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Cognitive functioning in children and adults with Smith-Magenis syndrome

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ABSTRACT

Smith-Magenis Syndrome (SMS) is a genetic neurodevelopmental disorder caused by a microdeletion on chromosome 17p11.2. This syndrome is characterized by a distinctive profile of physical, medical and neuropsychological characteristics. The latter include general mental disability, with the majority of individuals falling within the mild to moderate range. This study reports a detailed cognitive assessment of children and adults with SMS with the use of the Wechsler intelligence scales at three distinct levels of analysis: full scale IQ, factorial indices, and subtests. Child and adult samples were each compared to samples of age and gender-matched typically developing individuals. To our knowledge, this is the first study to systematically analyse the cognitive profile of individuals with SMS in Southern Europe. The present study confirmed mental disability, particularly within the moderate category, as a consistent feature of children and adults with SMS. Furthermore, both child and adult samples evidenced significant impairments in all four indices when compared with their typically developing counterparts. A specific pattern of strengths and weaknesses was discernible for both samples, with Verbal Comprehension emerging as a relative strength, whereas Working Memory appeared as a relative weakness. Finally, with the exception of two subtests in the perceptual domain, we found no evidence for a general cognitive decline with age.

1. Introduction

Smith-Magenis Syndrome (SMS) [1] is a rare neurodevelopmental disorder caused by a microdeletion on chromosome 17p11.2 which is believed to have an incidence of approximately 1 to 25000 live births [2]. Individuals with SMS display an unusual phenotype, which includes a distinctive profile of physical, medical and neuropsychological characteristics. One of the most salient aspects of their physical appearance regards the craniofacial phenotype: flattened mid-face, brachycephaly, depressed nasal bridge, down-turned mouth, prominent cheeks and jaw, synophrys, as well as a relative prognathism that increases with age [3,4]. Individuals with SMS also commonly display short stature, short fingers and toes, tooth abnormalities, and hoarse voice [5,6]. In what concerns their medical profile, they tend to present hearing and eye problems, hypercholesterolemia, hypertriglyceridemia, thyroid function abnormalities, poor motor coordination and low muscle tone [7], as well as an inverted circadian rhythm of melatonin, which is thought to cause sleep disturbances [2,8,9]. Furthermore, individuals with this syndrome display distinct behavioural patterns, which may include hyperactivity, impulsivity, attention seeking, attentional problems, sudden mood swings, explosive outbursts, prolonged tantrums, aggressiveness, and self-injury behaviours [2,10] which can persist into adulthood [11]. However, they may also show positive behavioural features such as endearing and appealing personalities, eagerness to please and a good sense of humour [10,12–14] with communicative and sociability intentions relatively preserved [15].

Despite the very limited research available, general mental disability is believed to be characteristic of SMS, with the majority of individuals falling within the mild to moderate range [2,4,16,17]. A study conducted in England with a relatively large sample of children and adults with SMS yielded some of the most comprehensive results on cognitive abilities in this syndrome to date [17].

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Although no differences were found between verbal and performance skills as assessed by the WISC-III and the WAIS-R, a pattern of relative strengths and weaknesses was discernible. Indeed, and similarly to what had been found by a previous study [4], long-term memory, perceptual skills and the ability to use computers were reported as relative strengths for both children and adults. In contrast, sequential processing, visuo-motor coordination, response speed and short-term auditory memory were considered relative weaknesses. The study also showed that contrary to what has been reported for other genetic disorders (e.g., Down syndrome and Williams syndrome), there does not seem to be a decline of cognitive abilities with age [18,19]. Curiously, a previous study [4] in which the Kaufman Brief Intelligence Test was administered to a small sample of 2 males and 8 females from the Northeast of the U.S.A., had also indicated reading as a relatively preserved ability, but this was not further confirmed [17].

Although it must be acknowledged that the two pioneer studies reported above [4,17] constitute important first steps towards a better understanding of the cognitive profile of individuals with SMS, there is still very limited information available and replication is undeniably needed. For instance, both studies lacked comparisons with a control group. Our study is the first to systematically study the cognitive profile in SMS, while including comparison samples of age- and sex-matched samples of typically developing individuals. The present paper aims to extend previous findings by reporting data on the cognitive functioning of a sample of 18 children, adolescents and adults with SMS while comparing and contrasting with the results of 18 typically developing age- and sex-matched controls.

