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Child characteristics associated with child quality of life and parenting stress in Angelman syndrome

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Abstract

Background Angelman syndrome (AS) is a rare neurodevelopmental disorder characterised by severe intellectual disability, movement disorder, epilepsy, sleeping problems, and behavioural issues. Little is known on child health-related quality of life (HRQoL) in AS. AS family studies have reported elevated parenting stress and a high impact of the child's syndrome on the parent. It is unclear which factors influence child HRQoL and parenting stress/impact in AS.

Methods We collected data prospectively through standardised clinical assessments of children with AS at the ENCORE Expertise centre for Angelman Syndrome at the Erasmus MC Sophia Children's Hospital. A linear regression analysis was conducted for the following outcome variables: (1) child HRQoL (Infant and Toddler Quality of Life Questionnaire); (2) the impact of the child's syndrome on the parent (Infant and Toddler Quality of Life Questionnaire); and (3) parenting stress (Parenting Stress Index). Predictor variables were child genotype, epilepsy, sleeping problems (Sleep Disturbance Scale for Children), cognitive developmental level (Bayley Cognition Scale), autistic features (Autism Diagnostic Observation Schedule) and emotional/behavioural problems (Child Behaviour Checklist). Covariates were sex, age and socio-economic status.

Results The study sample consisted of 73 children with AS, mean age = 9.1 years, range = 2–18 years. Emotional/behavioural problems were the strongest significant predictor of lowered child HRQoL. Internalising problems were driving this effect. In addition, having the deletion genotype and higher age was related to lower child HRQoL. Sleeping problems were related to a higher impact of the child's syndrome on the parent. Finally, emotional/behavioural problems were associated with higher parenting stress. Cognitive developmental level, autistic features and epilepsy were not a significant predictor of child HRQoL and parenting stress/impact.

Conclusions These results suggest that interventions aimed at increasing child HRQoL and decreasing parenting stress/impact in AS should focus on child emotional/behavioural problems and sleeping problems, using a family-centred approach.

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Keywords Angelman syndrome, Emotional/behavioural problems, Impact on parent, Parenting stress, Quality of life, Sleeping problems

Introduction

Angelman syndrome (AS) is a rare neurodevelopmental disorder with an estimated birth incidence of 1 in 15 000–24 500 (Petersen *et al.* 1995; Thomson *et al.* 2006; Mertz *et al.* 2013). AS is caused by loss-of-function of the *UBE3A* gene on the maternal chromosome 15q11-q13, which can be due to a deletion (70–75%), a pathogenic variant of the *UBE3A* gene (15%), a paternal uniparental disomy (UPD; 5–7%), or an imprinting centre defect (IC; 5–7%). Clinical criteria of AS entail a severe developmental delay, little to no expressive language and a movement disorder. Epilepsy, sleeping problems and behavioural issues (hyperactive behaviour, short attention span, anxiety, autistic features and disruptive behaviour) are highly prevalent (Williams *et al.* 2006; Bindels-de Heus *et al.* 2020).

As the symptoms of AS are severe, it is important to investigate health-related quality of life in these children. Health-related quality of life (HRQoL) is defined as an individual's perceived physical, mental and social well-being. The frequent laughing, smiling, excitability and sociability that typifies AS (Bower & Jeavons 1967) may give the impression that children with AS are happy and have good quality of life. In a highly cited scoping review of literature, Clayton-Smith (2003, p. 89) has stated that 'although patients are not able to live independently, many have a good quality of life with a semi-independent existence with round the clock supervision'. In other patient groups, such as Duchenne muscular dystrophy, patients have reported to experience high emotional and social quality of life despite large and progressive physical disabilities (Kohler *et al.* 2005). On the other hand, Wheeler *et al.* (2017) have argued that HRQoL may be lowered in AS, because of low functional independent living skills, low communicative means (in combination with a high need for socialisation), and high comorbid health risks (epilepsy and gastrointestinal syndromes). This idea was corroborated by a recent study on adults and adolescent with AS, who showed lowered HRQoL as compared with the general US population (Khan *et al.* 2023).

Parents or caregivers of children with AS experience higher levels of stress in comparison with parents of typically developing children and children with other neurodevelopmental disorders (Wulffaert *et al.* 2010; Griffith *et al.* 2011; Thomson *et al.* 2017). Parents have reported that their child's AS has impact on many domains of their own life: emotional (need for constant vigilance, worry/anxiety, guilt and depression), time (less time for other children and partner, for work, and for social and leisure activities), physical (reduced sleep leading to fatigue and exhaustion, back problems and injuries from aggressive behaviours) and financial (high health care costs coupled with less time to work) (van den Borne *et al.* 1999; Larson *et al.* 2014; Grieco *et al.* 2018; Willgoss *et al.* 2021). Important to note is that caring for a child with AS may also have a positive impact, such as feeling fulfilment and personal growth, that can occur simultaneously with the negative impact (Griffith *et al.* 2011).

Previous studies have put forward the notion that child characteristics may influence child HRQoL and parenting stress/impact. Parents of children with AS and clinicians have reported that epilepsy, sleeping problems, intellectual disability (ID), impaired expressive communication, behavioural/emotional problems, lack of independence and motor problems have a major impact on the individual and their families (Grieco *et al.* 2018; Willgoss *et al.* 2021). Previous research has shown that sleeping problems are associated with higher parenting stress in AS (Didden *et al.* 2004; Goldman *et al.* 2012; Miodrag & Peters 2015; Trickett *et al.* 2017). In addition, child emotional/behavioural problems have been associated with higher parenting stress in some (Miodrag & Peters 2015; Sadhwani *et al.* 2019), but not all studies in AS (Wulffaert *et al.* 2010). Lower child adaptive functioning relates to higher levels of maternal depression in a small study sample with AS (Adams *et al.* 2018). In a larger study sample, higher parenting stress relates to *lower* child adaptive functioning (parent-reported) but *higher* child developmental level (clinician assessment; Miodrag & Peters 2015). Finally, one study has investigated the effect of genotype on parenting stress in AS. Results indicate significant differences between genotypes on specific components of parenting stress (child-related stress

and parental feelings of isolation and incompetence), but not on the total parenting stress score (Miodrag & Peters 2015). The relation between autistic features or epilepsy with parenting stress exists in children with a general ID, but has not been studied in AS (Buelow *et al*. 2006; Staunton *et al*. 2020). Finally, the relation between child characteristics and child HRQoL has not been investigated in AS.

