Comparison of Autistic and Nonautistic Transgender Youth Attending Psychiatric Clinics Who Request Hormonal Therapy: A Retrospective Pilot Study

Livia Balan-Moshe MD PhD[1,4], Moran Shemesh-Iron[2], Daniel Assaf MD[2], Shira Goldman MD[2], Maya Schwartz-Lifshitz MD[1,4], Shlomit Tsafrir MD[1,4], and Doron Gothelf MD[1,3,4]

[1]Department of Child and Adolescent Psychiatry, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel
[2]Department of Pediatric Endocrine and Diabetes Unit, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel
[3]Sagol School of Neuroscience, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[4]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Transgender and gender diverse (TGD) adolescents often experience higher rates of psychiatric co-morbidities, autism spectrum disorder (ASD), and autistic traits. A few studies have described TGD adolescents who were referred to psychiatric clinics. To the best of our knowledge, no study has yet compared clinical characteristics of autistic vs. nonautistic TGD adolescents.

Objectives: To describe the demographic and clinical characteristics of TGD adolescents referred to a tertiary child and adolescent psychiatric clinic, and to compare the characteristics of autistic and nonautistic TGD adolescents.

Methods: We conducted a retrospective study of 28 TDG adolescents who were consecutively referred for psychiatric evaluation in a child and adolescent psychiatric clinic at a tertiary children's hospital between December 2020 and February 2023. Data were collected from electronic medical files.

Results: Of the sample, 67.9% first questioned their gender identity after the onset of secondary sex characteristics (pubertal onset) and 35.7% were identified as gifted. The gifted group had a higher rate of pubertal onset compared to the nongifted group. Our cohort exhibited a higher rate of ASD (39.3%) than the general population. Autistic compared to nonautistic TGD adolescents had a higher rate of giftedness and a lower rate of social transition.

Conclusions: TGD adolescents referred for psychiatric evaluation display distinct features, including high rates of ASD, giftedness, and pubertal onset. Autistic compared to nonautistic TGD are more likely to be gifted and less likely to have undergone social transition.

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KEY WORDS: adolescents, autism spectrum disorder (ASD), gender diversity, giftedness, social transition

In recent years, there has been a significant surge in the number of adolescents identifying as transgender and gender diverse (TGD) who seek gender-related care from gender clinics [1,2]. In addition to this increase, several notable changes have been observed. There is a trend toward a higher rate of TGD individuals assigned female at birth (AFAB), and a rise in nonbinary or abinary identities, now comprising about 12% of the gender-clinical population [3]. Littman [4] suggested the existence of a subgroup of youth who initially self-identify as transgender only after experiencing puberty-related physical changes. However, this study has not yet been replicated and has been criticized for gathering data from parents rather than directly from the adolescents themselves, raising concerns about the applicability of the findings to the lived experiences of transgender youths.

TGD adolescents exhibit elevated rates of psychiatric co-morbidities, such as anxiety and depressive disorders, as well as increased risk of suicidality [5]. Remarkably, the prevalence of autism spectrum disorder (ASD) diagnoses or autistic traits is significantly higher in the transgender population, with several-fold increases compared to the general population [6]. Estimates range from 6% to 26% of ASD diagnoses within the transgender community [7]. A notable portion of ASD adolescents identify as nonbinary [8] and a recent study has reported a higher prevalence of birth-assigned females among transgender compared to cisgender autistic youth [9].

To date, to the best of our knowledge there have been no studies comparing the longitudinal process of gender identity formation between autistic and nonautistic transgender and gender diverse (TGD) adolescents. In addition, no studies have provided a mental health perspective on an Israeli cohort of transgender youth.