2. Material and methods

2.1. Participants

Participants were drawn from two different groups: (a) 15 children, adolescents and adults with SMS (7 females), recruited at the Fundación Pública Galega de Medicina Xenómica (Santiago de Compostela, Spain); (b) 15 chronological age- and sex-matched controls recruited from the general population. Participants of the SMS group were aged 7 to 29 years ($M = 14.0$, $SD = 6.89$) and diagnoses had been previously established by the presence of the physical and behavioural phenotypes consistent with the syndrome (see appendix 1 for clinical characteristics of our group), as well as by the presence of genetic deletions on 17p11.2 (including RAI1) detected by fluorescent *in situ* hybridization (FISH). In one individual, a mutation was found in the coding region of RAI1 (c3265C > T). This is consistent with recent accounts of the occurrence of this type of genetic alteration as a cause for SMS in a minority of cases [20]. Exclusion criteria were the presence of sensorial or speech disorders, as well as comorbidity with severe psychopathology not associated with this syndrome. Participants in the control group were screened for sensorial, psychiatric or neurodevelopmental disorders. Informed consent was obtained from all participants in the study.

Most of the SMS participants had a history of attention problems, psychomotor delay and speech delay. The majority had also a history of aggressive behaviour and sleep disturbances. Most patients were medicated with antipsychotics (e.g., risperidone, aripiprazole). Some were also prescribed with melatonin supplements (for sleep disturbances) or stimulant drugs to improve attention span (e.g., methylphenidate).

All of the SMS children (up to the age of 18 years) attended special needs schools but were living with their families. In contrast, all adults spent their week in institutionalized settings where they attended specialized educational and/or professional programs, returning home on the weekends.

2.2. Instruments

General cognitive functioning was assessed by the Wechsler Intelligence Scale for Children-IV (WISC-IV [21]) for participants up to the age of 16,whereas for older participants the Wechsler Adult Intelligence Scale – III (WAIS-III [22]) was used. These scales are two of the most internationally used systems for assessing Intellectual Quotient (Full Scale IQ – FSIQ). In addition, they allow for the discrimination of 4 factorial indexes – Perceptual Reasoning/Organization, Processing Speed, Verbal Comprehension, and Working Memory – and also of the participant's performance on each subtest.

2.3. Procedure

After explaining the goals of the research, data on participants' socio-demographic, diagnostic and clinical history were gathered. Signed consent forms were also obtained. The Wechsler scales were then administered to the participants.

Some of the behavioural manifestations seen in this syndrome – such as hyperactivity, impulsivity, intense and prolonged tantrums, and aggressiveness – can constitute serious challenges for cognitive assessments. In our sample, one SMS participant refused to complete the assessment with our researcher, so we requested the collaboration of a psychologist with whom this individual was more familiarized. For other participants we typically asked for the presence of a person of reference (e.g., a close relative) who would help them complete the testing session. Because of the difficulties associated with testing individuals with this syndrome, assessments lasted around one and a half hours and were divided in two sessions.

2.4. Data analysis

Descriptive statistics were used to characterize all participants. The number of participants in each sample of individuals with SMS and controls ($n = 9$ for children and adolescents; $n = 6$ for adults) suggests the use of non-parametric tests. However, as advised by Fife-Schaw [23], we computed parametric tests as well as their non-parametric equivalents. Given that the pattern of results remained unchanged, we opted to present the results of the parametric tests as these are more robust and reduce the number of tests performed, thus decreasing the probability of Type I error. In addition, as mentioned above, one individual was found to have a genetic mutation (*versus* the typical deletion) on RAI1. To analyse the relative importance of this individual in the obtained results we repeated all analyses excluding this participant (and the paired control) and we confirmed that results did not change. Therefore, reported results henceforth include this participant. Parametric t-tests were used to compare the groups and repeated measures ANOVA were used to analyse intragroup variables.

3. Results

Table 1 contains the descriptive statistics regarding sex and age of the entire sample of individuals with SMS as well as of the sample of typically developing individuals. Information on age and sex distribution for children and adolescents (henceforth children) and adults with SMS is also displayed in Table 1. As anticipated, no age differences were found between children with SMS, $t(10) = 0$, $p = 1.0$, and adults with SMS, $t(10) = .20$, $p = .848$, relative to their control groups.

