Congenital Hydrocephalus in mono and dizygotic twins

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Background: Information regarding the occurrence of hydrocephalus (HC) in twins is important in establishing the significance of environmental factors as well as a genetic basis in congenital HC aetiology. This was the basis for this study.
Methods: A single institution retrospective study was conducted between August 1, 2006 and July 31, 2008. Only those cases of hydrocephalus (based on clinical and radiological tests-cranial Computeried tomographic or Magnetic resonance imaging scan) that required placement of a ventricular shunt or endoscopic third ventriculostomy were included in the study. Data regarding the patient's demographics, clinical history, examination and the maternal demographics were retrieved and analysed. DNA analysis was done to confirm the fraternity of the twins when applicable.
Results: Fifty-eight patients with congenital hydrocephalus presented to the unit over the study period. We identified three sets of twins in the study. Only one set were identical (both male) and both had hydrocephalus. In the remaining two sets only one out of each pair had hydrocephalus (one male and one female). Two of the patients (1male, 1female) were twins with discordant HC. All the children had normal thumbs. DNA analysis confirmed identical twins in both the like sex twins. The mothers were not known diabetics, hypertensive or sickle cell patients neither did they smoke or take alcohol. There was no family history of hydrocephalus in all patients.
Conclusion: Concordance for HC is likely if the twins are like sex and identical. Congenital hydrocephalus seems to be a multifactorial disorder, triggered by environmental factors in genetically predisposed individuals.

Introduction

Hydrocephalus (HC) has long been recognised and it remains a common disease in our paediatric Neurosurgical population. HC is a dynamic disorder of cerebrospinal fluid production, flow and or resorption; it is however far more complicated than a simple disorder of CSF circulation[1]. Although commonly considered a single disorder, HC is a collection of a heterogeneous complex and multifactorial disorders[2]. It has an estimated incidence of 1 in 1500 births[3].

There are two forms of hydrocephalus, the congenital and the acquired. Congenital hydrocephalus is an aetiologically diverse disorder, including environmental (infectious, teratogenic,) and genetic factors as the underlying mechanis[4-7]. The development and progression of congenital hydrocephalus is a dynamic process that is not yet well understood. It is estimated that about 40% of hydrocephalus cases have a possible genetic aetiology[8]. In humans, X-linked hydrocephalus (HSAS1, OMIM) comprises approximately 5–15% of the congenital cases with a genetic cause[8-12]. Although there is strong evidence for genetic causes, only one hydrocephalus gene (X-linked) has been identified in humans. Information regarding the occurrence of HC in twins is important in establishing the significance of environmental factors as well as the genetic basis. This has not been previously documented in our environment. Our study was conducted to evaluate the frequency of hydrocephalus in twins in our environment and to review the literature.

Patients and Methods

We conducted a single institution retrospective study. All the patients who presented to the Neurological Surgery unit and department of paediatrics of the Lagos State University Teaching Hospital, Ikeja, Lagos (LASUTH), Nigeria with clinical and radiological features of hydrocephalus between August 1, 2006 and July 31, 2008 were analysed for the study.

Only those cases of hydrocephalus (based on clinical and radiological tests) that required placement of a ventricular shunt or endoscopic third ventriculostomy were included in the study. Data regarding the patient's demographics, clinical history, examination and the maternal demographics were retrieved and analysed. DNA analysis was done to confirm the fraternity of the twins when applicable. Cranial Computerized tomography was done in all patients.

Results

Fifty-eight patients with congenital hydrocephalus presented to the unit over the study period. We identified three sets of twins in the study. Only one set were identical (both male) and both had hydrocephalus (Figure 1). In the remaining two sets only one out of each pair had hydrocephalus (one male and one female).The mother's ages were 20, 23 and 35years. Two of the mothers were primigravida and one had two previous healthy babies. The mothers were not known diabetics, hypertensive or sickle cell patients neither did they smoke or take alcohol. There was no family history of hydrocephalus in all patients. Two of the patients (1male, 1female) were twins with discordant HC. All the children had normal thumbs. DNA analysis confirmed identical twins in both the like sex twins. Isolated aqueductal stenosis accounted for HC in all the patients except in one where there was associated cervical spina bifida associated with Chiari II malformation.
Ventriculoperitoneal shunts were inserted in the two of the patients while one had endoscopic third ventriculosomy. One member of the set of twins set died from neonatal sepsis while awaiting surgery.

Discussion

The underlying cause of acquired hydrocephalus (HC) is usually quite clear. On the other hand, the aetiology of congenital hydrocephalus is not well established[13]. It is thought that congenital HC may develop at an important and specific embryonic time period of neural stem cell proliferation and differentiation in the brain[14,15]. Congenital HC may occur alone (non-syndromic) or as part of a syndrome with other anomalies (syndromic)[16,17].

