Lumanity

Quality of Life and its Drivers for Patients Living with Angelman Syndrome: A Systematic Review

Authors: Vyshnavi Telukuntla, Rishabh Verma, Nidhun Kandoth, Sukannya Mahapatra , Amit Ahuja and Inderpreet Khurana

Affiliations: Lumanity, Gurugram, India

INTRODUCTION

- Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by loss of *UBE3A* expression in neurons.[1] Patients exhibit intellectual disability, balance disorders, behavioural issues, seizures, sleep disturbances, and speech impairment[2]
- The most common genetic cause is a deletion on chromosome 15q11-q13 encompassing the *UBE3A* gene. Other causes include pathogenic variants in *UBE3A*, imprinting defects, and paternal uniparental disomy for chromosome 15, collectively known as non-deletion AS
- Most patients with AS have an approximately 4 Mb maternal deletion of 15q11-q13 (Class I). Others have paternal uniparental disomy of chromosome 15 (Class II), imprinting defects (Class III), or UBE3A mutations (Class IV)[3]
- In healthy individuals, certain genes are expressed only when they are inherited from a specific parent (i.e. the genes are imprinted). One of these imprinted genes is *UBE3A*, which is expressed only when it is inherited from the mother[4]

OBJECTIVES

To comprehensively identify the available evidence regarding the impact of AS on patients' health state utility values (HSUVs) and quality of life (QoL).

METHODS

- Embase® and MEDLINE® databases were systematically searched via Embase.com, in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines, by pairing relevant keywords to identify English-language studies reporting on the health-related quality of life in patients with AS
- Publications were limited to those reporting information on utility and QoL among adult patients with AS, as per pre-defined inclusion criteria presented in **Table 1**
- Two independent reviewers performed initial screening of titles and abstracts from the database search. Each potentially relevant record was further screened in full by two independent reviewers. Any uncertainty regarding the inclusion of a record was reconciled by a third reviewer

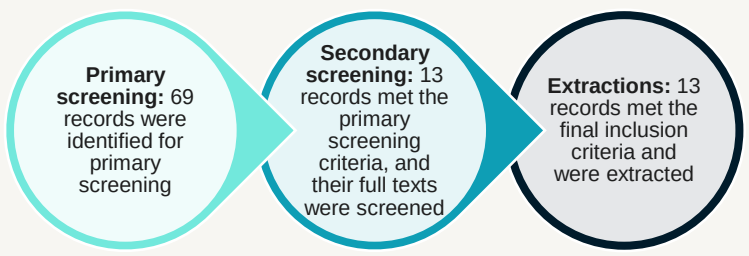
Table 1. Inclusion criteria

Population	Adults and children with Angelman syndrome
Intervention and comparator	No restriction
Outcomes	Utility values and quality of life
Study design	Studies reporting utility values and quality-of-life data
Country	No restrictions
Language	English

RESULTS

- A total of 69 records were screened using the predefined population, intervention, comparison, outcomes and study-based criteria; 13 records were identified and included that evaluated the health state utility values (HSUVs) and QoL in patients with AS (Figure 1)

Figure 1. Study flow diagram



- Out of 13 included studies, seven[5-11] were conducted in the US, four[12-15] were conducted in the Netherlands, and one study each was conducted in Spain[16] and Turkey.[17] Only one study reported HSUVs; the remaining studies provided QoL data
- Most of the studies (54%) adhered to observational/real-world study designs, including four prospective observational (31%), two cross-sectional (15%) and one retrospective (8%). The remaining three studies (23%) were randomized controlled trials. Three studies (23%) focused on data collection methods, i.e. surveys
- The sample size ranged from 16[16] to 301[8] patients with Angelman syndrome

