Regional and Temporal Trends in the Prevalence of Cryptorchidism and Hypospadias

Jorma Toppari
University of Turku, Finland

Thank you for the possibility to show these data today. Since time is short, I will rush into the talk.

Cryptorchidism is the undescended testis, and here we see 2 cases, one unilateral and one bilateral, cryptorchid boys. Here it is easy to see that this boy is cryptorchid and also the scrotum is underdeveloped as it often is in bilateral cases.

But diagnosis is never based on visual diagnosis but on palpation, where the testis is pulled down through its route to the lowest position one can manipulate it without force, and then that is the position that is then used in the classification of the case.

Testis can also be outside the normal descent route. Then it is in an incorrect anatomical position, so it is ectopic. Testis saltans is a term that is used in some countries for freely moving testis, retractile testis, and that is considered normal, it is not cryptorchid. So when I am referring to cryptorchidism I am referring to these categories. The high scrotal testis cannot be pulled down to the bottom of the testis, but it only comes to the upper portion and it is considered abnormal.

There are very little data on incidence of cryptorchidism in the past and very little data where one could compare the temporal increases in the same place with the same diagnostic criteria. But we do have some from England where Scorer published in the 60s data from London from boys that were born in the late 50s, and then from the Oxford area from John Radcliffe Hospital.

This is not the name of the author of the paper but from the hospital. It was published anonymously from that hospital's study group. It examined the boys in the late 80s, and this shows an increase in the full term boys of the cryptorchidism rate in England.

We wanted to see whether there would be any trends in Nordic countries, in Denmark and Finland, and planned a study where we included a cohort of boys born between 1997 and the end of 1999.

The mothers filled in questionnaires during pregnancy. The boys were studied at birth and at 3 months, and cases and controls at 18 months. In Copenhagen all the boys were studied also at 18 months and at the age of 3 years.

We collected some biological samples for analysis of chemicals and hormones later on. We also performed a case control study where we included all those cases that were diagnosed in the hospital during the study period and beyond it, and selected controls for this to include all the boys in our hospital.

During the 3 year period we had a little less than 6,000 boys born in Turku University Central Hospital, and about 30% of them were included in this prenatally recruited cohort. During the later period we had about 4,000 additional boys, and this is the prevalence of cryptorchidism in these study groups.

In the cohort at birth, it is 2.5%. In the total cohort including all boys born in our hospital during that time the percentage is very close to the same, it is 2.3%, and at 3 months it is around 1.0%.

At the same time, in the Copenhagen cohort the incidence rate is much higher, it is more than 8%, so the difference is 4-fold here. At 3 months, very many of the Danish cases became normal so the testis spontaneously descended during the first 3 months and at 3 months the prevalence rate in Copenhagen is 2.1%, which is double the figure of those of Finland.

We do not have any historical data on prevalence of cryptorchidism in Finland but in Denmark there are comparable studies from the 60s, which are here in the pink columns. Here there are 2 groups, all boys including the prematures. The figure in Denmark in the 60s was 4% and is now close to 9%. If we take only those who were full term or most of these are full term, more than 2.5kg, we see an enormous increase in the

incidence, from 1.8% to 8.3%. So there seems to be an increased rate in Denmark.

What is the etiology of cryptorchidism? In most cases it is unknown, but we have learned during the last years a lot about the genes that influence and hormones that influence testicular descent. From gene knockout studies we know that, for example, these genes do influence testicular descent and the first phase, the transabdominal descent is inhibited if these genes are not functional.

Then, we know that inguino-scrotal descent is very dependent on androgen action. So in the androgen resistant mice or in hypogonadotropic mice that also then lack androgen action or those that are treated with anti-androgens, the testis will not come through the inguinal canal.

So, could these hormones or genes explain some of the cases of cryptorchidism that we are seeing? We know that this insulin-like hormone 3 or RLF, a relaxin-like factor is produced by Leydig cells, the same cells that produce testosterone, and the knockout mice are cryptorchid.

The hormone influences the structure of the gubernaculum that is the ligament that pulls down the testis to the inguinal position. Testosterone also supports insulin-like hormone 3 in the gubernacular development and growth, and testosterone also causes the regression of the cranial ligament, the mesentery ligament, that keeps the gonad here. So the testosterone makes sure that this disappears and together with insulin-like hormone 3 stimulates the gubernaculum to develop and that pulls the testis down.

According to its name, insulin-like hormone 3 is like insulin. It is composed of 3 chains, and the C-peptide is cleaved off from the functional peptide. Thus far, although there are hundreds, if not thousands, of patients that have been analyzed for mutations, in this gene, there have been only 2 mutations that are found in the connecting peptide that have been connected to cryptorchidism.

