

A Review of Neuropsychological Findings in Coffin-Siris Syndrome

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ABSTRACT

Coffin-Siris Syndrome (CSS) is a rare genetic condition, with a variable display of phenotypes. Phenotypes can include physical, medical, and psychological impacts. Previous literature has focused primarily on genetic and medical characteristics of CSS, with little description of cognitive, emotional, behavioral and adaptive characteristics. Here, the psychological, neurological, and adaptive characteristics of CSS will be described as they appear through published literature.

Keywords: Coffin-Siris syndrome, Genetic disorders, Adaptive functioning, Psychology

Abbreviations: CSS: Coffin-Siris Syndrome

INTRODUCTION

Coffin-Siris Syndrome (CSS) is a rare, congenital malformation syndrome, with approximately 200 known cases worldwide Children's Hospital of Philadelphia [1]. To date, various studies have emerged discussing the genotypic and phenotypic elements of CSS, with little regard to social-emotional and behavioral functioning. Most researched has examined intellectual ability and developmental progression, but limited research has explained these differences from a neuropsychological framework. The purpose of the present study is to provide an overview of characteristics and genetic variations in CSS; discuss neuropsychological findings; and, to offer recommendations for future research on CSS.

CHARACTERISTICS AND GENETIC VARIATIONS IN CSS

The first reported case of CSS occurred in 1970 and indicated symptoms of intellectual disability (ID), delays in postnatal growth, lax joints and shortened fifth-digit phalanges with absence of the nail Coffin and Siris [2] With the expansion of case reports, researchers have identified and agreed upon five commonly reported features: Intellectual Disability (ID), Developmental Delay (DD), dysmorphic facial features and absence of hypoplastic fifth digit nails or phalanges Kosho [3-6]. Okamoto and Coffin-Siris Syndrome International Collaborators [7-11]. Additional identifiers can include: motor difficulties, speech impairment, growth impairment, low muscle tone, feeding difficulties in infancy, short stature, frequent infections, hypertrichosis, sparse scalp hair and physical anomalies in the heart, lungs and gastrointestinal tract [3-6]. Okamoto and Coffin-Siris Syndrome International Collaborators [7-12]. In

terms of facial features, individuals with CSS have been described as having a triangular facial shape, with a low frontal hairline, sparse scalp hair, bushy eyebrows and a wide mouth with a thin upper lip and thick lower lip Mari et al. [7].

However, some research has suggested significant variation in the phenotypic display of CSS. Particularly between 2012 and 2014, there was an attempt to define phenotypic facial features of CSS by creating two diagnostic types: Classical CSS (Type A) or Variant CSS (Type B) [8,10]. Type A is characterized by coarse facial features, with hypertrichosis, sparse scalp hair, dental anomalies, short stature, growth abnormalities, congenital heart defects and spinal anomalies. Type B individuals are identified as having thin eyebrows and a thin vermillion of the upper lip [10].

As research progressed, CSS was then associated specific genetic mutations associated with the BRG1/BRM associated factor (BAF), which are typically found on ARID1A, ARID1B, DPF2, SMARCA4, SMARCE1 and SMARCB1 [3,4,9,10]. In a 2017 study, reviewing a total of 150 patients with CSS, 100 of those patient demonstrating gene mutations in ARID1B, ARID1A, SMARCA4, SMARCB1 and SMARCE1 [3]. Since the discovery of BAF

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on a set number of genes, research has shifted its focus on understanding expressed differences between cases based on genotypic variations.

The most common mutation in CSS occurs on ARID1B [6,13]. Thus far, researchers have indicated that individuals with this mutation display a wide range of physical anomalies and intellectual deficits [6]. In one study, obesity, macrocephaly, hepatomegaly and hyperinsulinism were associated with the ARID1B gene mutation of other similar cases, individuals with the ARID1B mutation also experienced features of Autism Spectrum Disorder (ASD) and hypertrichosis [9]. Only a few cases displayed phalangeal differences [9].