The current study investigates the relative importance of child genotype, epilepsy, sleeping problems, cognitive developmental level, autistic features, and emotional/behavioural problems in predicting child HRQoL and parenting stress/impact in AS. Our goal is to increase knowledge on this important and understudied topic, in order to contribute to better care and guidance of children with AS and their families.

Methods

Participants

The current study sample entailed 73 children aged 2 to 18 years with a molecularly confirmed diagnosis of AS. Mosaicism was an exclusion criterion.

Procedure

Data were prospectively collected between 2011 and 2020 as part of our standard care in the outpatient clinic of the multidisciplinary ENCORE Expertise Center for AS at the Erasmus Medical Centre Sophia Children's Hospital in Rotterdam, the Netherlands (Bindels-de Heus *et al*. 2020). This clinical record study did not fall within the scope of the Medical Research Involving Human Subjects Act (MEC-2015-203). Participants (their legal representatives) who did not give consent to use data collected in clinical care for scientific research were not included in the study.

Measures

Clinical criteria of AS entail a severe developmental delay, but measures designed for this specific population are scarce. Therefore, we used instruments that are appropriate for the developmental age of children with AS, rather than for their chronological age. Most of the measures used in this study were developed for children between the chronological ages of 0 and 5 years. Age- and intellectual development-matched norm groups were not available; thus, raw scores were used in analyses instead of normed scores. Normed scores were added to the descriptive statistics to facilitate interpretation but should be interpreted with caution.

Predictors

Genotype. Genotype was molecularly confirmed. Children with a UPD, IC, and pathogenic variants of the *UBE3A* gene were grouped together into a 'non-deletion' group.

Epilepsy. Information on epilepsy status was collected in a clinical visit of the paediatric neurologist. Children were classified into the 'epilepsy' group when they had active epilepsy and when epilepsy was in remission with anti-epileptic drugs. Children were classified into the 'no epilepsy' group when they never had epilepsy or when epilepsy was in remission without anti-epileptic drugs.

Sleeping problems. Sleeping problems in the preceding 6 months were measured using the Sleep Disturbance Scale for Children (SDSC; Bruni *et al*. 2005). The SDSC is a 26-item parent-report questionnaire developed for use in school-aged children. A total score was calculated.

Cognitive developmental level. Cognitive developmental level was measured using the cognition scale of the Bayley Scales of Infant and Toddler Development (Bayley 2014). The Bayley Scales is a child assessment for children aged 1–42 months but is frequently used to measure developmental level in older children with (severe) developmental delays. The Bayley motor and language scales could not be included because of a high percentage of missing data.

Autistic features. Autistic features were measured using the Autism Diagnostic Observation Schedule (ADOS-2; Lord *et al*. 2013) Module 1. The ADOS is a semi-structured, standardised child assessment tool. Module 1 is intended for use in children with limited or no verbal speech and thus most appropriate for this population. All psychologists who administered the ADOS were fully certified (for clinical and research

use). The ADOS provides a total score and two domain scores: (1) social affect, and; (2) restricted and repetitive behaviours.

Behavioural/emotional problems. Behavioural and emotional problems were measured using an adapted version of the Child Behaviour Checklist (CBCL) for children 1.5–5 years (Achenbach & Rescorla 2013). The CBCL is a 99-item parent-report questionnaire. It provides a total problem score and two broad-band scales, namely, (1) internalising problems (anxious/depressed, emotional reactive, somatic complaints and withdrawn), and; (2) externalising problems (attention problems and aggressive behaviour). Because some items of the CBCL 1.5–5 years are not applicable for a child with AS or do not reflect problem behaviour in children with a low developmental/language level (e.g., the item 'Doesn't answer when people talk to him/her'), we adjusted the questionnaire in consultation with parents. As a result, 24 items were coded 'not applicable' in advance (items available in Appendix S1). Parents were still presented every original question and were able to change the pre-filled 'not applicable' to every other answer option. In the scoring, all 'not applicable' scores were recoded to 'not true'.

Covariates

Age, sex and socio-economic status (SES; objectified as highest education level of the parents) were taken into account as covariates.

Outcomes

Child HRQoL and the impact of the child's syndrome on the parent. Child HRQoL was measured using the Infant and Toddler Quality of Life Questionnaire – short form (ITQOL-SF47; Landgraf 2007). The ITQOL is a 47-item parent-reported questionnaire. Six subscales of the questionnaire concern HRQoL of the child: (1) behaviour; (2) temperament and moods; (3) general health; (4) physical abilities; (5) growth and development; and (6) bodily pain. The average of these six subscales was used as outcome, from now on called 'Child Health-Related Quality of Life (HRQoL)'. Two additional subscales of the ITQOL concern the impact of the child's syndrome on the parent. These are (1) parenting impact – time: the degree to which the child's health problem or syndrome impacts the parent's time to attend to personal needs; and (2) parenting impact – emotional: the degree of worry or anxiety the parent feels concerning the child's physical, emotional, cognitive and social development. The average of these two subscales was used as outcome, from now on called 'the impact of the child's syndrome on the parent'.

Parenting stress. Parenting stress was measured using the abbreviated version of the Parenting Stress Index (PSI; Abidin 1992). The abbreviated PSI is a 25-item parent-report questionnaire, originally developed for children aged 2 to 13 years. The PSI measures the stress a parent experiences in raising the child, in the relationship with the child, and in the other relationships within their family. Total PSI score was calculated.

