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Research Article

Increased Risk of Hydrocephalus in Adults with Isomerism

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Abstract

Background: So-called heterotaxy, or isomerism, is characterized by imagery of the thoracic organs across the midline and abnormal lateralization of the abdominal organs. Abnormalities of the central nervous system have also been associated with isomerism, particularly hydrocephalus. This study aimed to characterize the prevalence of hydrocephalus in those with and without isomerism and determine whether or not isomerism is an independent risk factor for hydrocephalus.

Methods: The 2012 iteration of Nationwide Inpatient Sample was utilized to identify admissions for patients hydrocephalus. The prevalence of hydrocephalus was compared between those with and without isomerism. Next, a logistic regression was conducted to determine if isomerism was an independent risk factor for hydrocephalus. Continuous variables were compared using a student t-test or Mann-Whitney-U test while categorical variables were compared using a chi-squared analysis. Logistic regression was carried out with backward elimination using hydrocephalus as the dependent variable.

Results: A total of 6,907,109 patients were included in this analysis. A total of 861 patients had isomerism and a total of 12 (1.4%) had hydrocephalus compared to 26,455 (0.4%) who did not have isomerism. Isomerism was found to be an independent risk factor for hydrocephalus after being adjusted for other variables (adjusted odds ratio 2.798, 95% confidence interval 1.557 to 5.028).

Conclusion: Adults with isomerism have an increased prevalence of hydrocephalus. Those with isomerism and hydrocephalus tended to have lengthier and more costly admissions. The association between isomerism and hydrocephalus is likely mediated by ciliary dyskinesia.

Keywords: *Hydrocephalus, Isomerism, asplenia, Ciliary dyskinesia*

Introduction

So-called heterotaxy, is characterized by isomerism of thoracic organs across the midline as well as abnormal lateralization of abdominal organs [1,2]. Thus, in the chest there are either two morphologically right or left bronchuses as well as two morphologically right or left lungs [3-5]. In the heart, isomerism is present as well and is confined to the atrial appendages, the morphology of which can be determined on the basis of the extent of the pectinate muscles [6,7]. Appendages with pectinate muscles extended beyond the appendage and surround the entire extent of the atrioventricular junction have right sided morphology while appendages with pectinate muscles confined to the appendage itself and not surrounding the entire extent of the atrioventricular junction have left sided morphology. It is indeed the atrial appendages that are the most constant feature and thus it becomes apparent that so-called heterotaxy, better referred to as isomerism, can be segregated into the subsets of right or left isomerism based on the morphology of the atrial appendages [2,8]. This, is in contrast to segregation of isomerism into the asplenia and polysplenia subtypes as splenic anatomy is a more variable feature [9,10]. In either right or left isomerism multiple organ systems may be effected including the central nervous, pulmonary, cardiovascular, immunologic, gastrointestinal, and genitourinary systems [11-16].

Isomerism goes beyond simple anatomic perturbations and impacts organ function. Congenital malformations of the heart, particularly those of a functionally univentricular nature, intuitively, impact hemodynamics [17]. Malformations in the cardiac conduction system often lead to arrhythmias in the setting of isomerism [18-20]. Left bronchopulmonary isomerism has been associated with higher risk of otitis media and sinopulmonary symptomatology, such as need for supplemental oxygen, while splenic malformation can lead to functional asplenia (may occur in the presence of multiple spleens and a solitary, normally appearing spleen as well) [21-23]. The underlying mechanism of all these anomalies is not completely delineated although it is suspected that ciliary dyskinesia is a likely a large contributor, with at least 40% of patients with isomerism being demonstrated to have ciliary dyskinesia [24]. Another consequence of ciliary dyskinesia is the development of hydrocephalus, with or without isomerism [25-28]. The objective of this study was to determine the prevalence of hydrocephalus in adult patients with isomerism, determine if the prevalence of hydrocephalus in these patients is higher than those without isomerism, identify other factors associated with hydrocephalus in these patients, and analyze if hospitalization characteristics differ in those with and without hydrocephalus in those with isomerism.

Methods

Institutional review board review approval was waived as this studied utilizes deidentified data from a national database. Consent was obtained from patients when this data was entered into the dataset. This study is in compliance with the Helsinki declaration.

