Advancing the Care of Children and Adolescents with Severe Obesity: A Reason for Clinical Subtyping

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Childhood obesity, a serious and urgent public health problem, affects 17 percent of children in the United States, almost a third of whom have severe obesity defined as an age and sex-specific body mass index above the 99th percentile on the 2000 Centers for Disease Control and Prevention growth chart (Ogden et al., 2014). The prevalence rates of children with severe obesity are increasing rapidly, with significant disparities noted: Higher rates of severe obesity are reported among lower socioeconomic status and ethnic and racial minority groups. Even more concerning is that the rate of conversion from obesity to severe obesity over a 4-year period among Pennsylvania middle and high school students is 42-44 percent (Lohrmann et al., 2014). Severe obesity affects more children than autism spectrum disorders, cystic fibrosis, and cancer combined (Centers for Disease Control and Prevention, 2013; National Cancer Institute, 2013) and can have devastating consequences in childhood such as early atherosclerosis, obstructive sleep apnea, hypertension, type 2 diabetes, metabolic syndrome, fatty liver disease, psychological problems, and a greater risk for obesity in adulthood and premature death (Kelly et al., 2013).

The medical, emotional, and financial burdens associated with obesity signal an urgent need for effective treatment modalities alongside multi-sector prevention efforts, a focus of the Institute of Medicine’s Roundtable on Obesity Solutions. Unfortunately, children with severe obesity respond poorly to current conventional lifestyle interventions, the treatment option most commonly available to them. As a result, weight loss surgery is being relied on more frequently as a treatment. From 2000 to 2009, the rate of the adolescent weight loss surgery increased by 300 percent (Steele, 2013); however, the number of bariatric surgeries performed is small (a total of 1,009 surgeries in 2009) given the large proportion of adolescents who may be eligible for this intervention. Long-term outcomes of adolescent bariatric surgery are still not well understood (Black et al., 2013). Although surgery can be an effective treatment, it is not without significant risk of morbidity. The procedure may not be desired by the family or the child or may be an inappropriate treatment option because of the child’s young age, lack of pubertal or emotional maturity, or cognitive impairments. In addition, bariatric surgery is not accessible to most families due to the limited number of adolescent programs.

Given this scenario, as a society we are compelled to make a concerted effort to identify effective medical treatment options for this vulnerable subset of children with severe obesity. Their poor response to lifestyle intervention may be due to our current approach that assumes that all children and adolescents with obesity or severe obesity are a homogenous group. Based

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http://nam.edu/wp-content/uploads/2015/06/obesitysubtyping
on our knowledge of other chronic disorders such as autism spectrum disorder and schizophrenia, this assumption is likely flawed (Betancur, 2011, Ehrenreich and Nave, 2014). As with these disorders, obesity presents a complex web of molecular, pathophysiological, and epidemiological pathways that extends beyond the simple mantra of “energy in and energy out.” Indeed, the literature indicates an intricate interplay between genes, epigenetic influences, child and family characteristics, and the environment that determines risk factors and response to treatment (Katzmarzyk et al., 2014).

These observations suggest characterizing this population of children with severe obesity to be the first step to unraveling appropriate treatment options. In doing so, we expect an emergence of subtypes or phenotypes that can be further studied and can serve as a basis for interventions. Such an endeavor, when properly implemented, has been proved invaluable in advancing the field. An example is the development of a phenotypic classification for urologic and chronic pelvic pain syndromes (Shoskes, et al., 2009). A “phenotype” refers to the observable traits of an organism. This can include deviations in normal genetics, physiology, morphology, or behavior that reveal a pattern of characteristics classifiable as a disorder or disease based on etiological pathways on which subtypes can be delineated. In turn, treatment protocols may then be applied, or new areas of genomic research informed (IOM, 2015). The first step in this process is pooling the knowledge, expertise, and evidence available about this population of children.

