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15q11.2 Deletion Syndrome: Expanding the Phenotype

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ABSTRACT

Background: Although multiple reports exist in the literature of patients with 15q11.2 deletion syndrome, the variability of the phenotype has made clinical delineation difficult. Neuro-developmental scores have not been previously reported. We present clinical findings in a group of 16 patients referred to our center for evaluation and management of neurodevelopmental difficulties. **Methods:** All patients were seen in our center between 2005 and 2016. They were seen by a clinical geneticist and their diagnosis of 15q11.2 deletion syndrome was confirmed by a microarray analysis. Bayley Scales of Infant Development was done and provided a mental developmental index and a motor developmental index. The data collected was then compared to previous reports in the literature of patients with 15q11.2 deletion syndrome. **Results:** The reviewed group consisted of 10 males and 6 female patients between the ages of 3 and 15 years. The most common clinical findings included developmental delay (94%), hypotonia (88%), ADHD (75%), anxiety (50%), feeding difficulties (44%), autism (31%), dolichocephaly (25%), 2-3 toe syndactyly (19%), seizure activity (19%), and congenital heart disease (13%). Additional findings included prominence of the metopic suture, epicanthal folds, micrognathia, ankle torsion, incontinence, and sleeping difficulties. Our developmental evaluation by the Bayley Scales of Infant Development indicated an average Mental Developmental Index of 75 (NL = >85) and Motor Developmental Index of 75 (NL = >85) in the patients less than 3 years old. Close to 43% of patients had an occipito-frontal circumference (OFC) greater than or equal to the 97th. **Conclusion**: The data provided here intends to expand the phenotype of the 15q11.2 deletion syndrome. Neurodevelopmental scores have not been previously reported in 15q11.2 del syndrome which were found to be in the mild developmental delay range.

Keywords: 15q11.2, deletion, phenotype

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INTRODUCTION

First reports of the clinical significance of the 15q11.2 deletion (Del) were made by Murthy and collaborators in 2007[1]; they described 2 consanguineous individuals. Additional reports rapidly follow (Doornbos et al. 2009; Von der Lippe et al. 2011)[2,3]. Each of these reports established a precedence of developmental, behavioral, and neurological issues in individuals with 15q11.2 Del. Subsequently, epilepsy, schizophrenia, and autism were independently reported (de Kovel et al., 2010, Stefansson et al., 2008; Rees et al, 2014, and Chaste et al, 2014)[4,5,6,7]. Cafferkey in 2014[8] emphasized general developmental delay, motor delay, and speech delay as important features of 15q11.2 Del syndrome. Cafferkey data[8] was confirmed by Cox and Butler in 2015[9].

Over 200 patients have been recognized with the 15q11.2 Del syndrome. The majority of affected individuals exhibit some form of abnormal findings (Cox & Butler, 2015)[9]. It is estimated that this deletion is inherited from a phenotypically unaffected parent in 51% of cases, from a phenotypically affected parent in 35% of cases, and de novo in 5-22% of cases (Cox & Butler, 2015) [9]. The penetrance of this condition is estimated to be 10.4% (Rosenfield, 2013)[10]. Copy number variants with high de novo frequencies often exhibit a higher penetrance (Cox & Butler, 2015) [9].There is no sex preference in the phenotype of the 15q11.2 Del syndrome, and the sex ratio for patients with and without the disorder is equivalent (Cafferkey et al, 2014)[8]. All patients included in this report are de-novo cases.

Because of the subtle physical features seen in affected individuals, this condition may escape recognition. Patients may not be referred to Medical Genetics for evaluation and testing. As more patients are recognized, the emerging phenotype suggests that this should be a recognizable pattern of abnormalities. The most common features include developmental, motor, and language delays; behavior and emotional problems; attention deficit disorders, and autism spectrum disorder. Other features may include congenital heart disease, clefting, broad forehead, ataxia and seizures. The neurocognitive and motor functioning of affected individuals has not been reported in the past. We present a unique set of Bayley Scales scores.

MATERIALS AND METHODS

Data was collected from 16 patients confirmed to have 15q11.2 microdeletion seen at the Medical Genetics and Neurodevelopmental Center at Peyton Manning Children's Hospital between 2005 and 2016. Patients were referred for behavioral issues, developmental delays, failure to thrive, and dysmorphic features. The group age range was between 3 and 15 years, and the sex distribution was 10 males and 6 females.

All patients were confirmed to have 15q11.2 deletion in the BP1-BP2 region (Table I shows deletion size and laboratory used for testing).