In what concerns the SMS child sample, the mean distribution of the FSIQ fell within the moderate mental disability category, $M = 52.78$, $SD = 12.90$ (Table 2). More concretely, the FSIQ of 66.6% of the children with SMS ($n = 9$) placed them in the moderate mental disability category (FSIQ between 40 and 54), while two children were classified in the mild mental disability category

Table 1
Socio-demographic data for the Smith-Magenis group and the control group.

	SMS ($n = 15$)		SM children ($n = 9$)		SM adults ($n = 6$)		Control group ($n = 15$)	
	M (SD)	Range	M (SD)	Range	M (SD)	Range	M (SD)	Range
Age	14 (6.89)	7–29	9.11 (1.96)	7–12	21.33 (4.37)	18–29	13.8 (6.65)	7–29
Sex	*n*	%	*N*	%	*n*	%	*N*	%
Male	8	53.3	4	44.4	4	66.7	8	53.3
Female	7	43.7	5	55.6	2	33.3	7	43.7

Note. SMS – Smith-Magenis syndrome.

(FSIQ = 60, 62), and one attained a FSIQ in the borderline normal range (81). It must be noted that the latter was found to have a mutation in the coding region of RAI1. Regarding the SMS adult sample, the mean FSIQ also corresponded to moderate mental disability, $M = 49.17$, $SD = 2.40$p (Table 3), with all adults with SMS being classified in the moderate mental disability category (FSIQ between 40 and 54). In addition, the highest and the lowest FSIQ were seen in the child sample (41–81), while adults' FSIQ ranged from 48 to 54. The standard deviation was also substantially larger for the child sample than for the adult sample, further suggesting a higher dispersion of the results in the former. Yet, no significant differences were found in FSIQ among children ($n = 9$) and adults with SMS ($n = 6$), $t(8.8) = .82$, $p = .435$, with both age groups performing similarly in these measures. Additionally, and as seen in Tables 2and 3, both children and adults with SMS (respectively) showed significantly lower FSIQ when compared with their typically developing counterparts.

Considering each of the four factorial indices, the highest mean scores obtained by the children with SMS were Verbal Comprehension and Processing Speed indices, while the lowest scores concerned Working Memory and Perceptual Reasoning (see Table 2). Although a repeated measures ANOVA did not indicate the presence of significant differences among the indices, $F(3,21) = 2.13$, $p = .128$, pairwise comparisons showed that children with SMS presented higher scores on Verbal Comprehension when compared with Working Memory, as well as higher Verbal Comprehension than Perceptual Reasoning. In addition, we found that the children with SMS significantly performed well under the typically developing group on all four indices (Table 2). The same was observed when comparing adults with SMS and their controls (Table 3). For the adult sample, the highest scores were again obtained for Processing Speed and Verbal Comprehension, and the lowest scores pertained to Working Memory and Perceptual Organization. A repeated measures ANOVA indicated the presence of marginally significant differences, $F(3,9) = 3.68$, $p = .056$,and pairwise comparisons revealed that adults with SMS presented higher scores on Verbal Comprehension than Working Memory as well as higher Processing Speed than Perceptual Organization. In what concerns differences among children and adults with SMS, we found that both samples performed similarly in terms of Perceptual Reasoning/Organization, $t(8.9) = 1.09$, $p = .306$, Processing Speed, $t(11) = .42$, $p = .684$, Verbal Comprehension, $t(10.2) = 1.38$, $p = .196$, and Working Memory, $t(10.6) = 1.20$, $p = .256$.

Regarding their performance on each of the subtests, both children and adults with SMS tended to score significantly lower relative to controls (Tables 4and 5). Nevertheless, on closer inspection some children with SMS were able to attain scores within the normal range in several subtests (e.g., Coding, Similarities, and Picture Concept) whereas in other subtests scores were consistently low (e.g., Arithmetic and Cancellation). Indeed, the mean values for these subtests were some of the highest and lowest, respectively for the children with SMS. Regarding Cancellation, the differences between children with SMS and controls did not reach statistical significance. As for the adult sample, when considering both the range as well as the mean scores, the subtests Block Design, Letter-Number Sequencing, and Arithmetic, presented the lowest scores, whereas Information, Picture Arrangement, and Similarities had the highest scores. Furthermore, there were significant differences between children and adults with SMS in two subtests: Block Design and Picture Completion. In Block Design, children ($M = 2.67$, $SD = 1.50$) tended to obtain significantly higher scores than adults ($M = 1.17$, $SD = 0.41$), $t(9.7) = 2.85$, $p = .018$. As for Picture Completion, once again children ($M = 4.67$, $SD = 2.69$) tended to perform significantly better than adults ($M = 1.83$, $SD = 1.33$), $t(13) = 2.37$, $p = .034$.

