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Gender, head size and disease: A hypothesis related to posterior fossa growth

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Summary This hypothesis proposes that the difference in head size between the genders has a bearing on disease incidence. Smaller head size predisposes to spina bifida and larger head size predisposes to autism. In the fetus, the posterior fossa has a regulatory influence on maximum intracerebral cerebrospinal fluid (CSF) pressure. CSF pressure pulsations are generated by movements in the chest and abdomen and transmitted to the intracranial CSF spaces via the posterior fossa. The efficiency of transmission of pressure to the head is influenced by the size of posterior fossa CSF spaces. The larger posterior fossa in the male fetus allows higher peaks of pressure in the lateral ventricles than the female, resulting in larger head size. Restriction of posterior fossa growth has a greater influence on females than males. This leads to a greater incidence of spina bifida in females, where reduced head size is characteristic in the fetal stages. Fetal surgery for spina bifida expands posterior fossa CSF spaces and improves transmission of pressure waves generated in the fetal abdomen and thorax into the head. This results in an increase in head circumference following surgery. Males are susceptible to autism where head growth is accelerated in early childhood. This is because they have a larger average head size.

Introduction

It is proposed that the normal gender difference in skull and brain size influences susceptibility to central nervous system disease. The growth of the posterior fossa and its contents influences the growth of the cerebrum and skull in the fetus. This occurs due to a regulatory effect of the posterior fossa on CSF pressure in the lateral ventricles. The mechanism involves the size of CSF spaces. This role for the posterior fossa, combined with the morphology of the cerebral ventricle system, influences the growth of the fetal skull.

Gender and disease

Males have larger skulls, brains, and lateral ventricles, and smaller grey matter thickness than females [1]. Differences are present at birth [2]. Head size plotted against frequency results in a normal distribution. Male and female head size plotted separately will form adjacent curves, with males on the right. The extremes of normal are more likely to represent abnormality than the mode. Disease processes that cause restricted head

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growth are likely to have a greater incidence in females because they have smaller heads. Conversely accelerated head growth is more likely to affect males. This may be true for both genetic and environmental causes of disease. A gender difference in disease incidence suggests genetic factors are important in the etiology of disease. The male susceptibility to autism is well known and females are more susceptible to anencephaly and spina bifida [3].

Head growth

Head circumference is influenced by intracranial pressure. Pressure affects growth of the anterior and middle cranial fossae, as demonstrated by enlargement of the head that occurs with hydrocephalus prior to fusion of the cranial sutures. If a child's ventricles are shunted excessively, skull growth may be limited. This may occur to the extent that intracranial pressure becomes abnormally high [4]. This implies that both the presence of cerebrospinal fluid in the lateral ventricles and pressure are required to promote skull growth. Pressure waves are possible in fluid and enhance maximum wall tension within a cavity. Skull suture fibroblasts have been demonstrated to respond very rapidly to stretching forces [5]. This suggests that pulsatility is the driving force for skull growth. Restriction of skull growth, secondary to ventricular shunting may result from reduction in maximal rather than mean lateral ventricle pressure.

Ventricle size and shape distributes CSF pressure. Appreciation of how this occurs is assisted by understanding the law of Laplace. This Law states that; for any given fluid pressure, in a vessel or cavity, wall tension is proportional to the internal radius [6]. This means that within the ventricular system, tension will be greatest in the walls of the lateral ventricles because of their size. There will be less wall tension in the fourth ventricle and minimal tension in the walls of the aqueduct. Tension is a force [6]. According to this theory pressure pulsations in the intracerebral CSF spaces will exert their greatest force on the skull of the anterior and middle cranial fossae.

Intracranial pressure

CNS pressure is determined by the volume contained within the skull and vertebrae [7]. This is because of the rigid bone structure which limits space. Central nervous system pressure fluctuates constantly with changing volumes of blood, so that pressure is pulsatile. Venous volume fluctuates considerably with movement. These volume fluctuations can be measured as pulsations in CSF pressure in the lateral ventricles [7]. Pressure pulsations generated by the chest and abdominal cavities during physical exertion are transmitted into the central nervous system. This occurs as blood passes via the spinal venous plexus by retrograde flow into the vertebral canal. Pressure in the chest and abdomen transmits freely to the ventricles if CSF flow at the foramen magnum is unobstructed [8]. When flow is obstructed pressure transmission is attenuated or absent [9,10]. The efficiency of transmission of pressure waves from the spine to the ventricles will depend on the size and continuity of CSF spaces in the posterior fossa. The larger the CSF spaces, the greater will be the potential for peaks of pressure in the lateral ventricles.

