Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1

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ABBREVIATIONS

ASD	Autism spectrum disorder
NF1	Neurofibromatosis type 1
SRS	Social responsiveness scale
VADPRS	Vanderbilt ADHD Diagnostic Parent Rating Scale

AIM Difficulties in neurocognition and social interaction are the most prominent causes of morbidity and long-term disability in children with neurofibromatosis type 1 (NF1). Symptoms of attention-deficit–hyperactivity disorder (ADHD) have also been extensively recognized in NF1. However, systematic evaluation of symptoms of autism spectrum disorder (ASD) in children with NF1 has been limited.

METHOD We present a retrospective, cross-sectional study of the prevalence of symptoms of ASD and ADHD and their relationship in a consecutive series of 66 patients from our NF1 clinic. The Social Responsiveness Scale and the Vanderbilt ADHD Diagnostic Parent Rating Scale were used to assess symptoms of ASD and ADHD.

RESULTS Sixty-six participants (42 males, 24 females) were included in this study. Mean age at assessment was 10 years 11 months (SD 5y 4mo). Forty percent of our NF1 sample had raised symptom levels reaching clinical significance on the Social Responsiveness Scale ($T \geq 60$), and 14% reached levels consistent with those seen in children with ASDs ($T \geq 75$). These raised levels were not explained by NF1 disease severity or externalizing/internalizing behavioral disorders. There was a statistically significant relationship between symptoms of ADHD and ASD (χ^2=9.11, df=1, p=0.003, ϕ=0.56). Particularly salient were the relationships between attention and hyperactivity deficits, with impairments in social awareness and social motivation.

INTERPRETATION We found that symptoms of ASD in our NF1 population were raised, consistent with previous reports. Further characterization of the specific ASD symptoms and their impact on daily function is fundamental to the development and implementation of effective interventions in this population, which will probably include a combination of medical and behavioral approaches.

Neurocognitive and learning-related deficits in pediatric neurofibromatosis type 1 (NF1) are associated with the greatest level of disease morbidity.[1–3] In addition to neurocognitive deficits, extensively described elsewhere,[3,4] upwards of 50% of the population with NF1 meets DSM-IV-TR[5] diagnostic criteria for attention-deficit–hyperactivity disorder (ADHD), and the associated attention and executive function deficits are particularly problematical and functionally limiting in this population.[1–3,6] Such neurocognitive impairments are related to disruptions in academic functioning[1,7] and socialization.[4]

It is well accepted that social deficits occur in individuals with NF1.[4,8,9] Barton and North reported that nearly 40% of their population with NF1 had social interaction problems in the borderline/clinical range. They also noted the significant role of comorbid ADHD in poor social outcomes.[4] In addition, associations between neurocognitive deficits commonly seen in NF1 and poor social functioning have been described. Huijbregts and de Sonneville showed that cognitive control (i.e. a combination of processing speed, working memory, inhibitory control, and emotional processing functions) was associated with the presence of autistic traits.[10]

Pervasive developmental disorders include several currently distinct diagnostic categories: autistic disorder, Asperger disorder, and pervasive developmental disorders, not otherwise specified. All of these disorders are characterized by functionally disruptive impairments in social interaction and social communication. Disruptions in social interactions may manifest as poor use of non-verbal behaviors, lack of age-appropriate peer relationships, lack of spontaneous sharing, or no social/emotional reciprocity. Social communication impairments may include limited or delayed language development, an inability to communicate effectively despite adequately developed speech, stereotyped or repetitive use of language, or lack of developmentally appropriate imaginative play. A diag-

nosis of autistic disorder also requires the presence of some level of restricted repetitive behavior, interest, or activity, which can include preoccupation with restricted areas of interest or parts of objects, inflexibility, or stereotyped and repetitive motor behaviors.[5] Interest in the presence of symptoms of autism spectrum disorder (ASD) in NF1 has increased, as 1 to 15% of children diagnosed with an ASD have been found to also have NF1.[11,12] Additionally, Williams and Herch found 4% of their NF1 sample had comorbid ASD, suggesting that it should be regarded as one of the neurodevelopmental risks associated with NF1.[13]