Table 1. Demographics and clinical characteristics of gender diverse youth of the study sample

	Number of patients	(%)
Birth assigned sex		
Male	9	32.1
Female	19	67.9
Current gender		
Binary	18	65.3
Nonbinary	10	35.7
AMAB		
Binary	5	55.5
Nonbinary	4	44.5
AFAB		
Binary	13	68.4
Nonbinary	6	31.6
Parental marital status		
Married	17	63.0
Divorced	7	25.9
Other	3	11.1
Referral clinic		
Endocrinology clinic	13	46.4
Psychiatry clinic	15	53.6
Social transition		
AMAB	3	33.3
AFAB	15	78.9
Total	18	64.3
Timing of first preoccupation with gender identity incongruence		
Prepubertal	9	32.1
Pubertal	19	67.9
Binary identity		
Prepubertal	9	100
Pubertal	9	47.4
Prepubertal		
AMAB	3	33.3
AFAB	6	31.6
Giftedness		
Prepubertal (n=9)	1	11.1
Pubertal (n=19)	9	47.4
Total	10	35.7
Family acceptance of child's gender identity		
Conflicting	2	7.1
Partially accepting	11	39.3
Accepting	15	53.6

Age at first visit to psychiatric clinic in years, mean ± SD (range) 16.3 ± 1.4 (13.1–18.6)

AFAB = assigned female at birth, AMAB = assigned male at birth, SD = standard deviation

This study is the first report on an Israeli cohort of transgender adolescents referred for psychiatric evaluation. In this study, we present the demographic, gender, and mental-health characteristics of adolescents referred for psychiatric assessment due to gender-related needs and mental distress. Given the high rates of ASD in our cohort, we compared the clinical characteristics of autistic and nonautistic TGD adolescents. In addition, based on self-reports by the adolescents, we compared the clinical characteristics of TGD individuals who first self-identified as gender diverse during childhood (prepubertal) with those who did so during adolescence (pubertal).

PATIENTS AND METHODS

For this retrospective study, all data were collected from electronic medical records.

POPULATION

The study cohort comprised 28 adolescents with a mean age of 16.3 years (range 13.1–18.6 years, standard deviation = 1.4). The demographic characteristics of the cohort are detailed in Table 1, while the clinical characteristics are detailed in Table 2. All participants were referred to the child psychiatry outpatient clinic at Safra Children's Hospital, Sheba Medical Center, a tertiary medical center located in the center of Israel, between December 2020 and February 2023. Referrals to the clinic occurred through two avenues: self-referral for psychiatric evaluation due to gender-identity-related mental distress or a request for hormonal therapy approval, (n=13) and referral from the transgender endocrinology clinic, which coordinates the multidisciplinary treatment of transgender and TGD adolescents seeking hormonal therapy (n=15).

The study received approval from the Sheba Medical Center institutional review board, and the requirement for informed consent was waived due to the retrospective nature of the study (1643-24-SMC).

PROCEDURES

All patients referred to the child psychiatry outpatient clinic from the transgender-endocrinology clinic underwent an initial screening evaluation conducted by a senior psychologist (MSI). Those identified during the interview with suspected psychiatric co-morbidities or suspected ASD that may have interfered with medical decision making competence required to gender-affirming medical therapy, were subsequently referred for further evaluation by a child psychiatrist (LBM).

Table 2. Clinical characteristics of gender diverse youth of the study sample

Psychiatric disorders	Total (N=28)		Referral from Endo (n=15) vs. Psych (n=13)		
	Number of patients	(%)	Number of patients (Psych / Endo)	% of total (Psych / Endo)	*P*-value
ASD	11	39.3	3 / 8	23.1 / 53.8	0.137
ADHD-SLD	13	46.4	2 / 11	15.4 / 73.3	0.003
Depression	21	75.0	12 / 9	92.3 / 60.0	0.084
Anxiety	19	67.9	9 / 10	69.2 / 66.7	1.000
Eating disorders	8	28.6	6 / 2	46.2 / 13.3	0.096
Traumatic events and PTSD	8	28.6	5 / 3	38.5 / 20.0	0.410
Non-suicidal self-injury	18	64.3	8 / 10	61.5 / 66.7	1.000
Suicidality*	19	67.8	9 / 10	69.2 / 66.7	1.000

*Suicidality refers to both suicidal ideation and suicidal attempts

ADHD-SLD = attention deficit /hyperactivity disorder and/or specific learning disorders, ASD = autism spectrum disorder, Endo = endocrinology clinic, Psych = psychiatry clinic, PTSD = post-traumatic stress disorder

Chi-square tests two-sided were used for all variables

The psychiatric evaluation encompassed an assessment for DSM-5 psychiatric diagnoses, including ASD, as well as exploration of the developmental history of gender identity and expression. The distinction between pubertal and prepubertal transgender identity was based on the adolescent's recall of events. Prepubertal transgender identity was assigned when adolescents reported experiencing initial concerns regarding gender or gender incongruence before the onset of secondary sexual characteristics. Pubertal transgender identity was assigned when these concerns appeared after they were aware to their changing body. Giftedness was defined in accordance with the Ministry of Education guidelines, relying on the results of screening exams administered to all second grade children in Israel.