4. Discussion

The data gathered from our samples showed that all but one child with SMS and the totality of the adults with SMS had a FSIQ that placed them in the level of mild to moderate mental disability, therefore differing significantly from the typically developing child and adult samples. This result is in line with previous research [2,17] and further confirms mental disability as a feature of SMS. Curiously, however, one child with SMS scored on the borderline interval. This stands in contrast with the above-mentioned studies in which SMS samples consistently performed at levels of mental disability [2,17]. Interestingly, this child was found to have a genetic mutation in RAI1, rather than the typical 17p11.2 microdeletion. It is possible that the smaller genetic change could account for this milder form of cognitive impairment. Future studies are warranted to analyse the extent to which different genetic alterations translate into a varying degree of physical and behavioural manifestations. It must also be noted that improved clinical recognition of this syndrome, likely associated with an increasing awareness among professionals and parents in the last decade, may have increased the scope of referrals, allowing for individuals with milder manifestations of this syndrome to be submitted to genetic testing. Furthermore, the highest and the lowest FSIQ values were obtained by the children, whereas the adults scored more homogenously.

Table 2
FSIQ, PRI, PSI, VCI and WMI for children with Smith-Magenis syndrome and for controls.

	SMS children				Control group				*t*	*df*
	n	M (SD)	Median	Range	*n*	M (SD)	Median	Range		
Full scale IQ	9	52.78 (12.90)	48	41–81	9	115.67 (13.06)	117	90–128	−10.27[a]	16
Perceptual reasoning index	9	57.78 (12.85)	53	40–77	9	111.89 (14.66)	114	83–132	−8.320[a]	16
Processing speed index	8	62.88 (18.73)	57	40–97	9	106.89 (5.53)	107	99–115	−6.39[a]	8.1
Verbal comprehension index	9	63.44 (14.41)	59	45–93	9	117.56 (16.28)	125	91–134	−7.46[a]	16
Working memory index	9	56.11 (9.40)	54	50–79	7	111.71 (9.95)	110	99–127	−11.44[a]	14

[a] $p \leq .001$.

Table 3
FSIQ, POI, PSI, VCI and WMI for adults with Smith-Magenis syndrome and for controls.

	SMS adults				Control group				*t*	*df*
	n	M (SD)	Median	Range	*n*	M (SD)	Median	Range		
Full scale IQ	6	49.17 (2.40)	48	48–54	6	111.83 (10.98)	114.5	91–121	−13.65[a]	5.5
Perceptual organization index	6	53.00 (2.45)	53	50–57	6	107.5 (12.97)	111.5	87–120	−10.10[a]	5.4
Processing speed index	5	59.20 (6.22)	57	54–70	5	101.20 (6.69)	101	92–109	−10.27[a]	8
Verbal comprehension index	6	56.33 (4.50)	55.5	51–64	6	112.17 (8.84)	115	96–121	−13.77[a]	10
Working memory index	5	52.00 (3.08)	50	50–57	2	113.00 (–)	113	113–113	−44.24[a]	4

[a] $p \leq .001$.

Accordingly, the standard deviation observed for the children also suggested a higher dispersion of the results in this sample. However, the low number of adults in our sample could have not been sufficient to truly mirror the variability that may occur among adults with SMS. In addition, childhood is a sensitive period of development when a few months or years may result in important differences in FSIQ. Another limitation may be associated with differences between the two instruments used (WISC-IV and WAIS-III). On the one hand, important average increases have been documented in other studies assessing children and adults with these instruments [24]. On the other hand, the WISC-IV includes a recent re-norming aimed to compensate for the Flynn effect [25], which contrasts with the older version of the WAIS used in this study (WAIS-III). However, and despite the aforementioned shortcomings, there were no significant differences between the FSIQ obtained by children and adults with SMS. This result supports previous conclusions [17] of an apparent lack of cognitive decline with age, unlike what is seen in other genetic disorders such as Down syndrome [18] and Williams syndrome [19]. Nevertheless, longitudinal studies are needed to test this hypothesis more accurately.