Social deficits occur in as much as 50% of children with ADHD.[14] These children are more likely to be rejected by their peers, struggle to establish and maintain relationships, and be viewed as aggressive, intrusive, and to lack empathy.[15] Grzadzinski et al.[16] reported that among children with a primary ADHD diagnosis, a subgroup had raised ratings on core ASD traits. Elevations in ratings of ASD symptomatology were not solely explained by the behavioral impairments associated with ADHD; social reciprocity impairments are present in individuals with ADHD across the range of ASD symptoms.[14,16]

Although ADHD symptoms and social competence deficits are frequently identified in individuals with NF1, the relationship between these symptoms has not been systematically explored. The aims of this study therefore were to (1) document the prevalence of ASD symptomatology in a sample of children with NF1 and describe symptom patterns, (2) determine how the presence of comorbid ADHD symptomatology contributes to raised levels of ASD symptoms, and (3) determine if there are differences in sex or NF1 disease severity in the presence of raised ASD symptomatology. We hypothesized that individuals with NF1 would show a higher prevalence of ASD symptomatology relative to general population norms, with males surpassing females. We further hypothesized that raised symptoms of ADHD and ASD would overlap in this clinical population with NF1.

What this paper adds

- Confirmation of the prevalence of raised symptoms of ASD in children with NF1 relative to general population norms.
- Further description of the prevalence of symptomatology in specific ASD domains.
- In NF1, deficits in social awareness and motivation are associated with ADHD symptomatology.

METHOD

Participants

This study was approved by the institutional review board at the Children's National Medical Center, Washington, DC, USA and informed consent was obtained for each participant. As part of the intake process, all patients referred to the neurofibromatosis clinic at the Children's National Medical Center receive an intake screening pack, which includes the Social Responsiveness Scale (SRS),[17] the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS),[18] as well as demographic and family history questions. We had a 51% return rate on all screening packs dispersed after initial referral to the clinic. No information is available on patients for whom packs were not returned as they may not have ever been seen in our clinic. The final number for each of our analyses varies based on the measure used in the analysis and the statistical approach. To maximize power, our full sample of 66 participants was used in the cluster analysis as this analysis is based on individual item responses for individual participants (normative data is not relevant for this analysis). When reporting on descriptive sample characteristics relative to the presence or absence of raised levels of symptomatology, our sample was reduced as some participants were excluded based on age (outside of the age range for a particular scale). Specifically, 52 children were eligible for analyses related to clinical manifestations on the SRS, which is normed for ages 4 to 18 years. The VADPRS has a more restricted age range (6–12y), leaving us with 29 eligible participants for those analyses. Disease severity was operationalized as the number of National Institutes of Health-defined diagnostic criteria for NF1.[19]

Instruments

Social Responsiveness Scale

The SRS is a screening instrument designed to identify social impairments and to distinguish symptoms of ASD from other childhood conditions.[17] It comprises 65 items, which contribute to five categorical subscales: social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. The threshold for clinically significant impairment is a score of 60 or greater. Scores of 75 or more indicate levels of symptomatology consistent with an ASD. It is norm referenced for ages 4 to 18 years, and we used the parent report form for this study.

Participants were classified on the SRS based on published cut-off scores associated with clinically significant raised levels of symptomatology (T≥60). In addition, participants were grouped using the cut-off of 75 or more, which is associated with diagnosis of an ASD.

Vanderbilt ADHD Diagnostic Parent Rating Scale

The VADPRS is designed to be a screening tool for evaluating the presence of ADHD, oppositional defiant disorder, conduct disorder, and anxiety/depression.[18] Questions are specifically based on the DSM-IV TR[5] criteria for each disorder. This scale is designed for use in children 6 to 12 years of age, and is completed by a parent or guardian.