Posterior fossa growth

Evidence indicating that posterior fossa growth is independent of intracranial pressure includes;

- Genetic determinants of posterior fossa growth
- Growth dissociation between the cerebellum and posterior fossa
- The small size of the fourth ventricle
- Absence of a posterior fossa fontanelle

Posterior fossa hypoplasia is a feature of several diseases with genetic origins and can be familial [11]. Growth of the posterior fossa has been found to be independent of cerebellar growth whereas anterior and middle cranial fossa growth is linked to cerebral hemisphere growth [12]. Brain tissue does not protrude through the fontanelles when pressure is high. In contrast when hindbrain growth exceeds posterior fossa growth, soft tissue herniates through the foramen magnum. This implies that posterior fossa growth is not pressure dependent. Cerebral hemisphere growth is however linked to cerebellar growth [13]. It has not previously been argued that this may involve any pressure related phenomenon.

The fontanelles attenuate intracranial pressure because any defect in the skull tends to reduce mean pressure. The function of the fontanelles may be to attenuate pressure peaks generated by physical movement in the fetus. This is suggested by their distribution above the level of the tentorium. The small size of the fourth ventricle, and

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the absence of any posterior fossa fontanelle suggests that ventricular fluid pressure is not necessary to expand the posterior fossa.

Head growth in the fetus

Chiari malformation, related to small posterior fossa size, is more common in females [14]. This strongly suggests that the posterior fossa in females is less spacious relative to cerebellar size than the male. It indicates that CSF spaces are obliterated more easily when space is limited resulting in cerebellar herniation. Male fetuses have a larger lateral ventricle diameter than females [15]. The combination of a more spacious posterior fossa and larger ventricles lead to a larger skull in males at birth.

Spina bifida

The current view of spina bifida is that small head size during fetal development results from low intracranial pressure [16]. This hypothesis argues that mean intracranial pressure in the spina bifida fetus is relatively high and causes progressive hindbrain herniation. This has been proposed previously by Hans Chiari, and supported by others. This is in contrast to the normal fetus where there is relatively low intracranial pressure because the skull of the middle and anterior cranial fossae are growing under the influence of pulsatile pressure. As skull growth is promoted there is space for the developing brain. Peaks of pressure are attenuated by the fontanelles.

It is proposed that the mechanism outlined here leads to the observed improvement in cranial growth after myelomeningocele repair in utero [17]. In the spina bifida fetus there is foramen magnum CSF blockage which is caused by posterior fossa hypoplasia [18] early in development. CSF obstruction leads to failure of transmission of pulsatile pressure into the head and as the skull fails to enlarge hindbrain herniation progresses. Fetal surgery may enlarge CSF spaces in the posterior fossa [17]. This allows pulsatile pressure generated by fetal movement to expand the skull.

Autism

Head growth in the first five years of life is abnormally rapid in autism [19]. This means that at the time of diagnosis there is frequently a tendency for larger head circumference in affected individuals [20]. Brain size may also be increased [21]. At birth and after adolescence head sizes of affected individuals may not differ significantly from the normal range. This suggests that there is abnormal growth regulation during an important phase of neural development and learned behaviours. Growth factors may act independently of pressure [22]. Abnormal cerebellar growth is linked to abnormal cerebral development in autism, although the nature of these links is not known [23,24]. The reasons for the perpetuation of the larger head size after birth in males are likely to relate to the causes of autism.

The relationship between spina bifida and autism may be complex. Spina bifida and autism could according to this theory co-exist, as growth abnormality is occurring at different developmental stages under the influence of different genetic abnormalities. Head growth may be enhanced, before or after birth, with a small posterior fossa due to obstruction of fourth ventricle emptying. If CSF flow obstruction contributes to enhancing head growth in autism then there is some potential for common features. There are cognitive, emotional and behavioural changes with spina bifida which constitute a form of cerebral palsy, [25] however the genetics and pathology of the two conditions for the majority of cases would be expected to be different.

Conclusion

The growth of the posterior fossa and its contents affects ventricle size and influences brain growth. The ventricles distribute pressure generated by physical movement into the head and these forces stimulate growth of the skull. This hypothesis does not argue that regulation of head size is solely a function of pressure, but that skull and brain volume is influenced by hydrodynamic factors. Regulation of head size is an important feature of nervous system disease where there is a gender difference in incidence. Discovering the causes of CNS diseases with differing gender incidence will give insights into normal human brain development.

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