Data analyses

Analyses were performed using IBM SPSS Statistics (version 25; IBM Corp. Released, 2017) and R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria; R Core Team, 2021).

Multiple imputations were conducted in SPSS to account for missing data under the assumption that data were 'missing at random' (MAR). The number of participants with missing data for each variable is reported in Appendix S2, Table S2. All variables with missing values were imputed (predictors and outcomes), and all variables were included in the imputation model (covariates, predictors and outcomes). Outcome variables were imputed, as this increased the sample size (keeping in mind the rarity of the syndrome and the fact that we had three separate outcome measures that were not all available for the same participants). For each outcome variable, a complete case analysis was performed as a sensitivity analysis (i.e., to check if the conclusions were similar).

Three ordinary least squares (OLS) linear regression analyses were conducted to study if genotype, epilepsy, sleeping problems, cognitive developmental level, autistic features and behavioural/emotional problems were associated with (1) child HRQoL; (2) the impact of the child's syndrome on the parent; and (3) parenting stress.

Covariates were sex, age and SES. Covariates were entered into the regression model in a first block while predictors were entered into the regression model in a second block.

Given the ratio between the amount of predictors and observations, we performed Lasso regression analyses identical to the OLS regression analyses as sensitivity analyses (using the 'glmnet' package in R; Friedman *et al*. 2010). More information on the Lasso analyses can be found in Appendix S3.

Results

Descriptive statistics

Tables 1 and 2 illustrate the descriptive characteristics. The sample (N = 73) consisted of 44 children with the deletion genotype (60%) and 29 children with the non-deletion genotype (40%). Epilepsy was active or in remission with anti-epileptic drugs in 47 children. AS children had an 'above average' amount of sleeping problems, as compared with the general paediatric population. Their mean cognitive developmental age was approximately 16 months (range 5–34 months). On average, children with AS scored within the 'autism spectrum' range. Their level of behavioural/emotional problems was 'high average' as compared with healthy children from 1.5 to 5 years old. Parents of children with AS reported an 'above average' amount of parenting stress. The mean HRQoL for children with AS was classified as 'exceptionally low' to 'low average' in comparison with healthy infants and toddlers. The average impact on the parent was 'exceptionally high'.

To show the association between all predictor and outcome variables used in this study, a correlation matrix is presented in Appendix S4. Descriptive characteristics of all predictors and outcome measures per genotypical group (deletion, UPD, IC and *UBE3A* mutation) and for children with mosaic AS are provided in Appendix S5.

Associations between child characteristics and child HRQoL

Table 3 presents the associations between child characteristics and child HRQoL. A graphic illustration of these findings can be seen in Figure 1. A significant regression equation was found for the total model ($F_{9,\ 63}$ = 8.18, $P < .001$, R^2 = .55). The model with all predictors (step 2) had a significantly higher explained variance than the model with covariates only (step 1) (ΔR^2 = .49, $P < .001$). There were three significant predictors of child HRQoL. First, emotional/behavioural problems was the strongest significant predictor. Higher behavioural/emotional problems were associated with lower child HRQoL. Furthermore, genotype was a significant predictor. Having the deletion genotype was related to lower child HRQoL. Finally, the covariate age was a significant predictor. Higher age was associated with lower child HRQoL. To explore whether child HRQoL is influenced by emotional vs. behavioural

Table 1 Descriptive characteristics of the categorical variables

	Frequency
Covariates	
Sex	
Male	37
Female	36
Socio-economic status (highest education level of parents)[†]	
Low level education[‡]	1
Middle level education[§]	44
High level education[¶]	28
Predictors	
Genotype	
Deletion	44
Non-deletion	29
Paternal uniparental disomy (UPD)	12
Imprinting centre defect (IC)	3
UBE3A mutation	14
Epilepsy	
Yes	47
Yes, active	29
In remission with antiepileptic drugs	17
No	26
No	25
In remission without antiepileptic drugs	2

[†]If the highest education level was known for both parents (N = 55), the average was calculated. If highest education was known for one parent only (N = 8), this value was used. If highest education was not known (N = 10), multiple imputations were performed. Low and middle level education were taken together in the analyses, as only one person had low level education.

[‡]Low level education consisted of no education or primary education only.

[§]Middle level education consisted of secondary education only or middle level vocational education.

[¶]High level education consisted of high level vocational education, university education or PhD education.

Table 2 Descriptive characteristics of the continuous variables

	Raw score Mean (*SD*)	Norm score Mean (*SD*)†	Qualitative Description†
Covariate			
Age	9.13 (4.96)	–	–
Predictors			
Sleeping problems (SDSC)			
Total score	45.81 (9.24)	*T* = 63.91 (11.77)	Above average
Disorders of initiating and maintaining sleep	16.49 (4.91)	*T* = 70.84 (15.05)	Exceptionally high
Sleep breathing disorders	4.21 (1.72)	*T* = 53.07 (11.26)	Average
Disorders of arousal	3.25 (0.67)	*T* = 49.86 (7.70)	Average
Sleep wake transition disorders	9.69 (3.20)	*T* = 56.28 (12.13)	Average
Disorders of excessive somnolence	9.34 (2.68)	*T* = 58.66 (10.40)	High average
Sleep hyperhidrosis	2.58 (0.93)	*T* = 48.48 (5.54)	Average
Cognitive developmental level (Bayley)	47.27 (12.84)	Dev. Age = 15.83 (6.96)	–
Autistic features (ADOS)			
Total score	12.76 (6.00)	CSS = 4.5 (2.00)	Low level of symptoms
Social affect	10.36 (5.38)	CSS = 4.66 (2.26)	Low level of symptoms
Restrictive and repetitive behaviours	2.39 (1.64)	CSS = 5.19 (2.17)	Middle level of symptoms
Emotional/behavioural problems (CBCL)			
Total score	56.67 (20.73)	*T* = 61.31 (8.36)	High average
Internalising	14.65 (7.75)	*T* = 58.73 (8.85)	High average
Externalising	19.3 (7.76)	*T* = 57.98 (8.82)	High average
Outcome variables			
Health-related quality of life (ITQOL)			
Child health-related quality of life‡	59.09 (11.29)	–	–
General health perceptions	53.57 (21.95)	*Z* = −2.4 (1.74)	Exceptionally low
Physical abilities	46.94 (21.37)	*Z* = −6.16 (2.57)	Exceptionally low
Growth and development	53.4 (18.47)	*Z* = −3.67 (1.79)	Exceptionally low
Bodily pain	76.61 (19.42)	*Z* = −0.76 (1.49)	Low average
Temperament and moods	68.5 (15.82)	*Z* = −1 (1.31)	Below average
Combined behaviour	55.5 (15.52)	*Z* = −1.12 (0.91)	Below average
Impact of child's syndrome on parent§	64.06 (26.38)	–	–
Parental impact – emotional	64.3 (25.78)	*Z* = −3.45 (2.90)	Exceptionally low
Parental impact – time	63.81 (32.43)	*Z* = −3.7 (3.73)	Exceptionally low
Parenting stress (PSI) total score	77.42 (25.07)	*Z* = 1.37 (1.37)	Above average