Although a formal diagnosis of ADHD cannot be presumed without confirmatory ratings from another source (e.g. teacher), we dichotomized the group to raised or non-raised symptoms of ADHD. Participants were categorized as having ADHD-associated symptom levels (ADHD+) if they met the diagnostic criteria for ADHD based on the parent-reported VADPRS or were taking stimulant medication at the time of evaluation. We presumed that subclinical scores on the VADPRS in patients taking stimulant medication were related to response to ADHD treatment.

Statistical analysis

Frequencies and proportions were estimated for categorical variables, and means and standard deviations were calculated

for continuous variables. Categorical variables were compared using a χ^2 test. Continuous variables fitting both normality and homogeneity of variances were compared using the two-sample *t*-test and the non-parametric Mann–Whitney *U* test. These tests were performed to determine if patients with NF1 differed significantly by sex in the domains of the VADPRS and SRS questionnaires.

We computed pairwise Pearson's correlation coefficients to determine whether VADPRS and SRS scores were significantly correlated by domain, applying the false discovery rate[20] procedure to correct for multiple comparisons.

We used latent class cluster analysis to identify clusters and define symptom profiles among individuals. Latent class cluster analysis models containing 1 to 5 classes were fitted to the data using Latent GOLD 4.5 (Statistical Innovations, Belmont, MA, USA). Latent GOLD uses both expectation–maximization and Newton–Raphson algorithms to find the maximum likelihood for each model after estimating model parameters. In the latent class cluster models, separate analyses were performed for each of the domains of the VADPRS (inattention, hyperactivity, oppositional defiant disorder, conduct disorder, and anxiety/depression) and the SRS (social awareness, social cognition, social communication, autistic mannerisms, and social motivation). As covariates for all models, we used sex (male = 0; female = 1) and age at diagnosis as continuous variables following previous reports.[21–24] Individuals with incomplete information were excluded. For modeling, a tolerance of less than 10^{-6} between consecutive interactions and a maximum of 2000 interactions for both the expectation–maximization and Newton–Raphson algorithms were chosen. The number of clusters was selected using a likelihood ratio test evaluating whether increases in likelihood (L^2) associated with increased latent classes justified their inclusion. Further, certainty of these clusters was assessed calculating *p* values associated with L^2 values after running 500 parametric bootstrap replicates. As implemented in Latent GOLD, individuals are assigned posterior membership probabilities for belonging to each cluster based on their symptom profiles; individuals were additionally assigned to the cluster for which the posterior probability was highest.

We used hierarchical clustering to analyze clustering of component features in our sample. Hierarchical clustering uses an agglomerative algorithm that joins the most similar component features and then joins the next most similar using the first aggregation as a single combined unit such that clusters are generated via complete linkage. To assess the uncertainty of the analysis, approximately unbiased and bootstrap probability *p* values were calculated in R using 10 000 bootstrap samples as implemented in the pvclust package (Ryota Suzuki and Hidetoshi Shimodaira[25]). We used 85% as the cut-off for the approximately unbiased *p* values.

RESULTS

For our full sample (n=66; 42 males, 24 females), the mean age at assessment was 10 years 11 months (SD 5y 4mo). Males and females did not differ statistically in age (p=0.326). The mean number of NF1 stigmata was 2.8 (SD 0.66), with eight cases (12%) of optic glioma. Only 28% of our sample had familial NF1.

Twenty-four participants (nine females, 15 males) were categorized into the ADHD+ group based on meeting one or both of the criteria defined above (mean age 11y 4mo, SD 4y 6mo). Specifically, 46% met criteria based on raised scores on the VADPRS (n=11; eight males, three females), another 46% met criteria based on being actively treated for ADHD (n=11; seven males, four females), whereas the remaining 8% (n=2; both female) met both criteria (raised scores and active treatment). VADPRS and SRS scores did not differ significantly by sex (VADPRS p=0.108; SRS p=0.793).

Mean Total ASD score on the parent SRS (n=52) approached clinically significant levels defined as T≥60 (mean 57.9, SD 14.2), consistent with other clinical comparison samples.[10,26] Reported levels on the individual SRS subscales also neared clinically significant levels, particularly autistic mannerisms (Fig. 1a).