The ARID1A genetic mutation has the most severe phenotypical outcomes, with absent speech and ID being trademark features [6]. This mutation also shows varying phenotypic expression in terms of facial features, but also displays various physical complications involving the cardiovascular, gastrointestinal and genitourinary systems [6,10]. Subsequently, hearing impairment was found in 33%, while visual impairment was found in 75% of individuals with the ARID1A gene variation. Individuals are also prone to frequent infection, hypotonia, Central Nervous System (CNS) structural abnormalities and absence of speech [6].

In individuals with the SMARCA4 mutations, mild growth impairment and difficulty sucking and feeding difficulties almost always occur [6]. Physically, all individuals in a sample of 12 displayed hypertrichosis, thick eyebrows, long eyelashes, ptosis, thick lower lip vermilion, pointed chin (noted in older ages) and hypoplastic fifth digits. Occasionally, a cleft palate occurred. Hypotonia and structural CNS abnormalities were typical. Sometimes, they had severe DD/ID, yet they typically walked independently and could sometimes speak [6].

The SMARCB1 mutation typically results in significant developmental and growth delay, with accompanying sucking and feeding difficulties [6,8]. Facial features tend to be the coarsest, with thick eyebrows, long eye lashes, wide or flat nasal bridge, thin upper lip vermilion and thick lower lip vermilion. Hypoplastic fifth digit nails and other nails occurred in every case in a sample of 13 participants [6]. Hypertrichosis and sparse scalp hair is also common. These individuals also displayed prominent distal phalanges and scoliosis. Hearing impairment was also common and visual impairment occurred in about 60% of cases. Gastrointestinal complications, including hernia, were also common, with occasional cardiovascular and genitourinary complications. Typically, these individuals had severe DD/ID and did not acquire any language [6].

The SMARCE1 gene is the rarest mutation in CSS and phenotypes tend to include: moderate to severe ID and DD, anomalies in organ systems and the Type A appearance, specifically with sparse scalp hair, coarse facial features and

absent or hypoplastic fifth digit phalanges or nails [6,8,10,11]. The SMARCE1 mutation also leads to a higher frequency of growth delays and feeding difficulties [6,11]. Often, these individuals experiences cardiovascular complications, visual impairment, interphalangeal joints, scoliosis, seizures and were prone to infection. Hypotonia, cleft palate and severe DD/ID occurred occasionally. All 12 participants learned to walk, but frequently did not speak [6].

Although not a primary member of the BAF complex, the ARID2 gene was also analyzed as it relates to the development of CSS phenotypes Bramswig [3]. Individuals with ARID2 mutations display ID, hypotonia, behavioral anomalies, mild hypoplasia on the fifth fingernails, pronounced hypoplasia of the fifth toenails, coarse facial features, large forehead, flat nasal ridge, broad nose with upturned nasal tip and a wide mouth with thick lower vermilion [3,14].

Due to the distinct variability between genetic mutations and the overlap of phenotypes with other neurodevelopmental disorders, the clinical criteria for CSS is yet to be fully determined [10]. Some researchers have suggested that regardless of genetic mutation or type displayed, all individuals with CSS display DD, ID, hypoplasia to the fifth digit nails or phalanges, feeding difficulties in infancy and hypertrichosis [7,8,10]. However, other researchers have suggested CSS features are shared with other congenital anomalies and display a wide range of clinical variability within the diagnosis [8].

NEUROLOGICAL FINDINGS

Previous reports of neurological findings in individuals with CSS indicated neural abnormalities in the brain midline, Dandy-Walker Syndrome (DWS), partial or full agenesis of the corpus callosum, wide inner and outer cerebral spinal fluid spaces, hypoplasia microencephaly, Arnold-Chiari malformations and other abnormalities of the central nervous system CNS [2-4,6,8,9,15,16]. According to a study in 2012, of 15 cases, 60% experienced microencephaly, 10% had DWS and 23% had agenesis of the corpus callosum [8]. Subsequently, Kosho et al. [6] reported in a sample of 32 individuals with CSS, 44% experienced seizures. In the same report, 73% of a sample of 33 individuals had hypotonia and approximately 92% of a sample of 26 individuals with displayed other central nervous system abnormalities [6].