But these were heterozygous patients, so it is very uncertain still whether this really was the reason for the cryptorchidism in these patients. We, and others, have found a lot of polymorphism is this gene which has no connection to cryptorchidism.

We know something about the regulation of this hormone. It is strongly down-regulated by estrogens, and at least in the rodents it well explains why estrogens cause cryptorchidism in the animals. We do not know whether this would occur also in the humans. We do not have any insulin-like hormone assays yet, but I am sure that when they become available, we will have a lot of data on the hormone levels in boys and we may get an answer to this.

Also, the receptor for this hormone was characterized this year and it is the same type of receptor as that for relaxin, which is depicted here. It acts at least through cyclic AMP. Again, there is one patient where an inactivating heterozygous mutation was found, which might have contributed to cryptorchidism in this patient. But mutations in this hormone or in the receptor will not explain many of the cases of cryptorchidism.

What about androgens then? Here we measured in our material or a part of our material androgen bioactivity with the recombinant receptor assay. In cases of suprascrotal inguinal or nonpalpable cryptorchidism, none of the boys showed any androgen bioactivity at the age of 3 months, whereas the scrotal or the normal boys, the majority, do show clear androgen bioactivity at that age. Also those with high scrotal, many of them have good androgen bioactivity.

So there seems to be something wrong in those gonads and they produce less bioactive androgen than normal. It is reflected also in the pituitary gonadal axis, so that as a group the cryptorchid boys have higher LH levels than the control boys, suggesting that they have hypergonadotropic hypogonadism.

Androgens have a lot to do with hypospadias. In hypospadias the urethra does not open at the tip of the penis, but somewhere beneath the shaft of the penis. In the mild forms it is here in the glandular or coronal area and in the severe form it is more proximal.

Here are some of the real cases. This is how it should be then it may open at any position proximal from that. The Registry data suggests that there is an increasing trend, and this is the Paulozzi's data from

the USA, showing much higher numbers than any of these. I will come back to this, that these may be due to severe underreporting and are not very reliable data.

We also looked at hypospadias in the same analysis and found 19 cases and only one severe case, so the rate was very low. When it is given per 10,000 live births, it is 17. If we look at the Registry data from the 1970s to 80s, we see that it is between 3-7%. So what is wrong there?

It was known already in the early 90s that these data were not correct because there was severe underreporting. If one actively looks in the hospital registers, and that is what the Finnish Malformation Registry started to do and now from 1993-98, the rate is 15.

This is a study by Finnish urologists who found the rate 14.3, based on those cases that required surgical correction. These are well in line with what we found in our study.

Again in Denmark, the figure is much higher: it is 32. And in a recent study from the Netherlands in the Rotterdam area, the rate was even higher than in Denmark.

We know that androgens regulate the development of the urethra, and if there is anti-androgenic effect or if there is a lack of androgens, that causes hypospadias.

When we look at the association of these things and look at it from the point of view of cryptorchidism we know that it is associated to testicular cancer and to risk for infertility and it is often also together with hypospadias. They also share risk factors. Not all of these have been confirmed, but these have been reported.

Niels Jorgenson already showed this slide showing testicular cancer incidences in Denmark and in Finland and some other countries and you can appreciate the big difference. As you know Japan has also very low incidence of testicular cancer and high sperm counts like Finland.

This figure you have seen already twice showing the difference in the sperm counts between these countries.

This is the slide that Niels Jorgensen referred to on Testicular Dysgenesis Syndrome that Niels Skakkebaek and coworkers introduced 2 years ago, where all these male reproductive health problems are interconnected and have their origin during testicular development, and when something goes wrong sometimes due to genetic defects like sex chromosome mosaicism it is well known that it causes an increased risk for testicular cancer and for impaired semen quality, but also by environmental factors which lead to disturbed Sertoli cell function.

Sertoli cells and Leydig cells are communicating with each other during development. This leads to poor Leydig cell function which causes androgen insufficiency, impaired germ cell differentiation, and depending on how badly things go then you may have perhaps in the mildest cases reduced semen quality and in the worst case testicular cancer.

To conclude, prevalence rates of cryptorchidism and hypospadias are clearly lower in Finland than in Denmark. The prevalence of cryptorchidism has increased in Denmark and in England. These may be components of Testicular Dysgenesis Syndrome; therefore, it is useful to analyze these together.

The study groups for the cryptorchidism and hypospadias in Turku are listed here and these are the collaborators in Rigshopitalet in Copenhagen. Thank you.