The percentage of our NF1 sample that reached clinically raised symptomatology, with T scores ranging from 60 to 74 was 27% (n=31) for total symptoms, and ranged from 29 to 31% across the various subdomains. Scores of 75 or above are associated with raised levels of symptoms consistent with those seen in ASD, and 13% (n=7) of our sample reached that level for the total SRS score. Across subdomains, rates ranged from 2 to 13% reaching this level of clinical elevation (Fig. 1b).

The relationship between raised symptoms of ADHD and ASD (total T≥60) was statistically significant with a moderate effect size (χ^2=9.11, df=1, p=0.003, ϕ=0.56). Exploratory analyses were completed to examine the relationship of ADHD symptoms with specific subdomains of social functioning (SRS subscales). Statistically significant relations were found between ADHD symptoms and social cognition (χ^2=11.5, df=1, p=0.001) as well as social communication (χ^2=7.2, df=1, p=0.007), both with moderate effect sizes. The presence of raised ADHD symptoms was not significantly related to social awareness, social motivation, or autistic mannerisms.

To explore the relationship between anxiety and ASD symptoms, ratings on the VADPRS anxiety/depression scale were analyzed. We found no significant relationship for anxiety/depression (r=−0.01, p=0.97) or emotional problems (r=0.24, p=0.22).

Males and females did not differ significantly in being represented in the high ASD symptom groups (χ^2=3.16, df=1, p=0.08). However, statistically significant relationships emerged between sex and social communication (χ^2=9.4, df=1, p=0.002, ϕ=0.57), and social motivation (χ^2=4.4, df=1, p=0.04, ϕ=0.39), with males rated with a higher mean number of symptoms than females. Borderline significance was found between sex and social cognition (χ^2=3.8, df=1, p=0.05). We did not find a significant relationship between NF1 disease severity and ASD symptomatology (SRS total score; r=0.24, p=0.21).

Using latent class cluster analysis, we identified three significant independent and mutually exclusive clusters for the inattention, hyperactivity/impulsivity, oppositional defiant disorder, and anxiety/depression VADPRS domains in our