HSUVs and QoL in patients with Angelman syndrome

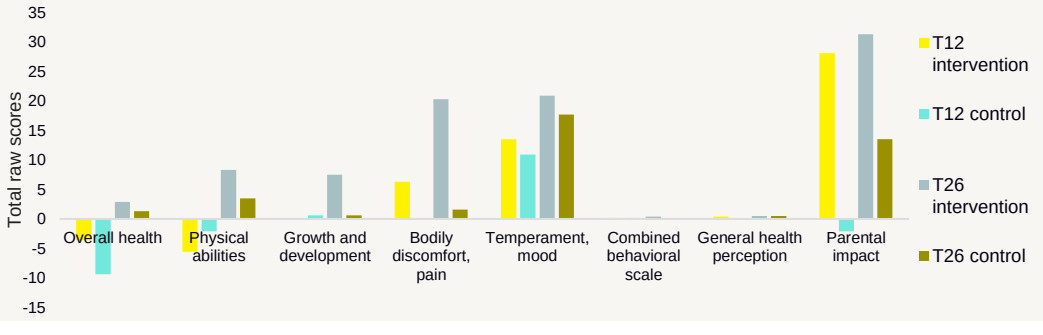
EQ-5D™ questionnaire

- The mean utility score was 0.44 ± 0.20, and the mean VAS score was 84 ± 1.5. The EQ-5D sub-scale date indicated that patients' self-care, mobility and daily activities were the most impacted dimensions[7]
- All adolescents (100%) and most adults (93%) had at least moderate problems with self-care activities, such as washing or dressing themselves. More than half (55%) of adolescents and adults had at least moderate issues with mobility and usual activities[7]
- The mean EQ-5D-5L VAS score was higher in patients aged 18 years or older (87.6) compared with those aged 1–4 years (82.7) and 5–12 years (82.2), and in patients with AS deletion genotype compared with those with AS non-deletion genotype (84.3 versus 81.4, respectively)[9]

ITQOL-SF47

- QoL in children was assessed using the 47-item parent-reported ITQOL-SF47
- Patients with AS participating in a behavioural interventional programme were compared with patients in a control group. Intervention included a standardized programme with home visits; psychoeducation; feedback based on direct observation and video footage of the bedtime routine; and behavioural treatment techniques by a therapist[12]
- A significantly greater positive change on parental impact was observed with ITQOL in the intervention group, compared with the control group at both 12 and 26 weeks from baseline ($p < 0.05$). Parental impact items concern the amount of worry and time limitations experienced by the parent due to his or her child's problems[12] **(Figure 2)**
- A positive effect on combined behaviour within the intervention group was shown at 12 and 26 weeks ($p < 0.0.5$). Combined behaviour items concern behavioural problems, such as not following directions, hitting, biting, throwing tantrums, being easily distracted and inability to cooperate[12]
- A positive effect on temperature and mood was found in both groups at 12 weeks ($p < 0.05$)

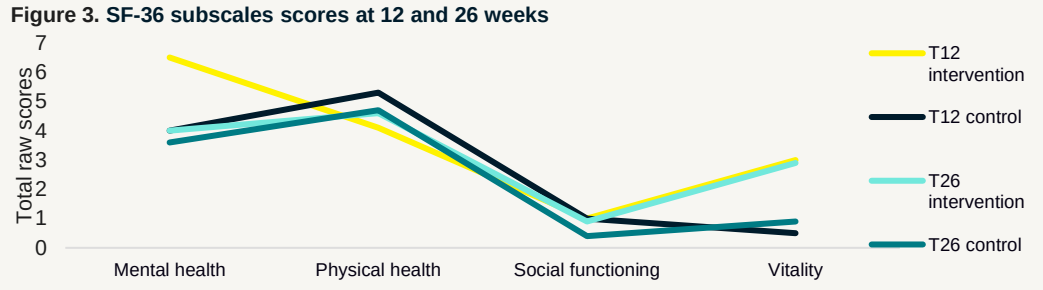
Figure 2. ITQoL-SF47 subscales mean difference scores at 12 and 26 weeks



SF-36

- The Short Form Health Survey – 36 items (SF-36) is a widely used tool to measure health-related QoL
- Patients with AS participating in a behavioural intervention programme were compared with patients in a control group. See the ITQoL-SF47 section for intervention details[12]
- Although no significant difference was observed using SF-36 between the groups, a significant effect was observed on vitality, mental health and social functioning within the intervention group at 12 weeks from baseline, with a persistent significant effect on vitality at 26 weeks. No effect was seen within the control group at 12 and 26 weeks[12] **(Figure 3)**