TABLE I Key: Del = Deletion, Kb=kilobases, lab: laboratory performing test

Patient	Min Interval	Del Size (Kb)	Lab
1	21,268,793-21,474,181	205.39	Signature
2	22,822,019-23,085,219	263.2	Signature
3	22,822,019-23,085,219	263.2	Signature
4	20,372,901-20,636,841	263.94	Signature
5	20,372,901-20,636,841	263.94	Signature
6	20,372,901-20,636,841	263.94	Signature
7	20,372,901-20,636,841	263.94	Signature
8	20,372,901-20,636,841	263.94	Signature
9	22,765,628-23,353,677	271	Gene DX
10	22,815,306-23,086,303	271	Gene DX
11	22,815,306-23,086,303	271	Gene DX
12	22,770,421-23,281,363	406	AMBRY
13	22,770,421-23,281,364	406	AMBRY
14	22,698,522-23,191,062	493	Gene DX
15	22,698,522-23,191,062	493	Gene DX
16	22,698,522-23,198,655	500	Gene DX

The interval of these deletions varied from 21,268,793 to 23,198,655 and the deletion sizes varied from 205.39 to 500 Kb. All patients were evaluated by a clinical geneticist. Their development was assessed by the Bayley Scales of Infant Development and the Kauffman Brief Intelligence test. The diagnosis of Autism and/or Attention Deficit Disorder was confirmed by a Nerro-psychology evaluation.

RESULTS

Table II summarize our clinical observations. Growth and developmental delays, dymorphic features, behavioral and psychiatric concerns, and other congenital abnormalities were prevalent in our cohort.

TABLE II: Key: MRI= Magnetic Resonance Imaging, OFC= occipito frontal diameter, VSD: ventriculoseptal defect, OGV= of great vessels

Finding	Cox & Butler 2015 (%)	Escobar et al, 2017 (%)
Developmental Delay	73	94
Speech Delay	67	56
Academic Learning	60	69
Behavioral Problems	55	50
Dysmorphic Ears	46	75
Thick Helixes		45
High anti-tragus		75
Prominent		75
Palatal Anomalies	46	13
Abnormal MRI	43	0
Attention disorder	35	75
Autism	27	31
Seizure Disorder	26	19
Other Findings:		
Generalized Hypotonia		88
Anxiety		50
Feeding Difficuleties		44
Hypothyroidism		6
Dysmorphic Findings		
Craniofacial		
Broad Forehead		88
Epicanthal Folds		69
OFC > 97 %ile		43
Thin upper lip		38
Facial asymmetry		31
Micrognathia		31
Cardiovascular		
VSD		6
Transposition OGV		6
Musculoskeletal		
Ankle torsion		88
Camptodactyly of 5th digit		18
Other		
Nocturnal Enuresis		25
Sleep Disorder		12

The group consisted of 10 males and 6 females between the ages of 3 and 15 years. Developmental delay was seen in 94% of the cases, generalized hypotonia in 88%, speech delay in 56%, feeding difficulties in 44%. Our developmental evaluation by the Bayley Scales of Infant Development indicated an average Mental Developmental Index of 75 (NL= > 85) and Motor

Developmental Index of 75 (NL= > 85). In terms of facial dysmorphism, 88% had broad forehead, 69% epicanthal folds, and 43% OFC greater than the 97th percentile, 38% thin upper lip, 31% facial asymmetry, and 31% micrognathia. General dysmorphic features also included ankle torsion (88%), dysmorphic ears (75%), 2-3 toe syndactyly (19%), congenital heart disease (13%), and palatal abnormalities (13%). Behavioral and psychiatric concerns included ADHD (75%), academic learning problems (69%), generalized behavioral problems (50%), anxiety (50%), and autism (31%). Other abnormalities included seizure disorders (43%), nocturnal enuresis (25%), sleep disorders (12%), and hypothyroidism (6%).