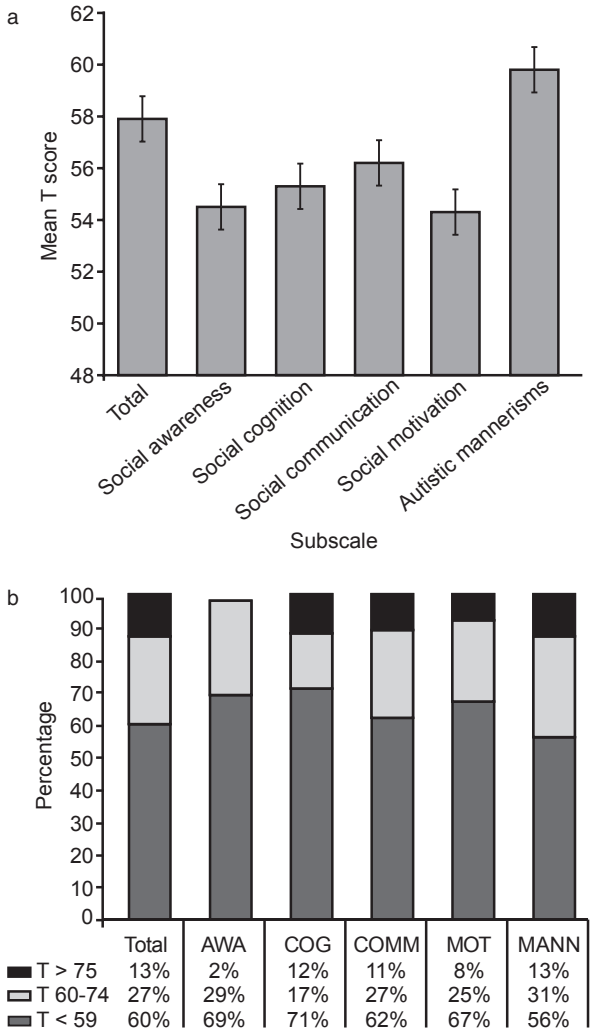

Figure 1: (a) Mean *T* score, by dimension of the Social Responsiveness Scale (SRS) scale, in our cohort of patients with neurofibromatosis type 1 (NF1). (b) Percentage of individuals with NF1 in our cohort with a *T* score <60 (not clinically raised) and those with a *T* score of 60 or greater (clinically raised) on the each of the domains of the SRS. AWA, social awareness; COG, social cognition; COMM, social communication; MOT, social motivation; MANN, autistic mannerisms.

maximally expanded sample (n=66; Fig. 2). Because of small variability in the predictors, a common problem when working with multinomial responses, latent class cluster analysis models could not be fitted to the VADPRS conduct disorder domain or to any of the dimensions of the SRS questionnaire.

Figure 3 presents the results of the hierarchical clustering and bootstrap-based validation for the VADPRS and SRS scores. In the first case, only the cluster defined by the inattention, hyperactivity/impulsivity, oppositional defiant disorder, conduct disorder, and anxiety/depression scores appear to be strongly supported by the data at the 85% level (Fig. 3). This result suggests that, in patients with NF1, all VADPRS scores except the performance score (Q48–Q55) tend to appear together more often. Furthermore, although not supported at the 85% level, the inattention and hyperactivity/impulsivity scores, as well as the oppositional defiant disorder, conduct disorder, and anxiety/depression scores, seem to co-occur within this cluster. For the SRS questionnaire, only the cluster defined by the social awareness, social cognition, autistic mannerisms, and social motivation scores is supported at 85% (Fig. 3). Within this cluster, the social awareness and social motivation scores seem to appear as an entity and the same is true for the social cognition and autistic mannerisms scores. However, only the first subcluster is supported at the 85% level.

When the scores of both questionnaires are considered together (Fig. 3), two clusters of clinical symptoms emerge supported by the data at the 85% level. Interestingly, domains from both questionnaires form the first cluster and only domains from the SRS define the second cluster.

After correction for false discovery rate, only five correlations remained significant, four of them involving the inattention score of the VADPRS and all the SRS scores, except the social awareness score, and one between the hyperactivity/impulsivity VADPRS score and the social cognition SRS score (r=0.32, 95% CI 0.084–0.52, false discovery rate corrected p value 0.022). Tables SI and SII (online supporting information) present item level means for both the VADPRS and the SRS.

DISCUSSION

Although most previous research has focused on general social dysfunction in children with NF1, we followed the approach in previous research by Huijbregts and de Sonneville[10] by targeting specific social impairment symptoms associated with ASD. We found the prevalence of ASD symptomatology in our population of children with NF1 to be consistent with levels reported by other NF1 researchers[4,10,26] (our sample vs Huijbregts: t=−0.32, df=41.5, p=0.62; our sample vs Constantino ASD or pervasive developmental disorders: t=−0.064, df=18.6, p=0.52) and notably higher than unaffected children.[10,26] The rate of syndromic-level symptoms (≥75) in our sample (14%) was notably higher than in a previous NF1 series (4%)[13] and in the general population (1%).[27] We found that 40% of our sample had total reported ASD symptoms reaching clinically significant levels (≥60), suggesting that these symptoms would be functionally impairing in daily life. The most common symptoms were in the 'autistic mannerisms' domain (44% of the sample reached clinically significant levels), which includes problems with flexibility and transitions, perseverative behaviors, and being regarded by others as atypical. Clinically impaired social communication, motivation, awareness, and cognition were also reported in approximately 30% of these children. Of clinical relevance, the presence of ASD symptoms was not related to externalizing behaviors (e.g. oppositional defiant or conduct disordered) or internalizing symptoms (e.g. anxiety or mood problems). In fact, we saw a strikingly low rate of these symptoms in our sample (≤3%). Disease severity, at least as indexed by number of NF1 stigmata, did not explain the increase in ASD symptomatology. This suggests that ASD symptomatology has

