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Can Bronchoscopic Airway Anatomy Be an Indicator of Autism?

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Abstract

Bronchoscopic evaluations revealed that some children have double branching of bronchi (designated “doublets”) in the lower lungs airways, rather than normal, single branching. Retrospective analyses revealed only one commonality in them: all subjects with doublets also had autism or autism spectrum disorder (ASD). That is, 49 subjects exhibited the presence of initial normal anatomy in upper airway followed by doublets in the lower airway. In contrast, the normal branching pattern was noted in all the remaining 410 subjects who did not have a diagnosis of autism/ASD. We propose that the presence of doublets might be an objective, reliable, and valid biologic marker of autism/ASD.

Keywords

Autism; Autism spectrum disorder etiology; Doublets; Airway double branching; Airway anomaly

Introduction

Autism spectrum disorder (ASD) is a pervasive, behaviorally defined range of complex neurodevelopmental disorders characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior (http://www.ninds.nih.gov/disorders/autism/detail_autism.htm). Persons with ASD also tend to have impairments in social imagination; strong, narrow interests; and a range of cognitive deficits (Ward 1970; Wing and Potter 2002; Rapin and Tuchman 2008; Miles et al. 2005; King and Bearman 2009; Mandell and Palmer 2005). ASD includes autism, pervasive developmental disorder not otherwise specified, and Asperger's syndrome. It is generally considered to be a “complex” disorder caused by mutations of multiple genes, each contributing small and cumulative effects, in combination with undefined environmental

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factors influencing the child's development (O'Roark et al. 2012; Sanders et al. 2012), but the etiology remains unknown.

Estimates of the prevalence of ASD vary widely, depending upon the researcher's methods, the geographical area under investigation, the criteria used for inclusion, plus numerous other factors. Estimates originally ranged from 4 to 5 per 10,000 births (Miles et al. 2005; Anney et al. 2010), but now 62 per 10,000 individuals is a more widely accepted number (Elsabbagh et al. 2012). In March, 2012, the CDC's (Centers for Disease Control) ADDM (Autism and Developmental Disabilities Monitoring Network) reported that 1 in 88 children presently have autism (Insel 2012). The increasing prevalence of identified autistic children has prompted varying degrees of concern (Fombonne 2001). The reasons for this increase include the availability of more funding for autism research; the redefinition of autism; more sophistication in diagnostic tools, knowledge, and criteria; better-trained educational staff and specialists; and increased access to pediatricians and school-based health centers (Mandell and Palmer 2005). There do not seem to be any signs that the incidence rate of autism is plateauing (Hertz-Picciotto and Delwiche 2009).

The two major classification systems for diagnosing ASD are the American Psychiatric Association's *Diagnostic and Screening Manual, Fourth Edition (DSM-IV)*, and the International Classification of Diseases (ICD), *Classification of Mental and Behavioral Disorders*.

At this time, diagnosis is rendered primarily through rating scales, structured observation in various settings, structured inquiries related to specific behaviors, history taking from the caregiver(s) (Baird et al. 2003). To date there is no biochemical or biologically based measure for autism (Wing and Potter 2002). Two rating scales in particular have been in use for more than four decades and are now well established, the Childhood Autism Rating Scale (CARS) (Schopler et al. 1980) and the Autism Behavior Checklist (ABC) (Krug et al. 1980). The CARS was found to correlate highly with the DSM-IV, but does not identify individuals with Asperger's syndrome. Another well-studied, standardized, popular set of scales is the Autism Diagnostic Observation Scale-Generic (ADOS-G) (Lord et al. 2000). Other popular developmental screening questionnaires include the Ages and Stages Questionnaire (Bricker et al. 1995), the Brigance Infant and Toddler Screens (Glasco 2002), the Child Development Inventories, and the Parents' Evaluations of Developmental Status (Glasco 2002). There is also a wide range of individual differences in children in terms of how they respond to different stimuli, strategies, milieus, and interventions. Because of these issues, there will continue to be limits to the certainty with which prognoses and conclusions can be made (Charman and Baird 2002). Autism continues to remain missed, unrecognized, and undiagnosed until pre-school age or later because definitive tools for screening for autism do not exist (Filipek et al. 2000; Mandell et al. 2005).

Although autism traditionally has been considered basically a neurological, behaviorally defined disorder, other etiologies have been investigated. Rubella infection has been implicated, as have phenylketonuria, anticonvulsant drugs taken during pregnancy, tuberous sclerosis, and encephalitis. However, specific medical causes for autism have been implicated in only 6–10 % of the autism cases (Baird et al. 2003).

Most studies of anatomical differences in persons with autism have centered on abnormalities in the cerebellum and cerebrum of autistic children. Of heightened interest was the discovery that persons with autism tended to have an increased volume of white matter in the cerebrum and cerebellum (Just et al. 2007). Significant attention was given to an apparent reduction in size of the corpus callosum (Hardan et al. 2000; Borger-Megiddo et al. 2006). Carper and Courchesne (2000) reported an increased volume of the frontal lobe cortex in ASD patients. Also, left superior temporal hypoperfusion is related to autistic severity (Meresse et al. 2005).

