The Prader-Willi syndrome and the hypothalamus

In 1956, Prader, Labhart and Willi described a syndrome in children characterized by mental retardation (mean IQ of 65), obesity, hypotonia, underdevelopment of the sexual organs and a variety of minor malformations including a small forehead, almond-shaped eyes, triangular mouth, small hands, feet and body height, decreased pigmentation of skin and hair, and ophthalmic disorders. In half of the patients a small part of chromosome 15 is missing, but other chromosomal disorders have been described as well.

The fact that Labhart's name has disappeared only goes to show how important it is for a scientist to be either the first author of a publication - because you have been doing the actual work - or the last - because you are the leader of the research team. Make sure your name is not in the anonymous middle, where it can disappear just like that!

The Prader-Willi syndrome occurs in 1 out of every 10,000 to 25,000 births. In the USA it is sometimes called the H₃O syndrome, after the 4 essential features: hypotonia, hypomentia, hypogonadism and obesity. Dysfunction of the hypothalamus, a part of the brain that is important in feeding, sexual development and behavior, may be implicated as a major cause of each of these symptoms.

The hypotonia is often noticed by the mother during pregnancy; the baby does not seem to move much. Apart from the baby's lack of movement, its position in the uterus at the onset of labor is often abnormal (either a transverse, face or breech presentation). It is often presumed that the fetal position is caused by hypotonia, the child being too weak to move itself in the correct position. However, there are other congenital disorders in the hypothalamus and pituitary - in which hypotonia is not present - which are also accompanied by abnormal presentation of the fetus at birth. The timing of the moment of birth is often also abnormal; too high a percentage of children with Prader-Willi syndrome are born either prematurely or too late. An abnormality of the hypothalamus, which plays a central role in the child's timing of its own birth, may explain these phenomena.

Prader-Willi children often have too low a birth weight, but from age two onwards tend to grow fatter than other children. Appetite control is more exacerbated when there is more severe mental retardation. The obesity may be caused by an increased drive to eat as well as an impaired mechanism

of satiation. Both functions are controlled by the hypothalamus. In particular, a group of nerve cells in the paraventricular nucleus of the hypothalamus is thought to play an important part in controlling eating. Regulation of eating behavior is often attributed to a particular set of neurons, containing the peptide oxytocin. We recently discovered, in the hypothalamus of two Prader-Willi patients, that the number of oxytocin cells in the PVN was only half of what is normally seen. If this observation is confirmed in a larger number of patients, it could mean that the eating disorder may be attributable to the low number of oxytocin neurons. It may even be possible to curb the children's appetites by administering some form of oxytocin or a related drug. As it is currently not possible to treat the eating disorder with medications, this could be a major advance.

The cause of mental retardation, and such behavioral problems as fits of temper, depression and sudden aggression, in Prader-Willi children also are not known. There are some abnormalities in the visual system in these children, including abnormal crossing of the optic nerves and a tendency for some parts of the brain involved in vision to fail to develop in a normal manner. It is not known whether similar abnormalities are found in other parts of the brain, but such problems in the hypothalamus could explain the development of mood disorders and aggressive behavior.

The hypothalamus also regulates many aspects of reproduction. Abnormal function of nerve cells in the hypothalamus containing luteinizing hormone-releasing hormone (LHRH) is thought to be responsible, in Prader-Willi children, for decreased levels of sexual hormones, resulting in non-descended testicles in boys, undersized sexual organs in children of both sexes, as well as decreased sexual behavior and insufficient growth during puberty, resulting in short stature. The onset of menstruation is often late in girls, if it occurs at all. In the absence of adequate levels of sexual hormones, certain parts of the hypothalamus (the sexually dimorphic nucleus) that develop differently in boys and girls (and may be involved in sexual behavior) are too small. It is not yet known whether proposed abnormality in LHRH production is due to absence of the LHRH neurons, their being located in an abnormal place, or possibly their producing too little LHRH or perhaps an abnormal form of the hormone. Research on the hypothalamus in Prader-Willi children can help to answer these questions.

Another Prader-Willi symptom that may originate in the hypothalamus is

the excessive need for sleep during the day. The hypothalamus contains a biological clock, which regulates our daily rhythms of behavior and hormonal cycles. Although there is no clear evidence, as yet, for abnormal function of this clock mechanism, the hypothalamus may still be involved in the abnormal regulation of sleeping pattern.

Although all of the essential features of the Prader-Willi syndrome could be associated with hypothalamic dysfunction this part of the brain has never been studied in a systematic way in Prader-Willi patients. In part, this lack of information is because the technical developments necessary for this type of research have only recently become available. By combining chemical staining of the brain with computerized imaging and counting techniques, it is now possible to visualize chemical systems in the brain and to determine the numbers and locations of neurons of specific types.

The major obstacle to further progress, however, is the small number of cases available for study. The Prader-Willi syndrome is still not yet well-known, even to doctors, so many children go undiagnosed. Also, the subject of autopsy is an emotional one and not easily talked about by either doctors or family members. Still, it is only by careful examination at autopsy that we will be able to learn the causes of symptoms such as hypotonia, mental retardation, obesity and sexual underdevelopment, or behavioral problems. Such research will be necessary if we are to develop better ideas for more rational treatment of Prader-Willi patients.

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