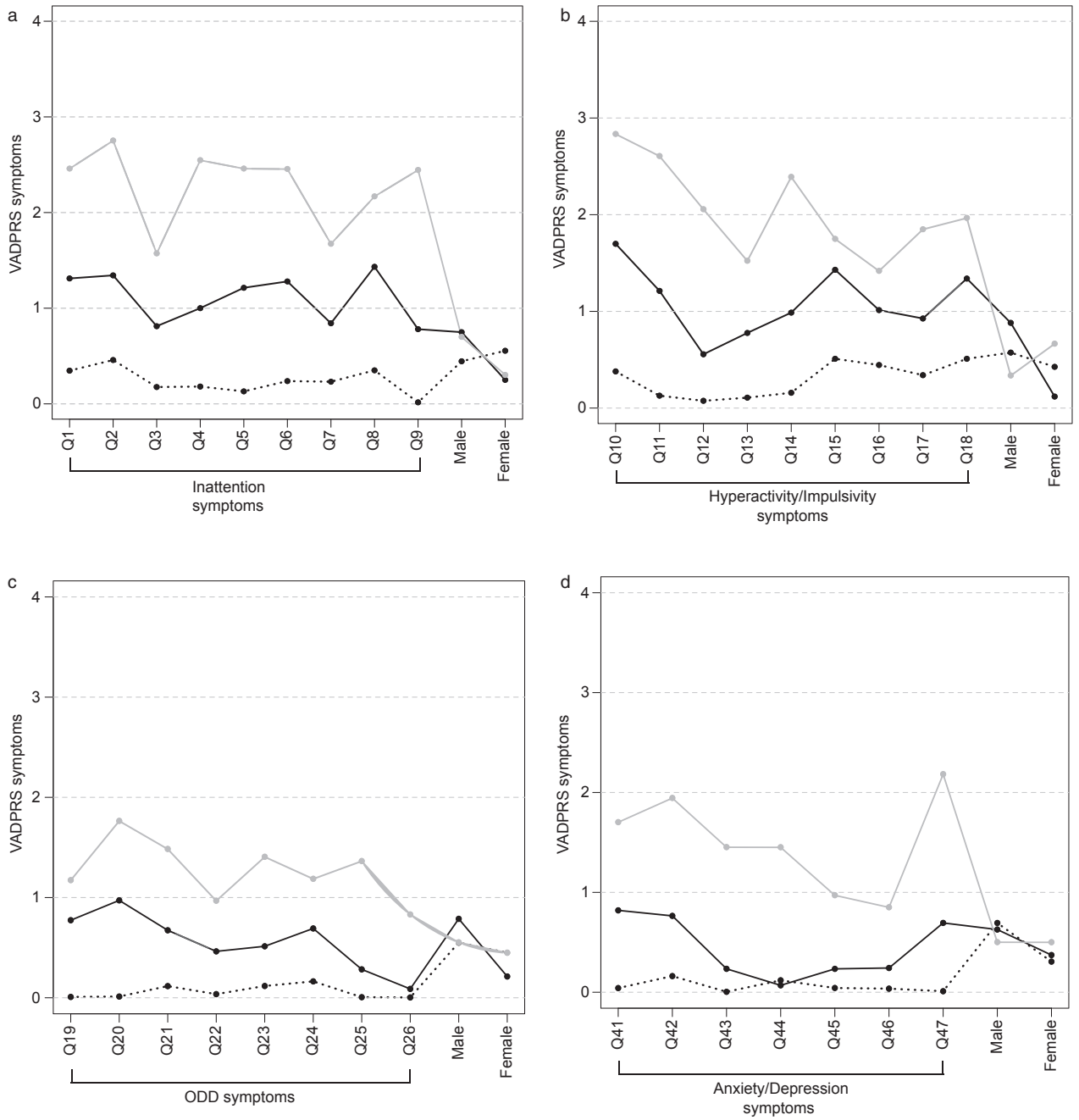

Figure 2: Profile plots derived using latent class cluster analysis applied to symptoms of attention-deficit–hyperactivity disorder (ADHD), measured by the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) questionnaire, in our cohort of patients with neurofibromatosis type 1 (NF1). VADPRS symptom profiles are shown in a scale from 1 to 4 (1, never; 2, occasionally; 3, often; 4, very often), whereas sex is shown in a scale from 0 to 1, representing the proportion of individuals with the characteristic. (a) Inattention (Q1–Q9). Individuals in cluster 1 (*n*=35, 53%) have minimal ADHD symptoms and are predominantly male; individuals in cluster 2 (*n*=20, 30%) present fewer ADHD symptoms and are mostly female; individuals in cluster 3 (*n*=11, 17%) are mostly inattentive with higher presence of symptoms in Q2, Q4–6, and Q9. (b) Hyperactivity/impulsivity (Q10–Q18). Individuals belonging to either cluster 1 (*n*=32, 48%) or cluster 2 (*n*=24, 37%) present minimal hyperactivity/impulsivity ADHD symptoms and are predominantly males, whereas those belonging to cluster 3 (*n*=10, 15%) are mostly female and present few symptoms, especially in Q10 and Q11. (c) Oppositional defiant disorder (ODD) (Q19–Q26). To clusters 1 (*n*=25, 38%) and 2 (*n*=25, 38%) belong individuals with NF1 with minimal symptoms of ODD. Individuals in cluster 3 (*n*=16, 24%) have few symptoms, especially in Q20 and Q21. Males predominantly constitute all clusters. (d) Anxiety and depression (Q41–Q47). Individuals with NF1 belonging to cluster 1 (*n*=32, 48%) are predominantly male and present minimal symptoms of anxiety/depression in all questions. To cluster 2 belong individuals with NF1 in the majority females, with minimal symptoms of anxiety/depression in all questions, except in Q41, Q42, and Q47. Cluster 3 (*n*=11, 17%) groups NF1 patients, mostly males, with few symptoms of anxiety/depression and high scores in Q42 and Q47.