In what concerns the four Wechsler indices, a pattern of relative strengths and weaknesses was discernible for both samples. There was a primacy of Verbal Comprehension over Working Memory as well as over Perceptual Reasoning for children with SMS. In the adult sample, Verbal Comprehension once again emerged as a relative strength when compared with Working Memory. In addition for this sample, scores on Perceptual Speed were significantly higher than scores on Perceptual Organization. Thus, Verbal Comprehension was a relative strength for both samples, whereas Working Memory constituted a common relative weakness. These results corroborate previous studies by documenting an impairment of attentional and executive control processes of short-term memory in SMS [4,17]. Furthermore, our finding of a relative preservation in the ability to form verbal concepts is also in line with previous studies, which had suggested long-term memory [4,17] and fund of information [4] to be relative strengths for this syndrome. In addition, our data expand extant research by reporting statistically significant differences that are not limited to specific subtests, but rather refer to broader cognitive domains. Children and adults with SMS performed similarly on the four indices, with both samples showing markedly impaired performance when compared to controls. This result once again reinforces how all assessed cognitive functions are affected in SMS. Interestingly, and in common with other rare genetic syndromes such as Williams syndrome (WS), individuals with SMS present a distinctive pattern of cognitive and behavioural features that make them more likely to be referred to mental health professionals. Curiously, the cognitive profiles of SMS and WS present with some similarities, namely, there are reports relative preservation of verbal abilities [4,19], as well as sharp attentional deficits [4,26] in both syndromes. In turn, this has important implications for cognitive interventions throughout the lifespan [16].

A detailed analysis of subtest performance highlighted significant heterogeneity in both SMS samples. While for some subtests, scores were consistently well under the normal range, for other subtests maximum scores approached those expected for typically developing individuals of the same chronological age. Nevertheless, both samples of SMS performed significantly worse than controls on each subtest (except for Cancellation, between SMS children and their controls). Curiously, children scored significantly higher than adults on Block Design and Picture Completion, two subtests involving perceptual skills. However, given the small sample size and the imbalance between the number of adults and the number of children, it is speculative to suggest that these differences constitute evidence for a specific decline in this cognitive domain. Further studies including both children and adults with SMS may help to clarify this issue.

In conclusion, the present study confirmed mental disability, particularly within the moderate category, as a consistent feature of children and adults with SMS. Furthermore, when compared with their typically developing counterparts, child and adult samples evidenced significant impairments in all four Wechsler indices. However, Verbal Comprehension emerged as a relative strength, whereas Working Memory appeared as a relative weakness. Finally,

Table 4
Wechsler Intelligence Scales Subtests' scores for the children with Smith-Magenis syndrome and the control group.

	SMS children			Control group			*t*	*df*
	n	M (SD)	Range	*n*	M (SD)	Range		
Arithmetic	8	2.00 (1.20)	1–4	5	12.60 (1.52)	11–15	−14.06[a]	11
Block design	9	2.67 (1.50)	1–6	7	10.29 (3.50)	6–14	−5.38[a]	7.7
Cancellation	6	1.33 (0.82)	1–3	3	6.33 (2.89)	3–8	−2.93[ns]	2.2
Comprehension	7	2.86 (2.73)	1–8	9	13.11 (2.47)	10–17	−7.85[a]	14
Coding	8	3.50 (4.34)	1–11	9	10.89 (1.45)	9–14	−4.58[**]	8.4
Digit span	9	2.44 (1.88)	1–7	9	11.0 (1.58)	9–13	−10.44[a]	16
Information	7	4.71 (3.73)	1–9	5	12.20 (2.39)	10–16	−3.91[**]	10
Letter-number	6	3.33 (1.75)	1–6	7	13.14 (3.34)	10–19	−6.44[a]	11
Matrix	9	3.44 (1.51)	2–6	7	13.00 (2.38)	10–16	−9.81[a]	14
Picture completion	9	4.67 (2.69)	1–9	4	9,25 (3.20)	7–14	−2.68[b]	11
Picture concept	9	4.00 (3.04)	1–10	8	13.38 (3.20)	8–18	−6.18[a]	15
Similarities	8	5.50 (3.25)	1–11	7	12.29 (4.23)	6–17	−3.5[**]	13
Symbol search	8	3.38 (1.69)	1–7	9	10.67 (1.41)	9–12	−9.69[a]	15
Word reasoning	8	3.13 (1.81)	1–6	3	14,67 (3.21)	11–17	−7.74[a]	9
Vocabulary	9	2.89 (2.03)	1–7	9	13.89 (3.33)	9–19	−8.45[a]	16