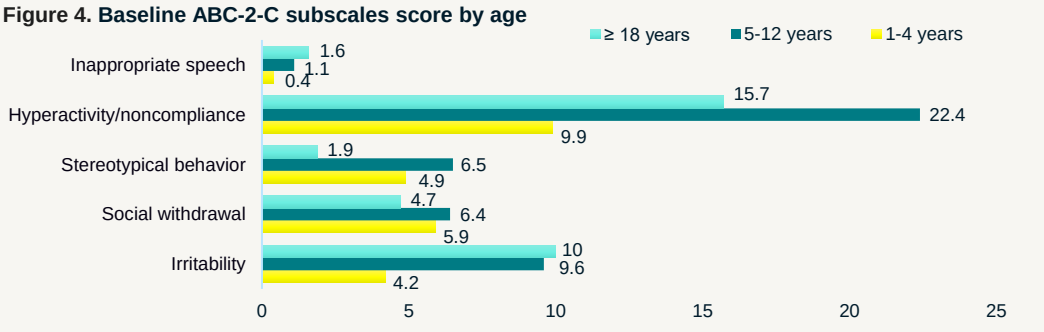
Figure 3. SF-36 subscales scores at 12 and 26 weeks



ABC-2-C

- The mean ABC-2-C subscales score for irritability was higher in patients aged ≥ 18 years compared with those aged 5–12 years and 1–4 years (10 vs 9.6 vs 4.2, respectively)[9] **(Figure 4)**
- Social withdrawal was higher in patients aged 5–12 years (6.4) compared with those aged 1–4 years (5.9) and ≥ 18 years (4.7). A similar trend was observed for stereotypical behaviour (6.5 vs 4.9 vs 1.9, respectively) and hyperactivity/noncompliance (22.4 vs 9.9 vs 15.7, respectively)[9]
- Inappropriate speech was higher in patients aged ≥ 18 years (1.6) compared with those aged 1–4 years (0.4) and 5–12 years (1.1)

Figure 4. Baseline ABC-2-C subscales score by age



- Age, gender and genotype are the most significant and widely reported drivers of QoL in patients with AS, while socioeconomic factors and comorbidities are reported less frequently **(Table 2)**

Table 2. Number of studies reporting key drivers

Key drivers	EQ-5D	ITQOL-SF47	ABC-2-C	Anxiety score
Age	1	1	1	1
Gender	0	1	1	0
Socio-economic status	0	1	0	0
Comorbidities	0	1	0	0
Genotype	0	1	1	0

Key: ABC-C, Aberrant Behaviour Checklist Second Edition Community version; ITQOL-SF47, Infant and Toddler Quality of Life Questionnaire–Short Form.

CONCLUSIONS

- AS profoundly impacts QoL through various drivers, including behavioural and emotional problems, sleep disturbances, and genetic factors. Age, gender, and genotype are the key factors that influence overall QoL
- Our work highlights the need for comprehensive, family-centred intervention strategies. Effective treatment and disease management can enhance health-related QoL for patients with AS

REFERENCES

1. Khan et al. *Mol Genet Genomic Med*. 2019;7(7):e00734. 2. Williams et al. *Am J Med Genet A*. 2006;140(5):413-8. 3. Lossie et al. *J Med Genet.* 2001;38(12):834-45. 4. Clayton-Smith et al. *J Med Genet.* 2003;40(2):87-95. 5. Grebe et al. *Am J Intellect Dev Disabil.* 2022;127(1):1-10. 6. Keary. *Value health.* 2020;23(1):S341-S2. 7. Khan et al. *Qual Life Res.* 2023;32(7):2059-67. 8. Sadhwani et al. *Am J Med Genet A.* 2019;179(6):983-92. 9. Tjeertes et al. *J Neurodev Disord.* 2023;15(1):22. 10. Wheeler et al. *J Intellect Disabil Res.* 2019;63(10):1234-47. 11. Xia et al. *Pediatr Neurol.* 2023;149:19-25. 12. Bindels-de Heus et al. *Res Dev Disabil.* 2023;135:104444. 13. den Besten et al. *Am J Med Genet A.* 2021;185(1):168-81. 14. Hagenaar et al. *J Intellect Disabil Res.* 2024;68(3):248-63. 15. P. *J Intellect Disabil Res.* 2021;65(9):805. 16. Morencos. *J Pediatr Gastroenterol Nutr*. 2023;76:1057. 17. Çınar et al. *J Pediatr Adolesc Gynecol.* 2023;36(4):363-71.

An electronic version of the poster can be viewed by scanning the QR code.

Poster presented at the 2024 ISPOR Europe; 17-20 November 2024; Barcelona, Spain.