Social transition at the initial visit was assessed through appearance and the psychiatric interview [Table1]. We also screened for the lifetime prevalence of neurodevelopmental diagnoses including ASD, psychiatric diagnoses, traumatic and adverse events (such as bullying and abuse), PTSD diagnosis, non-suicidal self-injury (NSSI), and suicidality (thoughts or attempts) [Table 2].

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA). Chi-square and two sample *t*-tests were used for comparing two subgroups within our sample, and one sample *t*-test when comparing to the general population.

RESULTS

COHORT DEMOGRAPHICS AND CHARACTERISTICS

Tables 1 and 2 outlines the clinical and demographic characteristics of our cohort. Among the 28 adolescents studied, 15 (53.6%) were referred from the transgender endocrinology clinic, while 13 (46.4%) were referred from the child psychiatric outpatient clinic. the mean age of our cohort was 16.3 ± 1.4 (range 13.1–18.6), with 67.9% identified as AFAB. Within this sample, 67.9% reported pubertal onset of TGD and 32.1% reported a prepubertal onset [Table 1].

Our cohort exhibited a significantly higher prevalence of gifted youth (35.7%) compared to the general population (3.0%, as defined and screened by the Israeli Ministry of Education, $P = 0.001$, one sample *t*-test, df=27). In addition, there was a notably higher prevalence of ASD diagnosis (1:2.6) compared to the prevalence in the general population (1:36) as reported by the 2020 U.S. Centers for Disease Control and Prevention ASD report [10] (n=11, 39.3%, $P = 0.001$, one sample *t*-test, df=27 [Table 2].

PREPUBERTAL VS. PUBERTAL

There were significantly more prepubertal TDG youth identified with a binary gender identity compared to pubertal TGD youth (n=9, 100% vs. n=9, 47.4%, respectively, $P = 0.01$, chi-square test, two-sided, df=1) [Table 1]. However, we observed no significant difference in the rate of pubertal onset of TGD identity between AMAB and AFAB [Table 1].

Table 3. Comparison of clinical characteristics of ASD vs non-ASD transgender and gender diverse youth

	ASD group, n (%) (n=11)	Nonautistic group, n (%) (n=17)	*P*-value*
AMAB	7 (63.6)	2 (11.7)	0.004
Prepubertal	4 (36.3)	5 (29.4)	0.50
Binary identity	6 (54.5)	12 (70.6)	0.39
Giftedness	7 (63.6)	3 (17.6)	0.019
Social transition	3 (27.2)	15 (88.2)	0.002
ADHD-SLD	7 (73.6)	6 (35.3)	0.14
Depressive disorders	8 (72.7)	13 (76.5)	0.58
Anxiety disorders	8 (72.7)	11 (64.7)	0.49
Eating disorders	1 (14.3)	7 (41.2)	0.077
Trauma and PTSD	1 (14.3)	7 (41.2)	0.077
Non suicidal self-injury	6 (54.5)	12 (70.6)	0.39
Suicidality	6 (54.5)	13 (76.5)	0.21

ADHD-SLD = attention deficit /hyperactivity disorder and/or specific learning disorders, AMAB = assigned male at birth, ASD = autism spectrum disorder, Endo = endocrinology clinic, Psych = psychiatry clinic, PTSD = post-traumatic stress disorder

*A *P*-value < 0.05 was considered statistically significant.

ASD VS. NON-ASD

Table 3 presents the comparison of clinical and demographic characteristics between ASD and non-ASD TGD youth within our cohort. We observed that the autistic subgroup exhibited significantly higher rates of gifted intelligence compared to the nonautistic subgroup (n=7, 63.6% vs. n=3, 17.6%, $P = 0.02$, chi square test, two-sided, df=1). In addition, we observed significant differences in the prevalence of social transition at presentation. Specifically, during the psychiatric interview, the majority of TGD youth with ASD had not yet socially transitioned, whereas most TGD youth without ASD had already done so (n=3 [27.2%] vs. n=15 [88.2%], $P = 0.002$, chi square test, two-sided, df=1) [Table 3].