For sleeping problems (SDSC), a higher score indicates more sleeping problems. For cognitive developmental level (Bayley), a higher score indicates better cognition. For autistic features (ADOS), a higher score indicates more autistic features. For emotional/behavioural problems (CBCL), a higher score indicates more emotional/behavioural problems. For parenting stress (PSI), a higher score indicates more parenting stress. For child HRQoL, a higher score indicates better child HRQoL. For impact of the child's syndrome on parent, a higher score indicates less impact for the child's syndromes on the parent's emotion and time to attend their own personal needs.

†Standard scores were based on the available norm groups for each instrument, consisting of typically developing children. These norm groups were not age-matched for the current study sample. Therefore, the standardised scores should be interpreted with caution and raw scores were used in the analyses. Qualitative descriptions were based on the clinical neuropsychology consensus statement on uniform labelling of performance test scores (Guilmette *et al.* 2020).

‡ITQOL Total Child Scale was calculated as the mean of scales 'general health perceptions', 'physical abilities', 'bodily pain', 'temperament and moods' and 'combined behaviour'.

§ITQOL Total Parent Scale was calculated as the mean of scales 'parental impact – emotional' and 'parental impact – time'.

Abbreviations: ADOS, Autism Diagnostic Observation Scale; CBCL, Child Behaviour Checklist; CSS, Calibrated Severity Score; Dev. Age, developmental age (in months); ITQOL, Infant and Toddler Quality of Life Questionnaire; PSI, Parenting Stress Index; SDSC, Sleep Disturbance Scale for Children.

Table 3 Multiple regression analysis predicting child HRQoL (ITQoL)

	B (*SE*)	*β*	t	*P*
Step 1				
Sex	2.03 (2.67)	.09	0.76	.447
Age	−0.36 (0.28)	−.16	−1.26	.209
Socio-economic status	−2.30 (2.97)	−.10	−0.78	.439
Step 2				
Sex	−2.74 (2.20)	−.12	−1.25	.213
Age	−0.56 (0.27)	−.25	−2.06	.044*
Socio-economic status	−0.43 (3.01)	−.02	−0.14	.888
Genotype	9.13 (2.99)	.40	3.06	.002*
Epilepsy	−2.52 (2.66)	−.11	−0.95	.345
Sleeping problems (SDSC)	−0.25 (0.14)	−.21	−1.82	.072
Cognitive developmental level (Bayley)	0.18 (0.13)	.21	1.39	.164
Autistic features (ADOS)	0.43 (0.25)	.23	1.71	.088
Emotional/behavioural problems (CBCL)	−0.24 (0.06)	−.45	−3.95	<.001*

R^2 = .04 for step 1, ΔR^2 = .49 for step 2 ($P < .001$), total R^2 = .55.

Covariates were added to the model in step 1. Predictors were added to the model in step 2. This allowed us to quantify the explained variance that can be attributed to the predictors (ΔR^2).

*Significant at the.05 level (two-tailed).

Abbreviations: ADOS, Autism Diagnostic Observation Scale; CBCL, Child Behaviour Checklist; ITQOL, Infant and Toddler Quality of Life Questionnaire; SDSC, Sleep Disturbance Scale for Children.