A magnetic resonance imaging study in 2019 consisting of 11 patients with CSS revealed structural brain abnormalities, which included brain midline deficits and DWS, which leads to the malformation of the cerebellum and can affect the third and fourth ventricles [4]. Patients with the brain midline deficits also possessed the ARID1B, SMARCE1 and SMARCB1 gene mutations, yet two of the patients ARID1B mutations did not show any structural abnormalities. This finding is contrary to previous reports, as one study found

the 29% of CSS cases with ARID1B mutations has complete agenesis of the corpus callosum and 17.7% had partial agenesis [16]. Other reports have also included the prevalence of agenesis of the corpus callosum, but indicated it was found in majority of individuals with SMARCB1, SMARCA4, SMARCE1 and ARID1A gene mutations [6]. However, according to Kosho et al. [6] agenesis of the corpus callosum appears across all gene mutation a variation of CSS. Patients with the DWS were found to also have the SMARCE1 and SMARCB1 mutations per Fillatova et al. [4] report.

NEUROPSYCHOLOGICAL FEATURES OF CSS

The first reported case of CSS included an overview of three female children, who displayed similar phenotypes Coffin and Siris [2]. All cases had reportedly normal prenatal histories but ranged in their postnatal development and displayed severe intellectual disability. Two of the individuals never learned to walk, while one walked at the age of 3. All the individuals were committed to state institution Coffin and Siris [2].

According to Mari et al. [7], DD and ID are cardinal features in CSS. However, few studies have indicated neuropsychological-related functioning in children with CSS, beyond identifying ID or DD. In the past ten years, two independent case reports have been produced regarding neuropsychological functioning in individuals diagnosed with CSS [17,18] while nine additional studies have mentioned the possibility of co-occurring ASD, along with social-emotional and behavioral symptomology [6-11,14] (Table 1). Of the produced literature, it has been suggested children diagnosed with CSS display global developmental delays, language delays, gross- and fine-motor dysfunction, social-emotional challenges, behavioral difficulties and adaptive functioning [6-10,17] yet majority of these findings do not occur in the context of neuropsychological, developmental or social-emotional assessment measures. For example, Mari et al. [7] suggested individuals with CSS may display aggressiveness, hyperactivity, psychosis and traits of ASD.

Table 1. Previously reported developmental and psychological factors in CSS.

Studies	n	Age(s)	Gender	Gene Variation	Intellectual Quotient	Language	Gross-Motor	Fine-Motor	Psychological Factors
Bender et al. [17]	1	7.5	---	---	Estimated Low	Limited	Low	Low	PDD ^a , traits of ASD
Bramswig et al. [3]	2	7	Male	ARID2	Severe ID ^b	Absent		---	---
		4.5	Male	ARID2	---	Absent	Delayed	---	---
Coffin and Siris [2]	3	2	Female	---	8	Absent	Absent	Absent	---
		7	Female	---	26	Absent	Delayed	---	---
		8	Female	---	15	Absent	Absent	---	---
Kosho et al. [6]	8	---	---	ARID1A	Mild to Severe ID ^b	No words to sentences	75% not walking	---	60% behavioral abnormalities
		---	---	SMARCB1	Mild to Severe ID ^b	No words to sentences	56% not walking	---	50% behavioral abnormalities
		---	---	SMARCA4	Mild to Severe ID ^b	No words to sentences	10% not walking	---	88% behavioral abnormalities
		---	---	SMARCE1	Mod. to Severe ID ^b	No words to sentences	Normal	---	50% behavioral abnormalities
Krause and Rose-Grayson [18]	1	12	Male	---	Average	Delayed	Delayed	Low	ADHD ^c , ASD ^d
Schrier et al. [8]	80	---	---	---	40-69 1 child=97	Typically Delayed	Typically Delayed	---	ASD ^d symptoms
Shang et al. [14]	4	15	Female	ARID2	89	On-time	Delayed	---	ADHD ^c , anxiety
		8	Male	ARID2	50	---	Delayed	---	ADHD ^c , aggression
		6	Female	ARID2	---	Delayed	Delayed	---	Sound sensitivity
		8	Female	ARID2	---	---	---	---	ADHD ^c , tics
Swillen et al. [19]	12	2.5 to 19	9 Female 3 Male	---	Mild – Mod ^e ID ^b	Delayed	Normal	---	PDD ^a , OCD ^f , stereotypies, unusual fears
Vals et al. [9]	1	16	Female	ARID1B	---	---	---	---	---
Zarate et al. [11]	3	2	Male	SMARCE1	---	Absent	Delayed	---	---
		1	Female	SMARCE1	---	---	Delayed	---	---
		8	Female	SMARCE1	---	Delayed	Delayed	---	Hyperactivity

