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Autism spectrum disorder, social communication difficulties, and developmental comorbidities in Sturge–Weber syndrome

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ABSTRACT

Sturge–Weber syndrome (SWS) is a neurocutaneous disorder characterized by the combination of a facial naevus flammeus and pial angioma, often associated with learning difficulties and/or epilepsy. Here, we report on the neuropsychological characteristics of a cohort of 92 children with SWS seen at a national referral center between 2002 and 2015. Almost a quarter (24%) had a diagnosis of autism spectrum disorder (ASD), with 45% overall having evidence of social communication difficulties (SCD). Autism spectrum disorder was more commonly seen in those individuals with bilateral angioma ($p = 0.021$). Significant behavioral difficulties were reported in 50% while 26% had difficulties with sleep. Difficulties with social communication, behavior, and sleep were closely associated with one another. They were not, however, significantly associated with markers of epilepsy severity and were noted to occur even in children without epilepsy. The prevalence of ASD/SCD, sleep difficulties, and behavioral disorders seen in SWS is high and reflects the complex needs of this group.

1. Introduction

Sturge–Weber syndrome (SWS) is a neurocutaneous disorder characterized by the association of a facial naevus flammeus (port wine stain) with an underlying leptomeningeal angioma. It occurs sporadically and has recently been shown to be due to a postzygotic mutation of the *GNAQ* gene, which encodes a cell-surface signaling protein [1]. Symptoms frequently include epilepsy, headaches, glaucoma, hemiplegia, and developmental delay [2].

Anecdotally, autism spectrum disorder (ASD), as well as other difficulties with social communication, is known to occur [3,4]. Perhaps surprisingly, however, there have been limited attempts to quantify the prevalence of ASD in SWS. Several previous studies have noted a high incidence of emotional and behavioral problems among people with SWS, especially those who have epilepsy [4–8]: these have included mood disorders [4–6,8], disruptive behavior [4–8], substance misuse [8], and disordered sleep [8]. Evidence on the relationships among and between these comorbidities and other aspects of SWS such as epilepsy remains conflicting, but overall, there appears to be a strong correlation between difficulties with mood and behavior and seizures [4,5,7].

Great Ormond Street Hospital provides a national service for pediatric SWS in the United Kingdom. This study aimed to determine the prevalence of ASD and social communication difficulties (SCD) in a cohort of patients with SWS and to identify associated comorbidities and potential etiological risk factors with a view to optimizing the support and advice provided to young people with SWS and their families.

2. Methods

A retrospective case note review was carried out in patients with SWS attending a specialist multidisciplinary service providing diagnostic, assessment, and management for children with SWS from all over the UK. Children are followed and assessed prospectively by the service from referral, frequently in infancy, until transition to adult services. The assessment includes a comprehensive medical and developmental history; neurological examination; and cognitive, language, behavioral, and social communication assessments.

Assessments were documented using a structured pro forma which recorded basic demographics (age and sex), details of epilepsy control (seizure types within the last year, history of epilepsy surgery, and history

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; CCC2, Children's Communication Checklist, 2nd edition; DQ, developmental quotient; ESES, electrical status epilepticus in sleep; IQ, intelligence quotient; SCD, social communication difficulties; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; SWS, Sturge–Weber syndrome.

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of status epilepticus), presence or absence of hemiplegia, medication use, developmental and psychometric assessments, and parental concerns.

Data from the most recent assessment were reviewed retrospectively. Where relevant, previous assessments were also referred to. Radiology reports for the most recent magnetic resonance imaging (MRI) scan were analyzed to determine the extent and laterality of the pial angioma. To make statistical analysis possible, a binary classification of the angioma as mild (involving four or fewer lobes) or severe (involving five or more lobes) was used. Electroencephalography (EEG) reports were also reviewed where available.

Social communication assessment included a social communication history taken by an assessor trained in identification and classification of SCD, screening tools for social communication (Social Communication Questionnaire (SCQ) and/or the Children's Communication Checklist, 2nd edition (CCC2) completed by parents and/or the child's teacher), as well as the Autism Diagnostic Observation Schedule (ADOS or ADOS-2) when indicated. In the case of the CCC2, a Social Interaction Deviance Composite (SIDC) score of −15 or below or of −1 to −15 in combination with a General Communication Competence (GCC) score below 55 was considered indicative of SCD. For the SCQ, a score of 15/40 or above (the threshold generally used to trigger further assessment for ASD) was used.

The records were systematically reviewed for a description of SCD and/or a diagnosis of ASD from their most recent complete multidisciplinary team (MDT) assessment. The term SCD was used to describe children who presented with some difficulties in the areas of social interaction, communication, and/or restricted or repetitive behaviors but did not meet full criteria for an ASD diagnosis under DSM-5. The diagnosis of ASD was made on the basis of the social communication history, ADOS, and in some cases, social communication screening questionnaires completed by parents and teachers.

