Puberty and smell in CHARGE syndrome

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In my presentation I will focus on two aspects of CHARGE syndrome: sense of smell and puberty. First, I will talk about sense of smell and puberty in general and then I will show the results of my study in which I wanted to answer 3 questions:

- How often does a smell deficit occur in CHARGE syndrome?
- How often do individuals with CHARGE syndrome have delayed or absent puberty?
- Are smell and puberty always correlated in CHARGE syndrome?

The third question is very relevant, because if a smell deficit is always seen in association with delayed puberty, one can use a smell test to predict whether spontaneous puberty will occur.

How do we smell?
We smell with our nose. Volatile odour molecules can enter the nostrils and will go to the top of the nasal passages to a patch of special neurons about as big as a postage stamp. These neurons have hair-like projections that can bind to specific odour molecules. When an odour molecule is bound, the neuron will be triggered and sends a signal to the brain via the olfactory nerve. The olfactory bulb, located in the frontal part of the brain, is the brain region that is involved in olfaction.

How does our body know when it is time to enter puberty?
Our brain will direct the timing of puberty. A specialized area of the brain, called the hypothalamus, will start to produce gonadotropin releasing hormone (GnRH). GnRH will in turn activate another region of the brain, called the pituitary gland, to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH) into the central blood circulation. In response to LH and FSH, the ovaries will start to make estrogens in girls and the testicles will make testosterone in boys. The rising levels of estrogens in girls and testosterone in boys will start pubertal development. Girls enter puberty around the age of 8 – 13 years, whereas boys enter puberty around 9 – 14 years of age. The first sign of puberty is breast development in girls and growth of the testicles in boys.

Why do we think smell and puberty could be related?
The areas in the brain that are involved in smell and puberty develop together during embryonic development. Therefore, a smell deficit is often seen in association with a delay in pubertal development, for example in persons with Kallmann syndrome.

Study on smell and puberty in CHARGE syndrome
Smell deficiency and delayed or absent puberty often occur in CHARGE syndrome, but few studies have looked if these features are associated in adolescents with CHARGE syndrome. Therefore, we studied smell and pubertal development in 35 individuals with CHARGE syndrome from the Netherlands. In this study, we included 19 boys and 16 girls aged 10 years or older who all had a mutation in the CHD7-gene. We performed a smell test (the University of Pennsylvania Smell Identification Test, see the picture below) in all persons without mental retardation, bilateral choanal atresia and/or severe feeding difficulties (26/35). Also, we re-analyzed MRI brain scans (whenever available) for abnormalities of the olfactory...
bulbs (the area in the brain involved in olfaction). Pubertal development was evaluated by a paediatric endocrinologist who did a physical exam and measured hormone levels in blood.

How often does a smell deficit occur in CHARGE syndrome?
Smell testing showed absent sense of smell in 21/26 (81%) individuals and normal or slightly decreased sense of smell in 5/26 (19%) individuals. History taking was not reliable for determining sense of smell. MRI brain scans were available in 10 persons, but could be analysed for olfactory bulb abnormalities in only three persons. These three persons all had abnormal olfactory bulbs.

How often do individuals with CHARGE syndrome have delayed or absent puberty?
23 individuals were old enough to distinguish between delayed or normal puberty. In 17 persons puberty was delayed or absent (74%), whereas 6 persons had experienced normal puberty (26%).

Was there a correlation between sense of smell and pubertal development?
From 15 individuals complete data on both smell and puberty were available: 11 persons had both a smell deficit and delayed puberty and 4 persons had normal sense of smell in combination with normal pubertal development. Seven boys were too young to know if they would enter puberty at a normal age, but they all had cryptorchidism or a micropenis, which is suggestive for delayed puberty. These seven boys had no sense of smell. Therefore, a total of 22 persons showed concordance between smell and (suspected) pubertal development. We conclude that smell and pubertal development are 100% correlated in this study.

Can a smell test predict whether spontaneous puberty will occur?
Because of the correlation between sense of smell and pubertal development, a smell test can probably predict whether spontaneous puberty will occur. When a patient with CHARGE syndrome is unable to smell, he/she will probably need hormone replacement therapy to enter puberty. We recommend timely start of hormone replacement therapy in children with CHARGE syndrome who have no sense of smell to make sure they enter puberty simultaneously with their peers. This will reduce social problems and risk of osteoporosis (brittle bone disease).

Reference

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