The American Academy of Pediatrics (AAP) Institute for Healthy Childhood Weight (IHCW) and the Children’s Hospital Association (CHA) have partnered to embark on a process of clinical subtyping for severe obesity, drawing on the greatest strengths of their members: clinical experience and expertise. They have convened the Expert Exchange, an interdisciplinary group of experts from tertiary care obesity programs at 21 children’s hospitals across the country. The initial effort will address children aged 0 to 5 years. Given our current body of knowledge, children who present with severe obesity by age 5 are a subgroup that is distinct and rare enough to potentially offer a number of specific subtypes. This age group allows for broader introspection of etiological and clinical characteristics across several stages of the life cycle: prenatal, natal, postnatal, early infancy, toddlerhood, and preschool phase. It also cuts across several developmental stages, environmental settings, and caregivers.

In the absence of a systematic genetic mapping effort for severe obesity, recognizing clinical patterns may offer an initial framework for subtyping on which researchers and geneticists can continue the task of phenotyping. This is a commendable first step, but there are several important considerations:

1. The process of subtyping will need to begin with a careful review of the literature incorporating different study designs and populations. The current literature on severe obesity in early childhood is limited; therefore, the Expert Exchange may be challenged in defining an “a priori” set of inclusion or exclusion criteria that will allow for a meaningful body of literature. A broader set of criteria that includes, for instance, studies of young children with obesity—and not only severe obesity—may be unavoidable. Most studies will be clinic-based and at risk for ascertainment bias; consequently, the data may not accurately reflect the true incidence of the risk factors or characteristics in the population. As certain subtypes may change or vary as children grow and develop new social and motor skills, cohort effects will be important to consider in the review. For example, children with a
predisposition for appetite dysregulation may present differently during periods of normal, rapid, or slow physiological growth seen at certain chronological ages.

2. Information from case studies, cross-sectional studies, and longitudinal observational studies should be used to develop initial group characteristics. Although the methodologic rigor of these types of studies is sometimes questioned, they offer several advantages for clinical subtyping. Historically, they have catalyzed our progress in identifying new disorders, understanding the epidemiology of several conditions and developing or refining treatments. In addition, with longitudinal observational studies, the stability of identified risk factors or characteristics can be studied.

3. This endeavor should include qualitative feedback from clinicians, the families, and the children, if possible, as the information garnered will be crucial in determining how individual characteristics may form recognizable subtypes. The perspective of clinicians who treat young children with severe obesity will be invaluable in capturing the nuances of experiential knowledge. A semi-structured interview or focus group study will yield helpful information to support the extant literature and illuminate which combinations of symptoms, signs, and patient characteristics can be used to arrive at subtypes. A similar process should also be carried out with the families of these children. If the study is limited to providers at tertiary care obesity programs often seen at children’s hospitals, it will be important to acknowledge the risk of health care access bias. The variability of expression of characteristics has to be accounted for in this work. Even in conditions due to a single gene mutation, not all individuals will demonstrate the characteristics of the condition consistently or have all of them present. How this concept should be handled when clinically subtyping is complex, as even wider heterogeneity is to be expected compared to genotyping. Perhaps the process used to subgroup diseases such as asthma into distinct clinical entities may offer a useful guide.

4. Considerations for further work in this area should include studies on molecular and pathophysiological etiological pathways, identifying appropriate comparison groups, and study designs that allow for empiric testing of any proposed subtypes. It will also be helpful to investigate the sensitivity and specificity of proposed subtypes.

The Expert Exchange initiative by the AAP IHCW and CHA is a tangible opportunity to advance the field, especially with regard to clinical care. The current deficit in our knowledge about early-onset childhood obesity makes young children with severe obesity an appropriate population to study and is a timely and reasonable first step, even in the face of methodological challenges. If successful, this initiative will: (a) offer an opportunity for thoughtful discussion on subtyping, and (b) identify subtypes that can then be confirmed, rebutted, or refined using additional studies. As this work evolves, the AAP IHCW and CHA will need a cogent plan to involve basic scientists and clinical researchers, as well as health, educational, and community systems, as the vision is that identifying clinical subtypes will ultimately lead to genetic/metabolic/environmental mapping. In summary, this work will provide a promising framework on which further research and treatment can be based.
REFERENCES