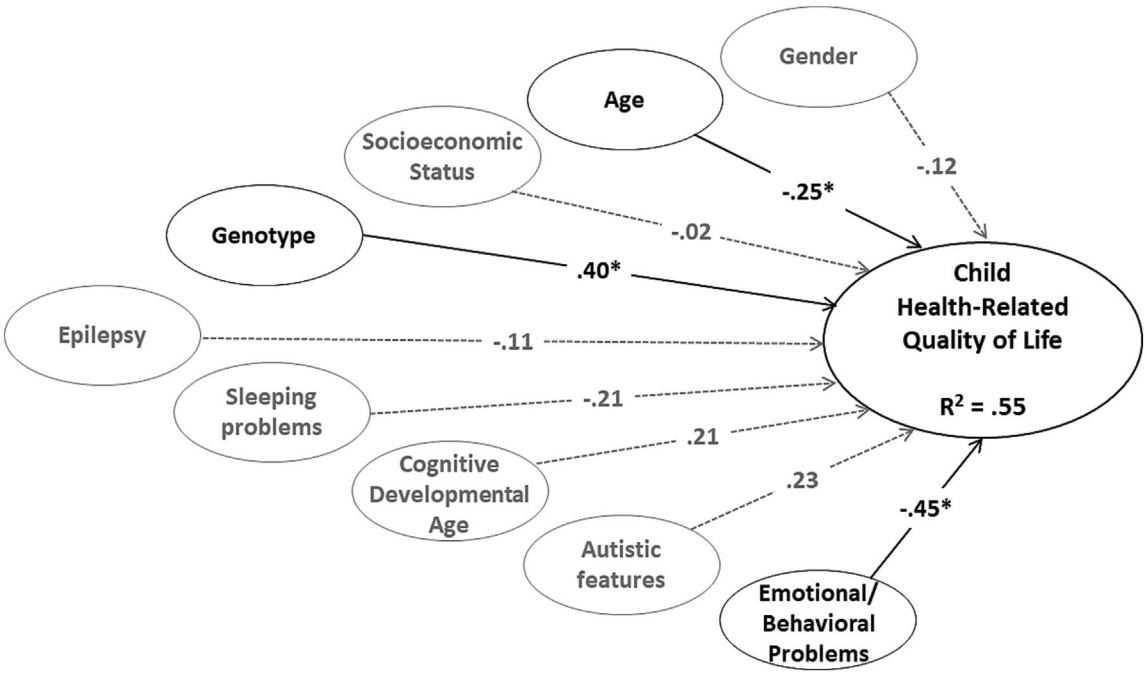

Figure 1. Graphic illustration of the regression analysis predicting child health-related quality of life (HRQoL). *Note*: This figure demonstrates the factors predicting child HRQoL in Angelman syndrome (AS). The numbers represent the *β* (standardised *B*) values of the predictors. A significant predictor is depicted by a continuous line, star and black colour. A grey dashed line represents a non-significant predictor.

problems, an additional analysis was performed with the CBCL subscales 'Internalising problems' and 'Externalising problems' added to the model (instead of the CBCL total problem score). Internalising problems were a significant predictor of child HRQoL [$\beta = -.42$, t (72) = −3.04, $P = .005$] while externalising problems were not [$\beta = -.02$, t (72) = −0.13, $p = .898$]. Results of the additional exploratory analysis are presented in Table S6a of Appendix 6.

Associations between child characteristics and the impact of the child's syndrome on the parent

Table 4 and Figure 2 show the associations between child characteristics and the impact of the child's syndromes on the parent. The final model was significant ($F_{9, 63} = 2.45$, $P = .047$, $R^2 = .26$) and had a higher explained variance compared with the model with covariates only ($\Delta R^2 = .22$, $P = .011$). Sleeping problems were the only significant predictor in this model, indicating that more sleeping problems related to a higher impact of the child's syndrome on the parent.

Associations between child characteristics and parenting stress

The results of the multiple regression analysis predicting parenting stress are shown in Table 5 and Figure 3. The final model explained a significant amount of variance in PSI score (F (9, 63) = 4.68, $p < .001$, $R^2 = .43$). In comparison with the model with covariates only, adding the predictors to the model significantly increased the explained variance ($\Delta R^2 = .26$, $p = .003$). Emotional/behavioural problems were a significant predictor for parenting stress. It was also the strongest predictor of this model (largest β of .32). This indicates that more child emotional/behavioural problems were associated with more parenting stress. An in-depth exploratory analysis was performed by adding the CBCL subscales 'Internalising problems' and 'Externalising problems' to the model. Both internalising and externalising problems did not significantly predict parenting stress (see Table S6b in Appendix S6).

Sensitivity analyses

Finally, two sensitivity analyses were performed. Lasso regression analyses identical to the

Table 4 Multiple regression analysis predicting the impact of the child's syndromes on the parent (ITQOL)

	B (*SE*)	*β*	*t*	*P*
Step 1				
Sex	−1.81 (6.37)	−.03	−0.28	.776
Age	0.60 (0.65)	.11	0.92	.359
Socio-economic status	−5.86 (6.68)	−.11	−0.88	.381
Step 2				
Sex	−6.83 (6.40)	−.13	−1.07	.286
Age	0.20 (0.71)	.04	0.28	.779
Socio-economic status	−3.99 (7.29)	−.07	−0.55	.586
Genotype	7.28 (9.31)	.14	0.78	.435
Epilepsy	−2.27 (7.53)	−.04	−0.30	.763
Sleeping problems (SDSC)	−1.05 (0.46)	−.37	−2.29	.029*
Cognitive developmental level (Bayley)	−0.03 (0.46)	−.01	−0.06	.953
Autistic features (ADOS)	0.77 (0.75)	.18	1.02	.306
Emotional/behavioural problems (CBCL)	−0.19 (0.19)	−.15	−1.00	.318

$R^2 = .04$ for step 1, $\Delta R^2 = .22$ for step 2 ($P = .011$), total $R^2 = .26$.

*Significant at the.05 level (two-tailed).

Covariates were added to the model in step 1. Predictors were added to the model in step 2. This allowed us to quantify the explained variance that can be attributed to the predictors (ΔR^2).

Abbreviations: ADOS, Autism Diagnostic Observation Scale; CBCL, Child Behaviour Checklist; ITQOL, Infant and Toddler Quality of Life Questionnaire; SDSC, Sleep Disturbance Scale for Children.

