the cell. Lg,Sg, Sa are less active. This means less transport into the cell, less re-uptake.Individuals using Paroxetin with these genetic combination a deficiency in the cells can be the result. Patients with the active transporter La/La are thought to develop depressions due to a low concentration in the synaps.
Hemorrhages
Before birth the foetus is more or less protected against external injuries by the mother and its own amniotic fluid. Bleeding perinatally can be associated with certain genetic profiles2.
During development in utero, the liver starts to produce the proteins necessary for a controlled coagulation in cooperation with blood platelets, endothelium, inhibiting factors and the fibrinolytic system. Blood platelets or thrombocytes are important for the first phase of coagulation. Platelets take up serotonin from the circulation. In the complicated process of coagulation serotonin is set free. It is important for aggregation and vasoconstriction and takes a part in other essential clotting processes. A deficiency of this serotonin in the thrombocyte is a risk for hemorrhage. Thrombocytes may develop a deficiency of serotonin if Paroxetin is used. Clinically a longer bleeding time is seen 3.
Bone formation
Since 200 million years animals with bone and blood make blood in their bones. Nature is using serotonin not only as a neurotransmitter involved in affective disorders but also in blood and bone formation. For that target circulating serotonin is produced in the enterochromaffin cells in the small intestine and serotonin works within a specialized neuro-endocrine network stimulating for instance the peristalsis in the gut. Serotonin is generated by an enzyme in the brain and in the small intestine. Yadav e.a. report that circulating serotonin can bind to a serotonin receptor (Htr1b) on the preosteoblast and suppress an intracellular transcription factor CREB thereby blocking osteoblast proliferation.This could provide a framework for understanding bone loss caused by SSRI's. Paroxetin can inhibit the proliferation and maturation of bone-forming osteoblasts 1,9.

Paroxetin

Paroxetin belongs to the group of SSRI's of which for instance Prozac is also a member. In the Netherlands with 17 million inhabitants 1.2 million people are using the drug and among them 5000 pregnant women. Paroxetin inhibits the re-uptake of serotonin in the cell. Paroxin crosses the placenta. Clinically the medication can be succesfull in severe depression, but there is a price:

As side-effects in pregnancy on the fetus and newborn are described:
(1) Congenital malformations like club feet, anus atresia, heart defects 4,5,6,
(2) Bleeding 7,8.
(3) Fractures and bone loss 9,1.
(4) Hypotonia 10.
(5) Hypoglycaemia in the neonate because of a hyperinsulinemic effect10.
(6) Persistent Pulmonary Hypertension in the Neonate 10.

The genetic mismatch between the mother using Paroxetin and the father results in transient hypotonia, coagulation problems and fractures in the offspring. It is known that the SERT membrane transporter has an important role when using Paroxetin and that certain combinations of the genetic make-up as described above might be disastrous. The platelets of individuals with a La/La genotype are the least sensitive to Paroxetin inhibition of serotonin uptake in contrary to the Sg genotype3.

All members of the family were analyzed for their genetic pattern of the genotype of the transporter. First of all , the 4 children had the same father and mother. The mother had a La pattern. The father has a Sg pattern. Therefore, one would expect that all children would be carrying a La and a Sg allele. However, this was not the case we found La/Sg and La genotypes. This can only be explained if the father would carry another allele which we do not detect with our test. This allele (X) could either be deletion, which would have even less activity than the Sg. In this case all 4 children are at risk, none of them has a La/La genotype.The eldest daughter has a La/Sg pattern, the second daughter a La/X pattern, the first boy has a pattern La/Sg and the second boy a La/X.

Conclusion: The genetic background of a baby can make him at risk for a severe effect of hypotonia, bleeding and fractures by the exposure to Paroxetin during pregnancy and in the first 6 weeks after birth.

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