Patient identification

Data regarding hospital admissions was obtained from the 2012 Nationwide Inpatient Sample which is the most recent iteration of the database. This database was developed for the Healthcare Cost and Utilization Project and was developed in partnership with the Agency for Healthcare Research and Quality. Patients with isomerism were identified using the International Classification of Diseases, Ninth Revision (ICD-9) code 746.87. Patients with situs inversus were not included in this group as not all situs inversus portends isomerism. Admissions associated with hydrocephalus were identified by multiple ICD-9 codes: 331.3 for communicating hydrocephalus, 742.3 for congenital hydrocephalus, 331.5 for normal pressure hydrocephalus, 741.0 for spina bifida with hydrocephalus, and 331.4 for obstructive hydrocephalus. An additional category was already created for “any hydrocephalus” which was an aggregate of all of the afore mentioned varieties of hydrocephalus.

Codes for hydrocephalus related procedures were also identified and searched for: 02.22 for an intracranial shunt placed from the cerebral ventricle to a location other than the peritoneum or abdomen, 02.34 for an intracranial shunt placed from the cerebral ventricle to the peritoneum or abdomen. These two codes represented shunts placed during the reported hospitalization. The code V45.2 was used to identify presence of a shunt at the time of admission.

Data identification and collection

Demographic information including, gender, and race were collected for each admission. Admission characteristics such as admission month, length of stay, and cost of stay were collected as well. Information regarding comorbid conditions was also collected. Hyperlipidemia was identified using 272.0, 272.1, 272.2, and 272.3 hypertension using 401.0, 401.1 and 401. Overweight or obese patients were identified using 278.00, 278.01, and 278.02 with current smokers being identified by 305.1.

Data of interest in regards to isomerism included cardiac anatomy as well splenic anatomy. The following congenital cardiac malformations commonly associated with isomerism were collected: functionally univentricular hearts using 745.6, double outlet right ventricle using 745.11, atrioventricular septal defect using 745.60 and 745.69, partial anomalous pulmonary venous connection using 747.42, and total anomalous pulmonary venous connection using 747.41. Splenic abnormality, either absence of a spleen or presence of multiple spleens, was collected using 759.0. It was not possible to distinguish between those with absence of a spleen or multiple spleens due to the ICD-9 coding strategy.

Statistical analysis

Continuous variables are reported using mean and standard deviation while categorical variables are reported using absolute frequency and percentages. Continuous variables were analyzed using a student t-test or Mann-Whitney-U test as appropriate with categorical variables being analyzed using chi-square analysis. Baseline characteristics such as age, gender, race, and comorbid conditions were compared between those with and without isomerism. A univariate cross tabulation analysis was conducted to determine the odds of having hydrocephalus and hydrocephalus-related procedures in patients with and without isomerism. Multivariate regression analysis was also conducted with presence of any hydrocephalus as the dependent variable and various independent variables including isomerism.

All statistical analysis was done utilizing SPSS Version 20.0 (Chicago, IL).

Results

Overall characteristics

A total of 6,907,109 admission were including in this analysis, 861 (0.01%) of which had isomerism. Overall characteristics of these admissions did differ between those with and without isomerism. The age at admission tended to be lower, length of hospital stay tended to be longer, and cost of hospital stay tended to be longer in those with isomerism versus those without. Admissions associated with isomerism tended to consist of more males, more Hispanics, and more Asian or Pacific Islanders. Current smoking, hyperlipidemia, hypertension, diabetes mellitus, acute kidney injury, chronic kidney disease, overweight or obesity, obstructive sleep apnea were all less prevalent with isomerism. All congenital malformations of the heart were more common with isomerism as well. Inpatient mortality was higher in admission with isomerism (Table 1).

	No isomerism (n=6,906,248)	**Isomerism (n=861)**	**p-value**
Age at admission (years)	51.28 ± 25.82	25.49 ± 30.21	< 0.0001
Female	4,007,523 (58.0)	379 (44.0)	< 0.0001
Current smoker	888,276 (12.9)	50 (5.8)	< 0.0001
Hyperlipidemia	348,536 (5.0)	19 (2.2)	< 0.0001
Hypertension	2,386,574 (34.6)	158 (18.4)	< 0.0001
Diabetes mellitus	1,509,816 (21.9)	85 (9.9)	< 0.0001
Acute kidney injury	629,878 (9.1)	56 (6.5)	0.008
Chronic kidney disease	812,138 (11.8)	63 (7.3)	< 0.0001
Overweight or obese	724,704 (10.5)	55 (6.4)	< 0.0001
Obstructive sleep apnea	302,485 (4.4)	28 (3.3)	0.106
Race *White* *Black* *Hispanic* *Asian or Pacific Islander* *Native American* *Other*	4,360,026 (66.9) 967,372 (14.8) 742,364 (11.4) 168,044 (2.6) 47,063 (0.7) 236,681 (3.6)	447 (56.2) 97 (12.2) 172 (21.6) 35 (4.4) 6 (0.8) 38 (4.8)	< 0.0001
Length of hospital stay	4.65 ± 6.73	11.39 ± 25.90	< 0.0001
In-hospital mortality	133,994 (1.9)	45 (5.2)	< 0.0001
Myocardial infarction	172,377 (2.5)	17 (2.0)	0.327