In summary, the prevalence of identified cases of autism is growing, and physicians and other professionals are seeing more children affected with autism. Whether this increase is a function of improved identification and discovery, or an actual increase in incidence, or a combination of these, has not been ascertained. The benchmark measures of diagnosis and identification continue to be the behavioral rating scales, although new and innovative methods are being developed. Until now, however, no objective biologic marker to diagnose a person with autism has been identified.

Since there is no term for the “double branching” anomaly in the literature (Wiebel 1962), we coined the term “doublet” and undertook the task of formulating its description and definition. This anomaly consists of a symmetrical double branching of bronchi throughout the lower airway (see Fig. 1). We are unaware of previous studies addressing the issue of significance, function, or role of variant branching patterns. Normal branching begins from the trachea to the bronchi. In each generation of the bronchi to the bronchiole(s), the lung divides like branches on a tree. In most cases that tree has single branches. Yet our bronchoscopic observations yielded many cases of children with two symmetric branches (doublets) instead of one. Each branch appears to split into two branches that are equal and parallel to each other. This splitting begins in the lower airway from the third generation and beyond. Although it is difficult to observe the branching pattern with a bronchoscope beyond the third to fourth generation, we observed that in larger lungs, doublets in the most distal airways could be observed. In contrast, such divisions do not seem to occur in a normal lung.

The purpose of this study was to both locate and identify the dual-branching bronchi (doublets), to determine what (if any) variables exist in common with doublets, as well as to suggest etiology of the ASD disorder.

Methods

Upon receiving Institutional Review Board approval, one of the authors retrospectively studied the results of bronchoscopies performed on patients at St. Joseph’s Hospital and Medical Center, Phoenix, Arizona, USA, between 2009 and 2011. Bronchoscopies had been performed as part of a diagnostic evaluation to observe the anatomy and dynamics of the airways in the lungs during work-ups for cough unresponsive to therapy on patients requiring further pulmonary investigations. Two bronchoscopists, one a board-certified and another board eligible pediatric pulmonologists with at least 5 year’s experience each in bronchoscopic procedures, performed the bronchoscopies and prepared the reports. Photographs were taken of all portions of the lungs, and the author analyzed each

photograph. A total of 459 children, ages 2 months through 18 years, underwent an evaluation by bronchoscope for (1) having a chronic cough with a serious underlying lung condition (e.g., congenital anomalies in the lung, bleeding, chronic bronchitis, ciliary dyskinesia, pulmonary aspiration, recurrent wheezing, stridor, immune deficiency, and related complications) and/or (2) evaluation to discover the reason for the cough.

Medical records of all 459 children were reviewed and 49 children, ages 2 years through 13 years, met criteria for further retrospective analysis because of abnormal doubling in the lower airways. We looked for similarities and differences among children with branching in airways that occurred in the third and fourth airway generations (Wiebel 1962).

Results

Bronchoscopic evaluations revealed the presence of normal anatomy in the upper airways, but unusual double take-offs (doublets) were found in the lower airway in 49 of the 459 patients studied (Figs. 1, 2, 3, 4). Detailed analysis of the medical history and clinical records of these 49 children revealed that they all had a diagnosis of autism or ASD. Developmental physicians, geneticists, neurologists, and/or professional teams had seen these children prior to referral to the pulmonology clinic and had documented autism/ASD by following recognized standardized behavioral assessments of autism according to the criteria of the DSM IV. All of the remaining 410 subjects (control group) exhibited normal airways with single take-offs (Fig. 1, 2, 3, 4). None of the control subjects had a diagnosis of autism/ASD, and the records do not indicate that their caregiver(s) observed and/or reported symptoms or behaviors to warrant testing them for autism.

Finding the link between autism/ASD and the lower airway branching pattern was entirely serendipitous. The study was designed specifically to develop a diagnosis and therapeutic intervention of cough unresponsive to therapy, and the subjects were included solely for that purpose. Since there was no way of anticipating the ASD link, any unconscious selection bias or biased interpretation of the data is logically minimal.

Discussion

Developmentally, segmental bronchi are formed early in embryogenesis, having begun forming during 3–6 weeks of gestation. Human lung branching continues during the pseudoglandular stage of fetal gestation, which occurs from the fifth to the sixteenth week of gestation. All sub-segmental bronchi are present during this stage, as early as 2 months of gestational age, and no further branching occurs after the conclusion of the pseudoglandular stage of embryologic development (Whitset and Wert 2006). Assuming doublets can be a marker for autism, this doublet formation occurs between the embryonic and pseudoglandular stage between the third and sixteenth weeks of gestation. Cartilage is present during the pseudoglandular stage of development, and all respiratory bronchioli are formed by the conclusion of this stage (Gaultier 1999). A variety of growth factors, growth factor receptors, epithelial mesenchymal interactions, and extracellular matrix molecules play important roles in directing lung development. Branching morphogenesis occurs during the canicular stage, which lasts an additional sixteen to 24 weeks in the human fetus when

multiple conducting airways are formed (Pinkerton and Joad 2000; Thurlbeck 1991). Further research is needed to determine where, when, and under what conditions doublets are formed.