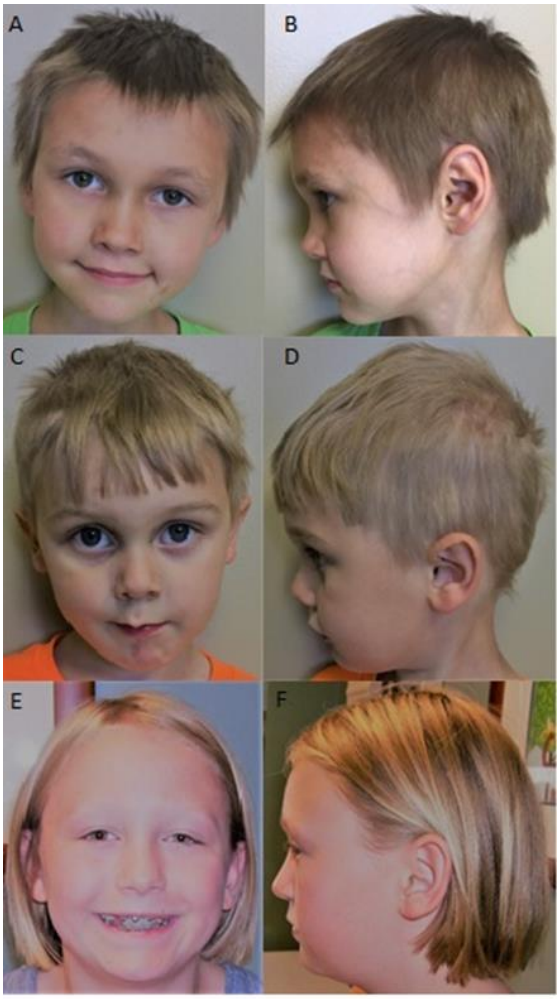

Figure 1:Notice mild dysmorphology: Broad forehead (A, C, E) Downslanting eyebrows (A, C) Short upturned nose (A, C) short nose (E), Smooth philtrum (A, E), Posteriorly set ears (B, D, F), Over folded helix (B, D, F), antitragus hypoplasia (B, D, F), mild micrognathia (B, D, F).

DISCUSSION

It is recognized that a pattern of dysmorphological and neurobehavioral abnormalities result from 15q11.2 chromosomal microdeletion. However, the extent of the phenotype is not clearly recognized. This is in part to due to the wide variability, expressivity and penetrance of this rare condition. Our observations present further information on the clinical implications of the 15q11.2 Del and expand the current known phenotype.

Chromosome 15 contains low copy DNA repeats in the proximal part of the long arm that can result in mispairings that cause duplication and deletions. Deletions in this region typically occur between three breakpoints: breakpoint 1 (BP1), breakpoint 2 (BP2), and break point 3 (BP3)

(Cook et al., 1997;Repetto et al.,1998)[11,12]. Deletions that involve BP1 and BP3 are classified as type 1 and deletions involving BP2 are classified as type 2. Other conditions such as Prader-Willi syndrome (PWS) and Angelman syndrome (AS) share the distal BP3, but the proximal breakpoint is BP2 for PWS and BP1 for AS (Butler et al., 2004)[13]. The 15q11.2 deletion traditionally involves NIPA1, NIPA2, CYFFIP1, and TUBGCP5, which are non-imprinted, highly conserved genes between breakpoints 1 (BP1) and 2 (BP2) (Doornbos et al., 2009)[2]. NIPA1 has been associated with autosomal dominant paraplegia and magnesium ion transport in neuronal tissue, NIPA2 with renal magnesium ion transport (and possible other unknown effects), CYFFIP1 with fragile X syndrome, and TUBGCP5 with behavioral phenotype such as ADHD and OCD (Chen et al., 2005; Rainier et al., 2003; Goytain et al., 2007; Jiang et al., 2012; De Wolf et al., 2013; Hagerman & Hagerman et al., 2002). To discern the causative mechanisms of pathology in 15q11.2 Del syndrome functional gene studies to establish the pathogenic mechanisms involved. Candidate genes should include NIPA1, NIPA2, CYFFIP1, and TUBGCP5.

Data from our center adds to the findings by Cox & Butler form 2015[9]. All observations suggest that indicators of the syndrome are most commonly developmental and speech delays, academic learning behavioral problems, mild dysmorpho- logy, palatal abnormalities, and attention disorders. We provide further observations that we believe are part of the expanding phenotype seen in 15q11.2 Del affected individuals (Table II) summarizes our findings. As the phenotype expands, clinicians should be able to recognize individuals at risk.

Our findings confirm the need of prompt referral to a medical geneticist of patients with neurodysfunction and mild physical phenotypic variances at risk of microdeletion syndromes. Early recognition of patients with 15q11.2 Del syndrome would allow the guidance for appropriate genetic testing, management of their pathology and avoidance of unnecessary evaluations. The combination of Hypotonia, ADHD/autism, Developmental Delay and mild dysmorphology should alert the clinicians to the diagnosis of 15q11.2 microdeletion syndrome. In expanding the phenotype of this syndrome, we might be able to provide more defined and standard physical and behavioral phenotype for the 15q11.2 Del syndrome. Recognition of the clinical risks involved will improve patient management.

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