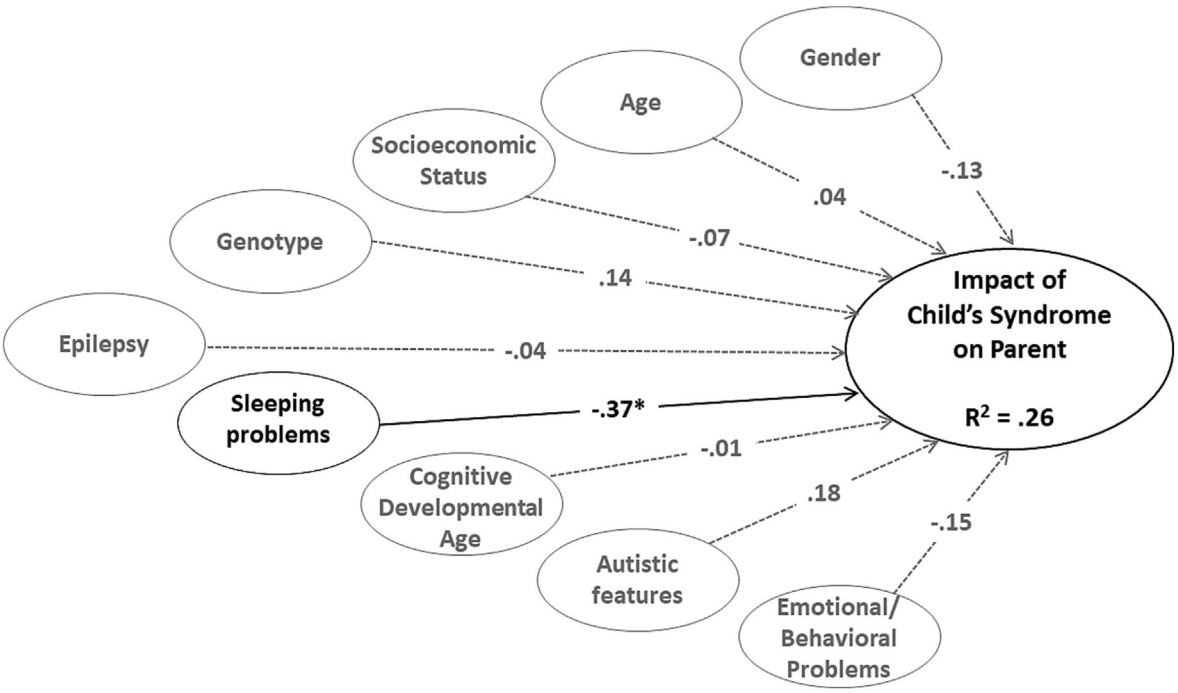

Figure 2. Graphic illustration of the regression analysis predicting the impact of the child's syndrome on the parent. *Note*: This figure demonstrates the factors predicting the impact of the child's Angelman syndrome on the parent. The numbers represent the β (standardised B) values of the predictors. A significant predictor is depicted by a continuous line, star and black colour. A grey dashed line represents a non-significant predictor.

Table 5 Multiple regression analysis predicting parenting stress (PSI total score)

	B (*SE*)	β	*t*	*P*
Step 1				
Sex	−10.41 (7.75)	−.21	−1.77	.078
Age	0.45 (0.60)	.09	0.75	.452
Socio-economic status	15.53 (6.07)	.30	2.56	.011*
Step 2				
Sex	−4.16 (5.80)	−.08	−0.72	.474
Age	1.08 (0.66)	.21	1.65	.103
Socio-economic status	13.83 (6.86)	.27	2.02	.054
Genotype	−9.48 (7.91)	−.19	−1.20	.232
Epilepsy	−5.16 (6.87)	−.10	−0.75	.454
Sleeping problems (SDSC)	0.64 (0.41)	.24	1.56	.132
Cognitive developmental level (Bayley)	0.10 (0.38)	.05	0.25	.804
Autistic features (ADOS)	−0.71 (0.89)	−.17	−0.80	.437
Emotional/behavioural problems (CBCL)	0.38 (0.18)	.32	2.16	.037*

R^2 = .14 for Step 1, ΔR^2 = .26 for Step 2 (p = .003), total R^2 = .43.

*Significant at the .05 level (two-tailed).

Covariates were added to the model in step 1. Predictors were added to the model in step 2. This allowed us to quantify the explained variance that can be attributed to the predictors (ΔR^2).

Abbreviations: ADOS, Autism Diagnostic Observation Scale; CBCL, Child Behaviour Checklist; PSI, Parenting Stress Index; SDSC, Sleep Disturbance Scale for Children.

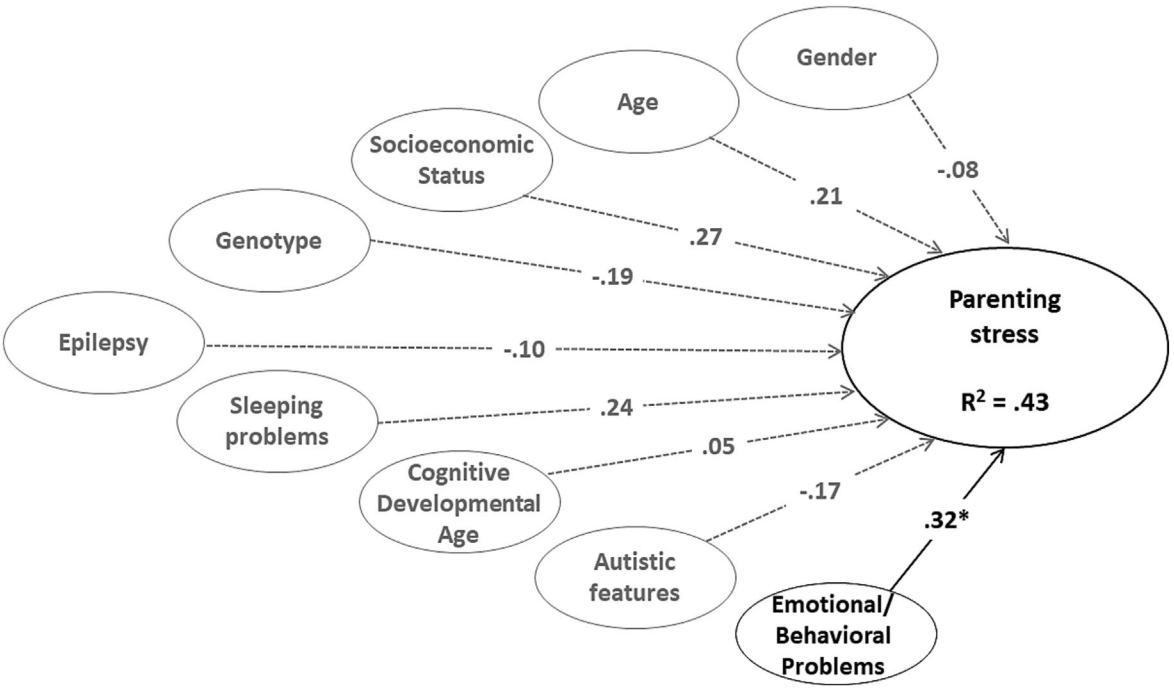

Figure 3. Graphic illustration of the regression analysis predicting parenting stress. *Note*: This figure demonstrates the factors predicting parenting stress in Angelman syndrome (AS). The numbers represent the β (standardised B) values of the predictors. A significant predictor is depicted by a continuous line, star and black colour. A grey dashed line represents a non-significant predictor.