No statistically significant differences were observed in other clinical aspects or rates of psychopathology between nonautistic and ASD GD youth in our study [Table 3].

REFERRALS FROM THE TRANSGENDER ENDOCRINOLOGY CLINIC VS. REFERRALS FROM THE CHILD PSYCHIATRY OUTPATIENT CLINIC

The following disparities were identified between adolescents referred from the child psychiatry outpatient clinic and those referred from the transgender endocrinology clinic: a higher rate of adolescents with a pubertal onset of transgender identity compared to pre-pubertal onset (n=12, 92.3% vs. n=7, 46.4%, respectively, $P = 0.01$, chi square test, two-sided, df=1), markedly lower rates of attention deficit /hyperactivity disorder and/or specific learning disorders (n=2, 15.4% vs. n=11, 84.6%, respectively, $P = 0.003$, chi square test, two-sided, df=1) [Table 2].

DISCUSSION

In our retrospective study, the cohort, consisting of a mixed population of adolescents who underwent clinical assessment, showed a remarkably high incidence of pubertal onset of TGD identity (67.9%), as well as elevated rates of gifted intelligence (35.7%) and ASD (1:2.6 of the sample).

To the best of our knowledge, this is the first study describing pubertal onset of TGD identity as reported by the teenagers themselves, rather than relying on parental accounts [4]. The high rate of pubertal TGD onset in our cohort may be due to referral bias by the TGD-endocrinology clinic, as this was one of the criteria for psychiatric evaluation. In addition, it may be due to increased referral by parents who perceived their teen's uncertainty with gender identity change as unusual or without previous apparent signs, leading them to seek psychiatric evaluation.

Interestingly, within our sample, all individuals identifying as nonbinary were exclusively of pubertal onset. The association between nonbinary TGD identity and pubertal onset may be linked to the recognition that during puberty, adolescents undergo a process of introspection regarding their identity, including their gender identity, which may encompass a spectrum of possibilities. Longitudinal studies may offer insight into the stability and trajectory of nonbinary gender identities, as well as those emerging during puberty.

The co-morbidity of TGD identity and ASD has been previously documented [7,11] with reported rates of ASD ranging from 5% to 26% among individuals who attend gender clinics. Conversely, studies have found that approximately 5% of autistic children identify as transgender or gender diverse, in contrast to 0.7% of nonautistic children [12]. In our study, we observed a notably elevated rate of ASD, a trend that could potentially be influenced by referral bias. This bias may stem from our inclusion criteria, which encompassed individuals either suspected or previously diagnosed with ASD. Moreover, autistic people experience distinct challenges in linguistic and cognitive domains, particularly in abstract think-

ing, which can potentially hinder their ability to articulate their thoughts, desires, self-image, personal projection, and self-conception. These challenges often result in the referral of autistic individuals for psychiatric evaluation to assess their competency in medical decision-making regarding hormonal therapy.

When comparing autistic adolescents to their nonautistic counterparts, we observed a notably lower rate of social transition within the ASD group. Social transition entails the alignment of an individual's name, pronouns, gender appearance, and behavior with their gender identity. Typically, adolescents are expected to explore their gender identity within social contexts prior to considering hormonal treatment. However, it is noteworthy that adolescents with ASD have predominantly not undergone social transition, yet many express a desire for hormonal therapy. The reduced rate of social transition we found within the ASD group may be attributed to a reduced necessity among autistic TGD teens to socially express their gender identity or to an increased mental strain stemming from the misalignment between their physical sexual characteristics and societal constructs of gender identity.

Notably, we found no significant difference in anxiety and depression rates between nonautistic and autistic adolescents, although autistic youth in the general population have increased rates of anxiety and depressive disorders [13].