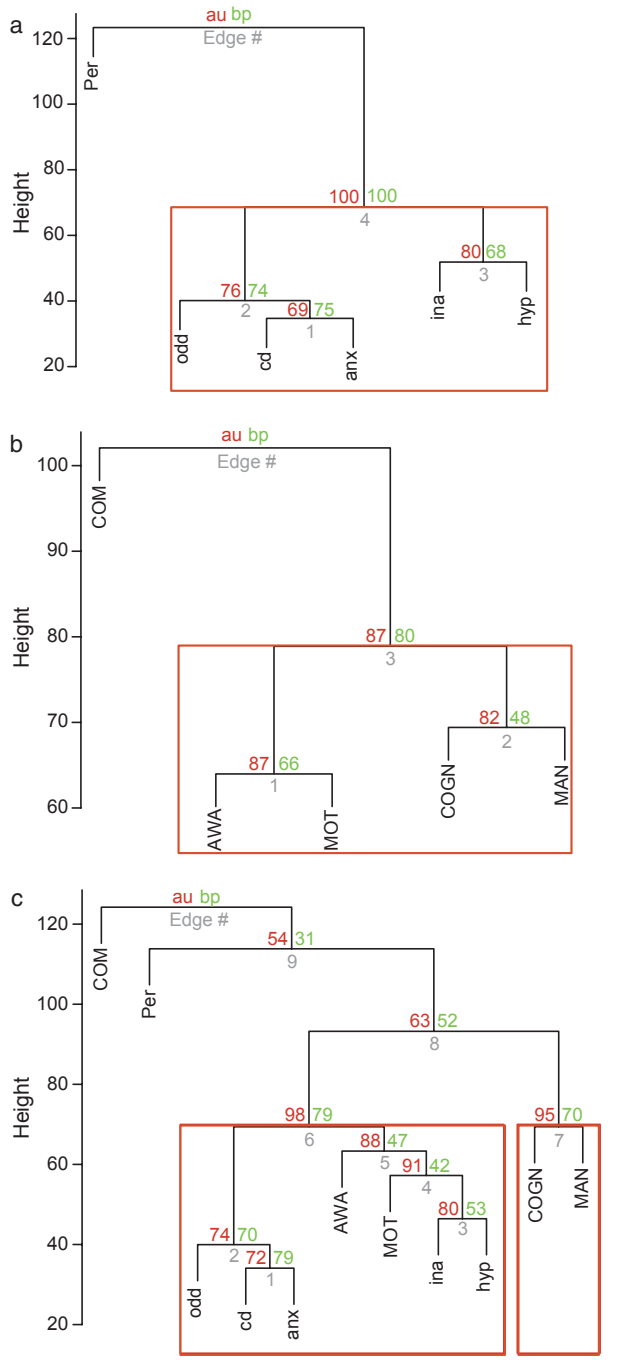

Figure 3: Hierarchical cluster dendogram of (a) Vanderbilt ADHD Parent Rating Scale, (b) Social Responsiveness Scale (SRS), and (c) the combination of both clinical scales with both approximately unbiased (au, in red) and bootstrap probability (bp, in green) *p* values. The *y*-axis indicates the likelihood that clinical symptoms will co-occur, with those that tend to co-occur being vertically closer. Red squares highlight subgroups of clinical symptoms co-occuring more than 85% of the time. Odd, oppositional defiant disorder; cd, conduct disorder; anx, anxiety/depression; ina, inattention; hyp, hyperactivity/impulsivity. AWA, social awareness; COGN, social cognition; COM, social communication; MOT, social motivation; MANN, autistic mannerisms.

been under-recognized and under-studied in NF1, further supporting the addition of ASD to the neurodevelopmental risks of NF1.[13]

Overall, male and female patients with NF1 did not differ significantly. However, detailed examination revealed significant differences in the rate of raised social communication and social motivation symptoms between males and females, with males exhibiting greater impairment in these domains.

Research has consistently demonstrated the relationship between ADHD and poor social skills,[14] and there is clear overlap in symptoms of ADHD and ASD.[28] Given the high prevalence of ADHD in individuals with NF1,[1–3] and the difficulties in socialization,[4] it is important to consider the relationship between these symptom presentations and how they might interact. Consistent with previous literature,[4,8] we found a significant positive relationship between the presence of raised ADHD and ASD symptoms in our sample of children with NF1. This relationship was particularly salient for problems with social communication and social cognition. Although an item analysis is beyond the scope of this paper, the lack of ability to focus and sustain attention and inhibit impulsive behaviors most certainly limit a child's pragmatic skills (making appropriate eye contact, interpreting non-verbal cues and tone of voice) and general social awareness (relating events to one another, social reciprocity).[29,30]