Clinically, we hypothesize that doublets reduce the space in distal airways, which might impair airway and secretion clearance. Cough might be a natural attempt to clear lungs of fluids and may provide one explanation for ASD subjects' unresponsive cough. This may explain the increased incidence of children with autism/ASD in our study (49 of 459) (10.7 %) when compared to the average in public at large (1 in 88) (1.1 %); our subjects were selected because they experienced unresponsive cough. In addition, because of the decreased airway diameter and the resulting greater airway resistance, long distance running and other athletic endeavors would likely be more difficult for ASD patients. Since the diagnosis of ASD is presently based on very subjective criteria (Anney et al. 2010; Avino and Hutsler 2010; Hu et al. 2011) it would be helpful to have more objective criteria for the diagnosis of ASD. The unusual doublet anatomy phenotype we describe here does portend to be a viable diagnostic biological marker for ASD. Because of the association between brain disorder and the biologically specified airways anatomy, we suggest that ASD is an embryologically specified disorder.

This explanation is also in accord with the high disease concordance observed with monozygotic twins. Biologic or genetic factors that cause reversed brain laterality during the development of the fetus could predispose carriers to develop breast cancer any time in later life (Klar 2011). Likewise, a biologic or genetic mechanism that causes abnormalities of brain development resulting in ASD most likely causes development independently of doublet branching patterns in the airways. The biology behind the association between ASD and an altered airways branching pattern should also be investigated. Pinkerton and Joad's (2000) detailed description of fetal lung development needs to be followed up with an in-depth exploration of the identification, morphogenesis, and genetics of doublets formation. Our study should help guide future research toward defining the genetic basis of the disorder.

Limitations and questions of the study

Although the age range was defined (2–13 years), there was no breakdown to age at time of bronchoscopy, or age when diagnosis of autism was made. Currently a diagnosis of autism may be suspected but will not be entertained through present subjective means until around age 2, while the average age for diagnosis of autism continues to be about 4 years. Future studies should be prospective, and should acquire data according to ages and events at diagnosis. Although there is no known cure, early intervention can reliably improve outcomes (Fennell et al. 2011; Strain and Bovey, 2011).

Our study did not break down the types/severity of autism/ASD by age. Are there any other correlations that might be made if the type/severity was known and charted? For example, does Asperger's Syndrome carry a discernibly different architecture than severe/profound autism? Future studies should also report and classify the relative prevalence and location of doublets. These data should be analyzed for further possible correlations and observations.

The authors did not conduct independent testing to diagnose autism. Future studies are required to test validity of our conclusions.

This study was done in a pediatric pulmonary clinic setting, geared toward children with chronic cough and serious underlying lung condition requiring a higher level of care. Further studies should avoid these limitations in establishing their criteria for admission to the study. Because of our selection procedure, the percentage of children with autism/ASD in our sample is higher than that found in the population at large.

Similarly, although we found that all 49 children with doublets also have autism/ASD, this is not to imply that this is a “perfect” diagnostic indicator of autism/ASD. Further bronchoscopy studies with larger populations to of children with reliable and valid autism diagnoses, and with greater controls of variables, might not yield the same results.

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Fig. 1.

Plates A (from a control subject) and B (ASD subject) were extracted from bronchoscopies of a right upper lobe. Plate A shows a picture of a normal lobe with three single, individual take-offs. Note that the two bottom branches are not doublets because the branches are not parallel to each other, and branch at different angles. Plate B shows three pairs of doublets, one pair in each segment. Both branches in each pair are parallel to that of the other, and thus appear to proceed to the same destination

Right Lower Lobe Airways

Fig. 2. Plates A (control subject) and B (ASD subject). Plate A illustrates a normal upper segment. The lower segment shows a fairly large branch to the *right* and a smaller branch to the *left*. Because they are highly asymmetric and differ greatly in size and shape, and branch at different angles, they are not doublets. Plate B contains multiple doublets. The lower segment divides into two branches. Moreover, doublets appear in each branch

Fig. 3.

Both Plates A (control subject) and B (ASD subject) represent the left upper lobe. Plate A demonstrates slight compression of the inferior segmental bronchus, but otherwise the anatomy is normal. Plate B representing upper segmental bronchus demonstrates a clear doublet in the superior aspect with a pattern similar to Figs. 1 and 2 of ASD subjects. The inferior doublet contains a small amount of mucus that semi-occludes the lumen of the inferior lateral space

Fig. 4.

Plates A (control subject) and B (ASD subject) represent the left lower lobe. Although the lower segmental branch in Plate A may appear to be a doublet, it is not a doublet: the branches are not symmetric, one branch appears to be larger than the other, and their angles are different. In Plate B, clear doublets are noted in the left lower lobe