Functionally univentricular	347 (0.1)	67 (7.8)	< 0.0001
Double outlet right ventricle	546 (0.1)	85 (9.9)	< 0.0001
Atrioventricular septal defect	0 (0.0)	0 (0.0)	--
Partial anomalous venous connection	196 (0.1)	11 (1.3)	< 0.0001
Total anomalous venous connection	236 (0.1)	15 (1.7)	< 0.0001
Absence of a spleen or presence of multiple spleens	687 (0.1)	39 (4.5)	< 0.0001
Tetralogy of fallot	1,414 (0.1)	12 (1.4)	< 0.0001
Ventricular septal defect	7,525 (0.1)	79 (9.2)	< 0.0001
Secundum atrial septal defect	29,410 (0.4)	126 (14.6)	< 0.0001
Pulmonary hypertension	176,306 (2.6)	48 (5.6)	< 0.0001

Table 1: *Characteristics of patients with and without isomerism.*

Hydrocephalus and related procedures

Any hydrocephalus was present in 12 (1.4%) of those with isomerism compared to 26,455 (0.4) of those without, resulting in an odds ratio of 3.675 (95% confidence interval 2.079 to 6.499, p < 0.0001). When the different categories were assessed individually there was no statistically significant difference in any category except for congenital hydrocephalus. Congenital hydrocephalus was present in 10 (1.2%) of those with isomerism compared to 2,720 (0.1%) of those without, resulting in an odds ratio of 29.824 (95% confidence interval 15.971 to 55.695, p < 0.001) (Table 2).

	No isomerism (n=6,906,248)	**Isomerism (n=861)**	**Odds ratio (95% confidence interval)**	**p-value**
Communicating hydrocephalus	1679 (0.1)	0 (0)	--	0.647
Congenital hydrocephalus	2,720 (0.1)	10 (1.2)	29.824 (15.971 to 55.695)	< 0.001
Idiopathic normal pressure hydrocephalus	6,456 (0.1)	0 (0)	--	0.369
Obstructive hydrocephalus	15,674 (0.2)	2 (0.2)	1.024 (0.256 to 4.100)	0.974
Any hydrocephalus	26,455 (0.4)	12 (1.4)	3.675 (2.079 to 6.499)	< 0.001
Ventriculoperitoneal shunt	3,989 (0.1)	1 (0.2)	1.817 (0.255 to 12.922)	0.545
Intracranial shunt other than ventriculoperitoneal	2,251 (0.1)	1 (0.2)	3.221 (0.453 to 22.913)	0.216

Table 2: *Hydrocephalus and need for intracranial shunts in those with and without isomerism.*

Placement of a cerebral shunt from a cerebral ventricle to the peritoneal cavity or abdomen occurred in 2,989 (0.1%) of those with isomerism compared to 1 (0.2%) of those without, with no statistically significant difference present (odds ratio 1.817, 95% confidence interval 0.255 to 12.922, p = 0.545). Placement of a cerebral shunt from a cerebral ventricle to a site other than the peritoneal cavity or abdomen occurred in 1 (0.2%) of those with isomerism compared to 2,251 (0.1%) of those without, with no statistically significant difference present (odds ratio 3.221, 95% confidence interval 0.453 to 22.913, p = 0.216) (Table 2).

Multivariate regression of all patients with the aggregate hydrocephalus category as the dependent variable demonstrated isomerism to be an independent risk factor for hydrocephalus (odds ratio 2.798, 95% confidence interval 1.557 to 5.028, p < 0.001). Other risk factors included being male, having a ventricular septal defect, and having an atrial septal defect.

Multivariate regression of only isomerism patients with the aggregate hydrocephalus category as the dependent variable demonstrated no independent risk factors for hydrocephalus in individuals with isomerism.

When admission characteristics were compared between those with and without hydrocephalus in the setting of isomerism, those with hydrocephalus did demonstrate differences. Mean length of hospitalization in those with isomerism and hydrocephalus was 41 days compared to 11 days in those with isomerism but without hydrocephalus ($p < 0.0001$). Mean cost of hospitalization in those with isomerism and hydrocephalus was $334,600.08 Compared to $134,240.44 in those with isomerism but without hydrocephalus ($p = 0.027$).