Every appointment included a review of developmental and psychological concerns. The psychometric assessment tools used varied depending on the age and developmental stage of the child, and on parental and clinical concerns. Intellectual and cognitive development was assessed in younger children using the Bayley Scales of Infant and Toddler Development (3rd edition), which is validated for children up to 42 months; the Griffiths Mental Development Scales (extended and revised), for children aged two to eight years; or the Wechsler Preschool and Primary Scale of Intelligence (4th edition), for two- to seven-year-olds. For older children, the Wechsler Intelligence Scale for Children (4th edition) was used. All these tests generated scores in the form of either an intelligence quotient (IQ) score or a developmental age equivalent. The latter could be converted to a developmental quotient (DQ) score using the formula (developmental age equivalent/chronological age) × 100. As there is no direct equivalence between DQ and cognitive composite scores such as IQ, these were analyzed separately.

Attention-deficit hyperactivity disorder (ADHD) was diagnosed through clinical assessment supported by the Conners' Parents and Teachers Rating Scale. For a smaller number of children, a diagnosis of ADHD had already been made by other services, external to the SWS clinic, and for the purposes of this study, this was accepted as valid.

The presence of behavioral and/or sleep difficulties was based on the interview with the parent or caregiver: the structured clinic pro forma included specific domains for any concerns about sleep or behavior. In some cases, results were available for the parental Strengths and Difficulties Questionnaire (SDQ), a screening tool for emotional and behavioral concerns with five subdomains (emotional distress, overall stress, peer relations, attention/hyperactivity, and behavioral difficulties). Each subdomain can be rated from “close to average” – a category designed to include 80% of typically developing children – to “very high”. Strengths and Difficulties Questionnaire results were considered to suggest difficulties in a given area when the score in that area was slightly raised, high or very high.

Patients with missing data were excluded via case-wise deletion from the relevant analyses. Chi-square statistics were used to analyze categorical differences between groups. Where assumptions for a Chi-square test are not fulfilled, Fisher's exact test is given. The Mann–Whitney *U* test was used for comparison of continuous variables between groups. Analyses were performed using SPSS statistical software version 21.0 at a significance level of 5% (SPSS Chicago).

This study was approved by Great Ormond Street Hospital Institutional Board (No: 1658).

3. Results

A total of 106 children had been seen by the SWS service between 2002 and 2015. Fourteen patients were excluded from the analysis for the following reasons: four were aged less than one year at the time of data collection; three had very limited clinical information available; and seven had a developmental age equivalent of less than one year, as most instruments for assessment of social communication and behavioral are not validated for this group. Therefore, records were available for 92 children aged between two and 19 years old who had been assessed in the SWS service.

Demographic characteristics of the group are summarized in Table 1. Where the denominator is less than 92, this indicates that data regarding the characteristic in question were missing for a corresponding number of children. Original MRI images were available in the majority of cases, but in some cases, we only had access to a summary report of MRI findings.

The prevalence of ASD was 24% (22/92), and SCD were described (including those in children with ASD) in 45% (41/92).

Autism spectrum disorder was more commonly seen in those children with bilateral angioma ($X^2 = 6.77$, df = 1, p = 0.021), and there was a trend for ASD to be present in those with more extensive angioma ($X^2 = 4.90$, df = 1, p = 0.065; Table 2). It was not, however, associated with presence of epilepsy or history of status epilepticus. The broader category of children with SCD did not show statistically significant association with any feature of the angioma or any feature of the epilepsy history.

Cognitive composite (IQ) data were available for 56 children with a mean score of 82.3 (SD: 17.1), and DQ was available for 15 children with a mean score of 47.9 (SD: 27.1). The total range of IQ and DQ scores was 7 (reflecting profound intellectual disability) to 127 (above average). The lower DQ scores reflect the fact that this assessment was used in children whose developmental level made them unable to participate in formal cognitive testing; besides very young children, this included older children with more severe developmental impairments who were outside the usual age limit of the assessment instrument used.

Formal assessments of linguistic ability were available for 83 children. Fifty-nine children were assessed using a cognition-based language composite score while 24 were assessed using a DQ-related language composite. Mean total language composite score was 80.9

Table 1
Characteristics of children in the study.

	Number (%)
Male	46/92 (50)
Severe pial angioma	13/89 (15)
Bilateral pial angioma	17/91 (19)
Right-sided angioma	31/91 (34)
Left-sided angioma	43/91 (47)
Epilepsy	78/92 (85)
Seizures in the last year	39/92 (42)
History of status epilepticus	49/77 (64)
History of epilepsy surgery	18/92 (20)
Hemiplegia	43/91 (47)
ASD	22/92 (24)
SCD	41/92 (45)
ADHD	5/92 (5)
Sleep difficulties	24/92 (26)
Behavioral difficulties	46/92 (50)