Note. Studies that did not include information regarding development or intellectual disability were excluded from the table This table includes several abbreviations: ^a PDD: Pervasive Developmental Disorder; ^b ID: Intellectual Disability; ^c ADHD: Attention Deficit Hyperactive Disorder; ^d ASD: Autism Spectrum Disorder; ^e Mod: Moderate; ^f OCD: Obsessive Compulsive Disorder

ASD has been the most theorized co-occurring psychological condition second to Attention Deficit Hyperactive Disorder (ADHD) [6,8-10]. In a sample of 7 individuals with CSS, autistic features were described in 71% [9]. In a more recent comprehensive review, one individual out of 23 participants was diagnosed with ASD, while another one showed some traits [6]. However, according to this same report, of 23 individuals: 65% displayed behavioral abnormalities, 31% were hyperactive, 9% engaged in self-injurious behaviors, 6% had a short-attention span and obsessionality also occurred in 6%. Findings surrounding ASD and other psychological diagnoses are significantly limited at this time. To further evaluate potential co-occurring psychological diagnoses and neuropsychological difficulties, studies within the context of psychological and developmental assessment are evaluated.

Prior to 2011, one study by Swillen et al. [19] evaluated development, behavior and social skills in a sample of 12 children. Results revealed 25% of these children displayed mild ID, while the remaining 75% had moderate ID. Of the 15 children included: five children were under the age of 6 years and seven children were between the ages 7 and 19. The younger children displayed a preference to visual-spatial materials over verbal materials and displayed severely delayed speech onset, with their first words occurring between ages 3 and 5. Out of the younger children, only one child could use more than eight words actively. Within the group of older children, all could speak in short sentences, while majority were able to use a full vocabulary and were able to comprehend language with ease. No differences in gross-motor functioning were found for either group. Socially, the younger group did not engage in much social contact with adults or peers, while the older group did not appear to have difficulties socializing. Parent and teacher rating suggested all children could engage in personal care, communication and social orientation, yet they struggled with task-orientation. Emotionally, the younger group displayed stereotypies and unusual fear, while the older children were more prone to obsessive interests and ritualistic behaviors. Of the total sample, two of the children displayed a clinically significant level of symptoms associated with Pervasive Developmental Disorder (PDD). Three children demonstrated subclinical levels of PDD and six did not have any indication of PDD. None of the children were assessed for ASD [19].

The most recent reports that involve assessment measures involve two individual case studies. In 2011, a 7.5 year old child diagnosed with CSS and comorbid partial epilepsy was administered a series of adaptive, developmental, social-emotional and behavioral tests [17]. IQ was not directly stated, but measures of adaptive functioning were generally [17]. Due to the overlap between IQ and adaptive functioning, it is predicted the child's IQ is below expected. In terms of this child's development, expressive language was limited to occasional single-word utterances, whereby

the child was required to use a Dynavox to express basic needs [17]. Receptive language was generally intact, but fine- and gross-motor skills were estimated to be at a low adaptive level. Further, the child was unable to fully control bladder and bowel movements. Parent raters did not endorse any emotional or behavioral challenges; yet social communication difficulties, stereotyped behaviors, self-stimulatory behaviors, restricted interests, play rituals and inappropriate use of objects were reported. However, researchers concluded the stated symptoms were better explained by the DSM-IV diagnosis of Pervasive Developmental Disorder, Not Otherwise Specified [17].