[a] $p \leq .001$. [b] $p \leq .05$. [**] : $p \leq .01$, ns : non significant ($p > .05$).

Table 5
Wechsler Intelligence Scales Subtests' scores for the adults with Smith-Magenis syndrome and the control group.

	SMS adults			Control group			*t*	*df*
	n	M (SD)	Range	*n*	M (SD)	Range		
Arithmetic	6	1.67 (0.82)	1–3	4	11.50 (3.11)	8–15	−6.17[b]	3.3
Block design	6	1.17 (0.41)	1–2	4	10.75 (3.59)	6–14	−5.30[c]	3.1
Comprehension	6	1.83 (0.98)	1–3	4	13.00 (4.08)	7–16	−5.36[b]	3.2
Coding	5	2.80 (1.10)	1–4	4	9.50 (1.91)	8–12	−6.64[a]	7
Digit span	6	2.00 (2.00)	1–6	4	12.75 (1.89)	10–14	−8.48[a]	8
Information	6	2.17 (1.60)	1–5	4	11.75 (0.96)	11–13	−10.63[a]	8
Letter-number	4	1.25 (0.50)	1–2	2	12.00 (1.41)	11–13	−14.96[a]	4
Matrix	6	2.17 (1.17)	1–4	2	10.50 (0.71)	10–11	−9.22[a]	6
Picture arrangement	6	2.83 (1.33)	1–5	4	9.25 (2.22)	7–12	−5.78[a]	8
Picture completion	6	1.83 (1.33)	1–4	4	11.75 (2.63)	8–14	−7.98[a]	8
Similarities	6	3.50 (1.52)	1–5	4	13.50 (4.43)	8–18	−4.33[c]	3.5
Symbol search	5	2.00 (1.73)	1–5	4	10.25 (1.50)	9–12	−7.5[a]	7
Visual puzzles	5	1.60 (1.34)	1–4	2	13.50 (0.71)	13–14	−11.45[a]	5
Vocabulary	6	2.00 (0.89)	1–3	4	11.50 (2.38)	9–14	−9.07[a]	8

[a] $p \leq .001$. [b] $p \leq .01$. [c] $p \leq .05$.

we found no evidence for a general cognitive decline with age, with the exception of two subtests in the perceptual domain. To our knowledge, this is the first study to systematically compare the cognitive profile of children and adults with SMS with age- and sex-matched typically developing individuals.

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Appendix 1

Clinical features and medication (SMS group).

Clinical Features	*Percentage of participants*	*Age range*
Cognitive delay	100	7–29 years
Language delay	73.3	7–29 years
Motor delay	86.7	7–29 years
Attention problems	100	7–29 years
Aggressive behaviours	66.7	7–29 years
Sleep disturbances	60.0	7–23 years
Repetitive behaviours	40.0	7–22 years
Brachycephaly[a]	20.0	7; 13; 23 years
Down-turned mouth	40.0	7–23 years
Small, wide nose	13.3	18 years
Prognathism	13.3	18; 23 years
Brachydactyly	20.0	12; 18; 23 years
Small, broad hands	33.3	7–23 years
Strabismus	26.7	7; 12; 18; 23 years
Myopia	20.0	7; 13; 18 years
Medication	*Percentage of participants*	*Age range*
Antipsychotics	46.7	9–23 years
Melatonin	20.0	9; 12; 18 years
Stimulants	26.7	7; 9; 13; 18 years
No medication	6.7	7 years
No information available	40.0	7–29 years

[a] Data regarding brachycephaly was unavailable for 11 SMS participants. There is report of no brachycephaly for one participant.

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