Discussion

Ciliary dyskinesia is now being understood to play a bigger part in isomerism [24]. This is congruent with the clinical picture which often shows overlap with ciliopathies, particularly with respect to renal, hepatic, cerebral, and sinopulmonary abnormalities [29-39].

Central nervous system anomalies present in ciliopathies that are also noted in patients with isomerism include hydrocephalus, cortical abnormalities, and neurodevelopmental impairments [36,38,39]. Our study, based on data from a large database, demonstrated a higher prevalence of hydrocephalus in those with isomerism. This risk is 2.8 times greater in those with isomerism. This increased risk is driven almost solely by congenital hydrocephalus, as there was no statistically significant difference in any of the other varieties of hydrocephalus.

Cilia are tiny projections present on the surface of nearly all epithelial cells. They are anchored to the cell by cytoskeletal structures known as the axoneme and basal body which consist of microtubules. Cilia have 9 pairs of microtubules along the circumference of the axoneme and may have or may not have a central pair of single microtubules. Those without a central pair are known as 9+0 (nonmotile or primary) cilia while those with a central pair are known as 9+2 (immotile) cilia [40,41]. The nonmotile cilia, despite their alternate name, are not always immobile. These cilia, which are present at the node during embryogenesis, move in a rotary fashion and help generate unidirectional flow which facilitates visceral laterality. These cilia also house various signaling receptors and mediators and have been demonstrated to have sensory roles [42,43]. Motile cilia move in a whip like fashion and play a role in fluid flow generation as well as clearance of other particles.

Cilia have been highly conserved and approximately 2,500 possible genes have been identified as part of the ciliome [44,45]. These genes have been associated with tubulin, fibulin, dynein, fibrocystin, kinesin, polycystin, radial spoke proteins, and intraflagellar transport proteins.

In the brain, motile cilia are found on ependymal cells. In mice, these motile generally begin to form at the time of birth [46]. The situation for the choroid plexus epithelial cells is different. These have nonmotile cilia, with these cilia beginning to form during embryogenesis [47,48]. The nonmotile cilia on the choroid plexus epithelia cells play a role in downregulation of cerebral spinal fluid with deciliation leading to increased production of cerebral spinal fluid [47,49,50]. Whether there is positive feedback mechanism as well is not clear at this time. Thus, overproduction of cerebral spinal fluid, even without abnormal ependymal motile cilia can lead to hydrocephalus [51].

While the above signaling properties of nonmotile cilia contribute to hydrocephalus, there are also contributions to this made by the motile cilia of the ependymal cells, although this may not play as large a role as previously thought. Planar polarity abnormalities of the ciliated ependymal cells has been found to be associated with directionality of cerebral spinal flow [52,53]. Tissir and colleagues have demonstrated that it may not be lack of ependymal cilia that causes hydrocephalus directly due to flow but that the lack of this ependymal cilia and resulting abnormalities in planar polarity may cause dysfunction of choroidal plexus epithelium and thus lead to hydrocephalus [52].

While not related to hydrocephalus, it is also of note that choroid plexus epithelial cells may also modulate immune response. Immune cells are found on the apical surface of choroid plexus epithelial cells. Cytokine release during acute illness leads to upregulation of various factors by the choroid plexus epithelial cells which then mediates increased influx of immune cells into the central nervous system. It is postulated that sensory cilia play a role in this process [54,55]. This is of particular interest as those with isomerism are known to have increased risk of bacteremia and bacteremia associated morbidity [56].

As it is becoming clear that ciliary dyskinesia mediates some of the effects of isomerism, it is critical to understand the spectrum of abnormalities found in ciliopathies and be aware that these may also be present in patients with isomerism.

This study is not without its limitations, however. Firstly, we were unable to segregate isomerism into right or left. Additionally, coding for congenital cardiac malformations is not ideal to help extract precise information about the cardiac anatomy that would be needed for this. Other anatomic findings to help segregate into right and left isomerism, such as splenic anatomy, are also not precise as both absence of a spleen and presence of multiple spleens were coded with a single code. Properly capturing the arrangement of the abdominal organs was not possible for similar reasons. Also, not all ICD-9 codes have been validated over the years, particularly those used to code for congenital cardiac malformations. A large percentage of those with isomerism didn't have a congenital heart defect that was documented or was coded under a nonspecific ICD-9 code which did not allow identification of a specific lesion.

Conclusion

Isomerism is an independent risk factor for hydrocephalus. Shunt placement in adulthood, however, is often not necessary and is not more likely in those with isomerism when compared to those without.

Those with isomerism and hydrocephalus tend to have longer and costlier hospitalizations when compared to those with isomerism but without hydrocephalus.

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