The most recent CSS case reported in 2018 included a 12 year old male diagnosed with CSS, accompanying fine motor ataxia, absent seizures (in-remission), and severe articulation difficulties. He further displayed emotional regulation difficulties, behavioral rigidity, restricted interests, poor adaptive functioning in terms of activities or daily living and sensory sensitivities [18]. His early childhood history was remarkable for low muscle tone, poor muscle control, early oral motor and associated feeding difficulties, delayed developmental milestones. A neuropsychological battery revealed an average Intellectual Quotient (IQ), yet tests of academic achievement, social functioning, executive functioning, attention and social/behavioral functioning indicated comorbid Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnoses of ASD with accompanying language impairment and without intellectual impairment, ADHD, combined type, Specific Learning Disorder in reading, written expression, and math, Developmental Coordination Disorder and Language disorder.

Conclusively, developmental, adaptive, social-emotional and behavioral findings are mixed. The most recent case studies are more suggestive of the presence of ASD and associated features, while prior literature has primarily focused on ID and DD. Future research should include measures of cognitive, academic, attentional, adaptive, behavioral and social-emotional functioning to further establish the comorbidity among CSS and psychological conditions.

DISCUSSION

When considering the neuropsychological impacts of CSS, all reported cases indicate DD, although severity varies [8,19]. Expressive language impairment appears to be the most prominent developmental delay in CSS, with one study indicating 63% of a sample of 30 individuals had no word speaking abilities, while 10% could speak several words and 27% could speak in full sentences [6]. Receptive language abilities are typically intact in individuals with CSS [8,17,18]. Motor impairments also tend to occur in individuals with CSS yet are less common and are typically resolved at some point in the individual's development. It is rare for an individual to experience soiling and urinary accidents with CSS.

Between all cases, IQ is variable ranging from ID to average. In a sample of 15 cases, IQ's ranged from 40 to 69, with only one individual at 97 [8], while in a sample of 32, 13% had mild ID and DD, 22% had moderate, 6% had moderate to severe and 59% had severe [6]. Thus, although ID is more likely to occur in individuals with CSS, it may not be a necessary diagnostic feature. In fact, researchers do not have a complete understanding of how gene alterations encoding the BAF complex lead to neurodevelopmental disorders or intellectual disability [4]. In addition, genetic variants are also associated with intellectual disability and other neurodevelopmental disorders. Thus, it can be difficult for healthcare professionals to parse apart CSS [4].

Continued research with the incorporation of neuropsychological evaluations is crucial in understanding the functioning of individuals diagnosed with CSS. Neuropsychological evaluations provide an overview of individual functioning in developmental, social-emotional, cognitive and behavioral contexts. Evaluation measures may include: a measure of intelligence or cognitive abilities, academic achievement tests, tests of expressive and receptive language, tests of early development, fine- and gross-motor assessments, objective measures of ASD symptoms, parent-report measures of emotional and behavioral functioning and tests of adaptive functioning [17,18].

When administered to a young child, neuropsychological measures can be used to gain an understanding of early development to provide early intervention recommendations. Re-evaluations can then track progress over time and provide follow-up treatment recommendations [10,18]. Further, neuropsychological evaluations are also useful in diagnosing co-occurring ASD symptoms. Previously reported cases have concluded individuals with CSS display self-stimulating behaviors, restricted interests, stereotypies, expressive language difficulties and fine and gross motor delays [17-19]. Early diagnosis can aid in creating a global approach in early intervention and therapy to optimize individuals with CSS's health, quality of life and intellectual potential [20].

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