Comorbid Psychiatric Aspects of Bainbridge-Ropers Syndrome

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ABSTRACT

Objective: Bainbridge-Ropers syndrome (BRPS) is a neurodevelopmental genetic disorder associated with mutations in the additional sex combs–like *ASXL3* gene on chromosome 18q12.1. The objective of this study is to describe the comorbid psychiatric aspects of BRPS.

Methods: A retrospective review was conducted of the electronic medical records of patients diagnosed with BRPS from 2013 to 2020 at an academic medical center. Results were deidentified and presented as frequencies and percentages.

Results: Seven cases (5 White males and 2 White females) of BRPS were identified. The mean age at the time of referral was 12 years, while the mean age at diagnosis of BRPS was 7 years. Comorbid psychiatric symptoms and diagnoses associated with BRPS included global developmental delay: 6 (86%), sleep impairment: 5 (71%), autism spectrum disorder: 3 (43%), speech impairment: 2 (29%), disruptive behavior: 4 (57%), attention-deficit/hyperactivity disorder: 3 (43%), self-injurious behavior: 3 (43%), aggression: 4 (57%), and seizures: 3 (43%). All 7 patients (100%) had multiple *DSM-5* diagnoses.

Conclusions: These data highlight the need for awareness of the psychiatric comorbidity of BRPS. The findings also underscore the need for further research and emphasize the importance of multidisciplinary collaboration in the prompt assessment, diagnosis, and management of patients presenting with BRPS.

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Bainbridge-Ropers syndrome (BRPS) (Online Mendelian Inheritance in Man[1] [OMIM] #615485) is a novel genetic condition due to alteration in the function of the additional sex combs–like *ASXL3* gene on chromosome 18q12.1, which is probably caused by denovo mutation in the *ASXL3* gene during egg or sperm development prior to fertilization.[2] Additional sex combs–like (*ASXL*) proteins are mammalian homologs of addition of sex combs (*ASX*), a protein that regulates the balance of trithorax and polycomb function in Drosophila.[2] BRPS was first described in 2013 by Bainbridge et al.[2] It is characterized by severe feeding difficulties, failure to thrive, and neurologic abnormalities with significant developmental delay. Although all 4 subjects first described by Bainbridge et al[2] shared similar clinical findings, these characteristics were mostly nonspecific but distinct craniofacial features such as prominent forehead, arched eyebrows, and hypertelorism. For example, the severe feeding difficulties present from birth requiring intervention occurred in 3 of 4 subjects. The subjects were a small size at birth (3 of 4), with microcephaly (3 of 4) and severe psychomotor delay, with missed milestones (4 of 4) at their most recent evaluation. Deep palmar creases (4 of 4) and slight ulnar deviation of the hands (3 of 4) combined with a high arched palate (3 of 4) were also common.[2]

The *ASXL3* gene has a functional role in the process of deubiquitination and is also expressed in several organ systems including the central nervous system.[3] Although the function of the *ASXL3* gene/protein is still a subject of continuing research, there is emerging evidence that it may modulate early brain development among other functions.[3]

There are approximately 30 cases documented in the scientific literature so far, while a total of 200 cases are estimated to exist worldwide, mostly in children and adolescents[4] and more recently in a middle-aged adult.[5] A *ASXL3* support group for BRPS families currently has approximately 180 registered families with a child that has an *ASXL3* variant.[4] The risk of behavioral and psychiatric symptoms is increased in persons with neurodevelopmental disorders, particularly those with underlying genetic conditions.[6] However, relatively little has been published on the psychiatric phenotype of BRPS. Thus far, some behavioral phenotypes mentioned, in no order of occurrence, include severe intellectual disability, nearly absent speech and language, hypotonia, and feeding difficulties as well as aggressive and autistic traits with rocking and hand flapping, periodic agitation, and sleep disturbances.[2,4,5] In a minority of the patients, tonic-clonic seizure or absence seizure occur in childhood.[5,7–10]

Given the paucity of literature regarding the prevalence of comorbid psychiatric issues associated with BRPS,[2,4,5,7–10] this article aims to add to the body of literature by describing the comorbid psychiatric aspects of BRPS.