above-mentioned OLS regression analyses showed that conclusions were comparable. Beta coefficients are depicted in Table S3a-c of Appendix S3. Second, complete case analyses showed that conclusions were identical to the analyses with imputed outcome variables, except for child HRQoL. Here, sleeping problems were an additional significant predictor. Results are given in Table S7a-c of Appendix S7.

Discussion

In this study, we investigated the association of child characteristics with child HRQoL and parenting stress in a large clinical cohort of children with AS. Results show that child HRQoL was exceptionally low in AS, while parenting stress was above average and the impact of the child's syndrome on the parent was exceptionally high. Emotional/behavioural problems were the strongest significant predictors of child HRQoL. Internalising problems (anxious/depressed, emotional reactive, somatic complaints and withdrawn) were driving this effect. Having more internalising problems was associated with lower child HRQoL. In addition, genotype and age were significant predictors for child HRQoL. The deletion genotype and higher age were related to lower child HRQoL. Furthermore, sleeping problems were clearly the strongest significant predictor for the impact of the child's syndrome on the parent. Finally, emotional/behavioural problems were the strongest significant predictor for parenting stress. More emotional/behavioural problems were related to more parenting stress.

Although earlier studies interpreted the typical AS smiling and laughing behaviour as indicating good quality of life (Clayton-Smith & Laan 2003), our finding that HRQoL was lowered in AS corroborates more recent attention to the impact of AS symptoms on the individuals and on their family (Wheeler *et al.* 2017; Grieco *et al.* 2018; Willgoss *et al.* 2021; Khan *et al.* 2023). We found that parenting stress and the impact of the child's syndrome on the parent are elevated in AS, which is in line with previous literature (Wulffaert *et al.* 2010; Griffith *et al.* 2011; Thomson *et al.* 2017).

Having more emotional/behavioural problems was the strongest predictor of lowered child HRQoL, and internalising problems were driving this effect. Having AS may lead to stressful experiences that induce emotional/behavioural problems. For example, when children with AS cannot express their thoughts and feelings due to communication difficulties, these feelings may be internalised. The finding that internalising problems predict HRQoL is in line with the recent focus of the AS community on anxiety. Anxiety is thought to occur frequently in AS and is regarded by parents as an invalidating symptom (Wheeler *et al*. 2019; Keary *et al*. 2021; Grebe *et al*. 2022). In addition to internalising problems, we found that genotype and age were significant predictors of child HRQoL. We know that children with the deletion subtype generally have a more severe phenotype (Gentile *et al*. 2010; Bindels-de Heus *et al*. 2020). The finding that higher age is related to lower child HRQoL may be explained by the knowledge that as children with AS age, the difference to their peers increases and becomes more notable, comorbid health risks increase and anxiety increases (Prasad *et al*. 2018). Finally, sleeping problems were not a significant predictor of child HRQoL in the primary analysis, but were significant in the complete case analysis and in the analysis with the CBCL subscales. Consensus criteria state that people with AS have a diminished *need* for sleep (Williams *et al*. 2006). Therefore, some studies have argued that sleeping problems do not affect the person's daytime alertness, activity level and quality of life (Pelc *et al*. 2008) while other studies have concluded that daytime somnolence is characteristic for individuals with AS (Spruyt *et al*. 2018). We suggest that future studies investigate the possible effect of sleep on HRQoL in a larger sample, collect more detailed information on sleep and explore possible explanations for this effect.

Child sleeping problems were the strongest predictor for the impact of the child's syndrome on the parent. Child emotional/behavioural problems were the strongest predictor for parenting stress. Both factors were identified in earlier studies in AS (Didden *et al*. 2004; Goldman *et al*. 2012; Miodrag & Peters 2015; Trickett *et al*. 2017; Sadhwani *et al*. 2019). The current study goes one step further, showing that even in comparison with other factors (genotype, epilepsy, cognitive developmental level and autistic features), sleeping problems and emotional/behavioural problems have the strongest impact on parents. Sleeping problems of the child may impact sleep quality and duration of the parent(s), therefore leading to daytime exhaustion and irritability. Disruptive behaviour such as biting, yelling, hair pulling and hitting may lead to parenting stress during daily routines and community outings. Constant attention-seeking and hyperactive behaviours may induce parenting stress through the need for constant vigilance and not having time to attend one's own personal needs. In this light, it is surprising that our explorative analyses of CBCL subscales indicate that externalising behaviour was not a significant predictor of parenting stress. This could be due to our small sample size or due to the use of the CBCL, which contains only one question on hyperactivity. Finally, the relationship between behaviour of the child and stress of the parent is thought to be bidirectional: behavioural problems of the child will lead to more parenting stress, but more parenting stress will also lead to less effective parenting and deterioration of the child–parent relationship. In turn, this can contribute to the worsening of child behavioural problems (Gottlieb 2007; Neece *et al*. 2012).