Gifted TGD youth compared to their non-gifted counterparts demonstrated a higher propensity to recognize their TGD identity during puberty. Furthermore, among gifted TGD youth, there was a heightened likelihood of meeting diagnostic criteria for ASD. Last, gifted TGD adolescents with ASD exhibited a higher likelihood of pubertal onset. To the best of our knowledge, this is the first documentation of the association between giftedness and TGD. Overall, there is a paucity of studies comparing gifted and non-gifted youth rates of psychopathology [14]. However, existing research indicates that gifted children encounter higher incidences of bullying [15].

van der Miesen et al. [16] proposed a theoretical framework elucidating the association between ASD and transgender identity. They attributed this association to rigidity in gender identity formation, heightened preoccupation, disparate comprehension of social norms and socially ascribed gender roles, and diminished theory of mind. The association between gifted abilities and ASD-TGD identity may be explained by increased theory of mind capabilities in gifted individuals, which could be similarly observed within the autistic population [17]. The heightened capacity of theory of mind as well as hyper-rumination and associated anxiety, coupled with concrete thinking and challenges tolerating uncertainty regarding identity [18] may collectively intersect to elucidate the elevated prevalence of giftedness among autistic TGD adolescents.

LIMITATIONS

The limitations of our study are the small sample size and the naturalistic nature of the study, which limits the ability for appropriate control.

CONCLUSIONS

Our findings focus on one population of TGD adolescents who began to self-identify as gender diverse only following the onset of puberty. This population exhibits a high prevalence of ASD and gifted intellectual abilities, with the majority not having undergone social transition at the time of their presentation to the psychiatric clinic. Still, they expressed a desire for hormonal treatment. Additional research is required to ascertain whether this subset of autistic-gifted TGD adolescents represents a distinct subpopulation within the TGD community. Longitudinal studies are necessary to gain deeper insights into the trajectory, outcome, and mental health needs of both the pubertal onset TGD and gifted-autistic TGD adolescents.

Correspondence

Dr. L. Balan-Moshe
Dept. Child and Adolescent Psychiatry, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: (972-3) 530-2663
Fax: (972-3) 530-2593
Email: livia.balanmoshe@sheba.health.gov.il

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Capsule

Prenatal paracetamol exposure and child neurodevelopment: a systematic review and meta-analysis

D'Antonio et al. included 43 studies in a systematic review and 17 studies in the meta-analysis. When considering sibling comparison studies, paracetamol exposure during pregnancy was not associated with the risk of autism spectrum disorder (OR 0.98, 95%CI 0.93–1.03; *P* = 0.45), ADHD (0.95, 0.86–1.05; *P* = 0·31), or intellectual disability (0.93, 0.69–1.24; *P* = 0·63). There was also no association between paracetamol intake during pregnancy and autism spectrum disorder (OR 1.03, 95% CI 0.86–1·23; *P* = 0.78), ADHD (0.97, 0.89–1.05; *P* = 0·49), or intellectual disability (1.11, 0.92–1.34; *P* = 0.28) when considering only studies at low risk of bias according to QUIPS. This absence of association persisted when considering all studies with adjusted estimates and those with more than 5 years of follow-up. Current evidence does not indicate a clinically important increase in the likelihood of autism spectrum disorder, ADHD, or intellectual disability in children of pregnant individuals who use paracetamol as directed, supporting existing recommendations on its safety.

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Eitan Israeli

Capsule

Spatial fibroblast niches define Crohn's fistulae

McGregor et al. constructed a subcellular-resolution spatial atlas of 68 intestinal fistulae spanning diverse anatomical locations. The authors described fistula-associated epithelial, immune and stromal cell states, revealing abnormal zonation of growth factors and morphogens linked to establishment of tunnelling anatomy. They also identified fistula-associated stromal (FAS) fibroblasts, which are assembled in concentric layers: a proliferative, lumen-adjacent zone beneath neutrophil and macrophage-rich granulation tissue, an active lesion core of FAS cells and a quiescent, pro-fibrotic outer zone. They examined the architecture of the extracellular matrix in the fistula tract and demonstrate that FAS populations associate with distinct collagen structures, exhibiting properties ranging from proliferation, migration and extracellular matrix remodeling to dense collagen deposition and fibrosis. The authors defined niches supporting epithelialization of fistula tunnels and a FAS-like population that is detected at the base of ulcers in non-penetrating Crohn's disease.

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Eitan Israeli