Clinical Points

- Common comorbid psychiatric issues associated with Bainbridge-Ropers syndrome include global developmental delay, sleep impairment, disruptive behavior, autism spectrum disorder, attention-deficit/hyperactivity disorder, self-injurious behavior, and aggression as well as seizure and speech impairment.
- Given that Bainbridge-Ropers syndrome affects multiple systems, early identification and prompt referral to a multidisciplinary team including the medical geneticist is critical to reduce the morbidity associated with the condition.

METHODS

This study was conducted in accordance with the Declaration of Helsinki, and appropriate Institutional Review Board approval was obtained. A waiver of informed consent was deemed appropriate by our institution. We conducted a retrospective review of patients diagnosed with BRPS between 2013 and 2020 at an academic medical center. The search was conducted using the health information technology electronic medical record search engine program. The clinical notes (dictated or typed) within the electronic medical record were reviewed.

Deidentified data including demographic information such as age, ethnicity, race, sex, and age at diagnosis were captured in addition to the physical examination and psychiatric problem list. Data were deidentified and presented as frequencies and percentages.

RESULT

Seven patients with a BRPS diagnosis were identified (Table 1). All of the patients met the clinical diagnostic criteria for BRPS and 6 were confirmed with a genetic test at the time of this writing.

The mean age of the patients with BRPS at the time of referral was 12 years old, while the mean age at diagnosis was 7 years old. The age range of the patients was from 6 to 24 years. There were 5 male patients and 2 female patients with BRPS (see Table 1). Common comorbid psychiatric issues associated with BRPS included global developmental delay: 6 (86%), sleep impairment: 5 (71%), autism spectrum disorder: 3 (43%), speech impairment: 2 (29%), disruptive behavior: 4 (57%), attention-deficit/hyperactivity disorder: 3 (43%), speech delay: 2 (29%), self-injurious behavior: 3 (43%), aggression: 4 (57%), and seizure: 3 (43%). All 7 (100%) had multiple *DSM-5* diagnoses. The race of the patients was non-Hispanic White: 7 (100%).

Table 1. Demographics, Clinical Characteristics, and Associated Comorbid Aspects of Bainbridge-Ropers Syndrome (BRPS)

Variable	Patients With BRPS (N = 7)
Demographics	
Age (at time of review), mean, y	12
Age at diagnosis, mean, y	7
Age range, y	6–24
Male, n (%)	5 (71)
Female, n (%)	2 (29)
Non-Hispanic White, n (%)	7 (100)
Physical signs, n (%)	
Low-set ears	3 (43)
Down-slanting palpebral fissures	2 (29)
Prominent forehead	2 (29)
Scoliosis	2 (29)
Prominence of philtrum	2 (29)
Microcephaly	1 (14)
Macrocephaly	1 (14)
Upturned nose	1 (14)
Flattened philtrum	1 (14)
High arched palate	1 (14)
Preauricular pit	1 (14)
Café au lait spots	1 (14)
Comorbid psychiatric aspects/conditions, n (%)	
Global development delay	6 (86)
Sleep impairment	5 (71)
Disruptive behavior	4 (57)
Aggression	4 (57)
Autism spectrum disorder	3 (43)
Seizures	3 (43)
Self-injurious behavior	3 (43)
Attention-deficit/hyperactivity disorder	3 (43)
Speech impairment	2 (29)
Multiple *DSM-5* diagnoses	7 (100)

DISCUSSION

BRPS is an autosomal dominant genetic condition due to alteration in the function of the additional sex combs–like *ASXL3* gene on chromosome 18q12.1.[2] The function of the *ASXL3* gene/protein is still a subject of discussion within the scientific community, with some data showing that it may help with modulation of early brain development among other things.[3] Aside from the first 4 described cases by Bainbridge et al,[2] the largest published case series[4] examined 12 subjects and described the common physical signs and medical issues associated with BRPS.