We also identified factors that were less important in relation to parenting stress/impact and child HRQoL. First, cognitive developmental level was not a significant predictor. Previous literature using univariate analysis showed a small but significant (positive) correlation between cognitive developmental level and parenting stress (Miodrag & Peters 2015). The current study did not confirm this in a multivariate model. Children with AS typically have a severe developmental delay, and slight variations in cognition may have less impact. Furthermore, the Bayley-III Cognition Scale may be less sensitive to measure daily functioning in AS than parent reports of adaptive behaviour (such as scales for adaptive functioning). Finally, the relation between cognition and HRQoL might be more variable. Intuitively, higher cognitive abilities would lead to higher adaptive functioning, which is an element of HRQoL. On the other hand, non-deletion AS genotypes have been associated with higher cognitive abilities, but also with higher levels of irritability and anxiety (Gentile *et al*. 2010; Wheeler *et al*. 2019). A possible explanation is that children

with higher cognitive abilities are more aware of their difficulties in meeting the demands of the environment, and their difference compared with peers (Wheeler *et al.* 2019).

Second, autistic features were not a significant predictor. In the general ASD population, HRQoL is lowered (van Heijst & Geurts 2015; ten Hoopen *et al.* 2020), and parenting stress is elevated (Hayes & Watson 2013), with autism symptom severity relating to parenting stress (Hastings & Johnson 2001). In children with AS, there is an ongoing debate on whether the 'autism symptoms' should be interpreted as ASD or whether they are associated with their developmental level (Trillingsgaard & Østergaard 2004). Further, the ADOS has been found to over-diagnose autism in children with IDs (Sappok *et al.* 2013), questioning its validity in this population.

Finally, epilepsy was not a significant predictor. This is surprising, as parents and clinicians report epilepsy as a symptom with major impact on the individuals with AS and their families (Grieco *et al.* 2018; Willgoss *et al.* 2021). Possibly, our classification of the presence or absences of epilepsy is unable to capture the differential impact of seizure type, frequency and severity of epilepsy, and the (side-) effects of anti-epileptic medication.

Strengths of the current study are the use of a nationwide clinical prospective cohort, which is large in the context of the incidence of AS. This cohort does not have the potential selection bias of a research cohort. Moreover, the extensive assessments we offer to our patients enable us to analyse all these characteristics in one multivariate model, making it possible to investigate their relative importance in predicting HRQoL and parenting stress in AS. In addition, a multivariate model approaches reality better than a univariate model. Finally, the results of the OLS regression model were corroborated by the results of the Lasso regression model, which minimises the chance of overfitting and maximises the generalizability of results. Limitations of this study are that not all potentially important variables to children with AS and their families, such as communication and motor skills, were measured in this study. Further, some of the measurement instruments (e.g., CBCL and ITQoL) may have a lower validity when used in the current population, as they were originally designed for use in typically developing children. The use of an adjusted version of the CBCL may have countered elevated problem scores due to behaviour appropriate for low developmental age, but therefore limits comparison with other studies. Children with AS are unable to self-report on HRQoL; thus, we rely on parent-reported questionnaires. Parenting stress and worry may influence their response to these questions.

In summary, the current study confirms that HRQoL is lowered in children with AS, extending previous findings on adolescents and adults with AS (Khan *et al.* 2023). This is the first study investigating the relation between child characteristics and child HRQoL in AS, showing that child emotional/behavioural problems, genotype and age are significant predictors. In addition, we confirm previous research showing that parenting stress/impact is heightened in parents of children with AS and that child sleeping problems and emotional/behavioural problems are important predictors. We extend these findings using a multivariate model, demonstrating that sleeping problems and emotional/behavioural problems have a stronger impact on parenting stress than genotype, epilepsy, cognitive developmental level and autistic features.

These findings are valuable for future research and clinical practice. We propose that clinical trials should prioritise measuring child HRQoL, parenting stress, sleeping problems and emotional/behavioural problems. An area that requires future research is the development of measures that are especially tailored to individuals with AS (or those with IDs). In addition, monitoring child HRQoL and parenting stress/impact should be part of standard clinical care for AS families. When considering interventions aimed at increasing child HRQoL and decreasing parenting stress in AS, we suggest that targeting child emotional/behavioural problems and sleeping problems will be beneficial not only for the child but also for the parent(s). Interventions aimed at decreasing child emotional/behavioural problems could, for example, involve identifying new and adaptive ways for the child to express their emotions using Augmented and Aided Communication. Sleeping problems may be reduced through behavioural interventions (Allen *et al.* 2013; Bindels-de Heus *et al.* 2023) or sleep medication (Braam *et al.* 2008). Parenting stress could also be

directly targeted, for example, through mindfulness interventions (Neece 2014), teaching adaptive coping styles or by validating and supporting parents in prioritising their own sleep and well-being and help them organise respite care for their child. Because child behaviour problems and parenting stress reinforce each other in a bidirectional manner (Neece *et al.* 2012), interventions should focus on both the child and the parents (and the rest of the family) in a systemic approach.

Conclusion

Emotional/behavioural problems were the strongest significant predictor for child HRQoL in AS, and internalising problems were driving this effect. In addition, having the deletion genotype and higher age were related to lower child HRQoL. Child sleeping problems and emotional/behavioural problems were related to the impact of the child's syndrome on the parent and to parenting stress. We suggest that tackling child behavioural and sleeping problems is likely to improve HRQoL of the whole family and that these problems should be a regular subject of each consultation in AS.

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Conflict of interest

Marie-Claire Y. de Wit is the Erasmus MC study site leader for the Roche Tangelo study, and the hospital received funding for this study. The hospital also received compensation from Roche and Jazz Pharmaceuticals for giving advice. The Department of Child and Adolescent Psychiatry/Psychology (Erasmus MC) is the Dutch distributer of the Achenbach System of Empirically Based Assessment (ASEBA) measurement instruments, which include the Child Behaviour Checklist (CBCL). The department receives financial compensation for selling the measurement instruments. All other authors have no conflict of interest to declare.

Ethics statement

This clinical record study did not fall within the scope of the Medical Research Involving Human Subjects Act (MEC-2015-203). Participants (their legal representatives) who did not give consent to use data collected in clinical care for scientific research were not included in the study.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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