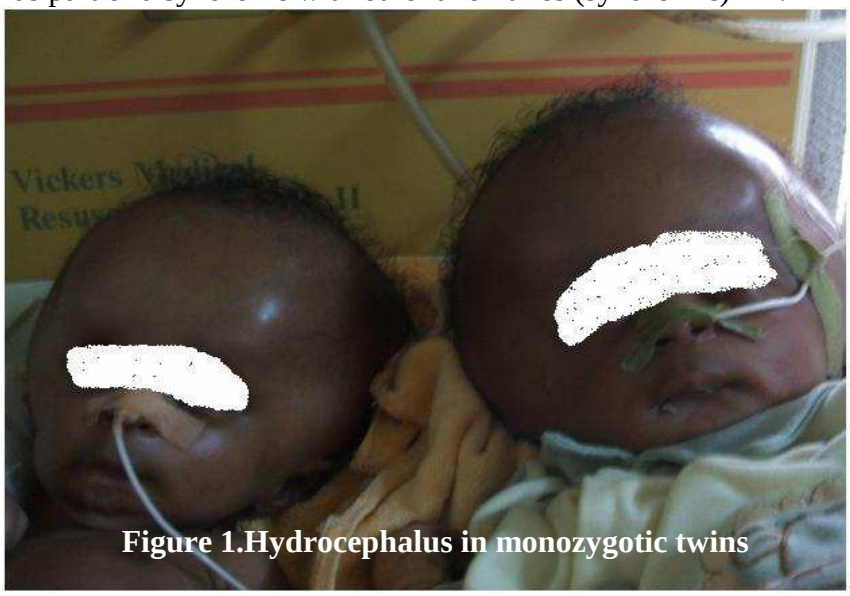

Figure 1.Hydrocephalus in monozygotic twins

In syndromic forms, it may be hard to define the defective gene because of the association with other anomalies. Congenital HC may be associated with chromosomal abnormalities for example trisomy 13, trisomy 18, triploidy, Mendelian conditions such as Walker-Warburg syndrome, Meckel syndrome, Fanconi anemia, other central nervous system (CNS) malformations such as Dandy-Walker malformation, Chiari malformation, neural tube defects, or it may be isolated[18].

In isolated cases of congenital hydrocephalus, a genetic basis is strongly suggested[19-22]. Record et al[23] reported 17 twin pairs and the rate of concordance for hydrocephalus was 11.8%. Aside from research on twins, Lorber[20] carried out a longitudinal study on 270 babies with isolated congenital hydrocephalus; they had 453 siblings of whom 5 were hydrocephalic (1.1%). In our study, further genetic studies could not be carried out due to lack of facilities, but there were no recognizable patterns of malformation. Piatt[24], reporting monozygotic twins discordant for external hydrocephalus, stated that, whatever the genotype of the twins, their different phenotypes show that hydrocephalus is not set in motion during a critical window of foetal development.

The role of environmental factors in the pathogenesis of congenital hydrocephalus is also well documented in the literature[18]. Prenatal infections such as toxoplasmosis, rubella, syphilis and cytomegalovirus seem to demonstrate the strongest association[21]. The risk of hydrocephalus may be increased by the maternal consumption of drugs containing misoprostol, dextromethorphan, nalidixic acid, cephalosporins, for example[25,26]. Maternal smoking does not appear to affect hydrocephaly rates[27]. Although the association between hydrocephaly and maternal diabetes is not clear, a recent study demonstrated an increased risk among infants born to obese but non-diabetic women[28].

Interestingly, hydrocephaly risk seems to be lower in infants born to women living at high altitudes[29]. Wachi et al[22] reported a pair of identical twins presenting with external hydrocephalus. Neuroimaging, doppler sonography, and intracranial pressure (ICP) monitoring were performed, delineating the anatomical and biomechanical similarities of the intracranial space, and thereby noting the importance of the genetic basis. The recurrence risk for congenital hydrocephalus excluding X-linked hydrocephalus is low. Empiric risk rates range from <1% to 4% [30-32], indicating the rarity of autosomal recessive congenital hydrocephalus[8,12,27,28]. However, multiple human kindred's with congenital hydrocephalus have been reported[8,12,16,33,34]. The loci or genes for human autosomal recessive congenital hydrocephalus have not yet been identified, but there is at least one locus for this trait. Furthermore, like in animal models, since there is heterogeneity among clinical phenotypes, there may be more genetic loci in human autosomal recessive congenital hydrocephalus. To date, at least 43 mutants of hydrocephalus have been described, and 10 congenital hydrocephalus genes have been identified. Among them, only one hydrocephalus gene has been identified in humans (L1CAM)[35].

Conclusion

Our study though limited to three sets of twins does highlight the findings by Record et al[24] that higher concordance rates for HC in like sex and identical twins. This study also suggests that congenital HC seems to be a multifactorial disorder, triggered by environmental factors in genetically predisposed individuals.

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