Research[3] has suggested that BRPS may be associated with variable physical and neurologic symptoms including seizures 3 (43%). A report by Verhoeven et al[5] described the case of a 47-year-old severely intellectually disabled man who developed late-onset partially treatment-resistant tonic-clonic epilepsy in his 40s.

Furthermore, there is ample evidence showing that psychiatric disorders tend to cluster among families, suggesting a need to characterize the psychiatric manifestations of genetic anomalies.[6] There is a complex interaction between genes and behavior among humans. As previously noted, the literature is sparse regarding the prevalence of comorbid psychiatric issues observed in patients with BRPS. Just like the first case described by Bainbridge et al,[2] the first subject within our sample was diagnosed in 2013.

Previous studies[4] reported an average age at diagnosis of 11 years old, which was similar to the mean age of 12 years old noted in our patient cohort, with an age range of 4 to 20 years. Our study had a preponderance of male cases: 5 (71%) boys versus 2 (29%) girls. This finding is at

odds with a prior study[4] that reported 5 (42%) male and 6 (50%) female subjects with BRPS. We are not sure what the implication of this sex difference suggests. It appears that the older patients in our sample (the oldest being aged 24 years) may have had their diagnosis missed when they were younger, since the first case documented in the literature was in 2013.

Sixty-eight percent of our patients had global developmental delay. Genetic disorders presenting in early childhood are estimated to cause approximately a quarter of cases of global developmental delay.[4] Balasubramanian et al[4] reported that patients with BRPS are prone to having intellectual disability and delayed walking.

Our study revealed sleep impairment in 71% of patients, which is a similar finding to that of prior research.[4] Sleep problems have been documented in children with neurodevelopmental disorders.[11] It has been speculated that hypotonia may contribute to sleep apnea in these children, which was confirmed in our case series by referrals for sleep study. Forty-three percent of our subjects had autism spectrum disorder diagnosis, which was also observed previously.[4] Autism spectrum disorder may exhibit genetic heterogeneity by being caused by both de novo gene mutations and inheritable means.[3]

Twenty-nine percent of our patients had speech impairment described mostly in terms of delayed speech. In addition, 43% exhibited self-injurious behavior and 57% demonstrated aggression. Research in the autism spectrum disorder population has shown increased incidence of speech impairment, self-injurious behavior, and aggression.[5]

We were unable to delineate prevalence of obsessive-compulsive disorder, generalized anxiety disorder, depression, or suicidality, and little information is known about their prevalence in BRPS patients. One plausible explanation for the lack of data is that anxiety and depressive symptoms could be hard to delineate in patients with developmental delays including autism spectrum disorder, particularly those with very limited verbal skills. Nevertheless, it can be difficult to tell whether a symptom (such as repetitive questioning) is part of an anxiety disorder or the genetic syndrome itself. Thus, it is important to carefully assess changes in behavior from baseline, especially the neurovegetative symptoms (ie, disturbances in sleep, changes in appetite and energy level) and obtain as much qualitative information as possible. Also, it is possible that subjects with no speech/language impairment might better convey their depressive/anxiety feelings than a neurodevelopmentally challenged or autistic child with limited language ability.[6]

Another limitation of our study is the retrospective observational design in which we reviewed the problem list and charts of BRPS cases within our institution with pediatric genetic and other specialties' referral, diagnosis, and treatment. No detailed neuropsychological battery or assessments were incorporated, as they were not completed or available on file during our review.

This study reveals that it is likely atypical for a patient with BRPS to not have comorbid psychiatric symptoms. The presence of comorbid psychiatric issues associated with BRPS should be expected when managing patients with this syndrome. It is imperative that a thorough mental health evaluation be offered promptly to patients with suspected BRPS to ensure appropriate and prompt management of any behavioral or psychiatric sequelae. Additionally, attention should be paid to sleep impairments often of the sleep apnea type, which may be related to hypotonia that is highly prevalent in patients with this syndrome.[11] More studies on BRPS are needed to further elucidate the impact of these findings with regard to the management of these patients.

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