Taking this relationship further, we were interested in interrelationships among groups of symptoms in our patients with NF1 through cluster analyses. For ADHD symptoms, we found generally low endorsement of symptoms of hyperactivity and impulsivity, oppositional or conduct disordered behaviors, and anxiety or mood disturbance for both sexes. Instead, our patients with NF1 exhibited higher symptoms of inattention, particularly for tasks requiring sustained mental focus and effort, organization, and task completion.

Because of the significant relationship between the presence of ADHD and ASD symptoms, we sought to understand how these symptoms tend to present in our sample of children with NF1. Distinct patterns of symptom clusters emerged. The presence of attention deficits and hyperactivity co-occurred specifically with deficits in social awareness and social motivation. It makes sense that poor vigilance and impulse control would be associated with less awareness of social rules and cues, which can certainly relate to diminished motivation to socialize. This pattern has been observed in ADHD.[14] Social cognition and autistic mannerisms were independently related to each other, but not to ADHD symptoms. Interestingly, social communication deficits were distinct from raised levels of other ASD symptoms as well as ADHD symptoms, anxiety, or depression, suggesting that the presence of such limitations may relate to some other factors or processes not identified here, such as general language impairments. Although oppositional behaviors, conduct problems, and anxiety co-occurred with each other, these were independent of social impairments or ASD symptomatology.

The strengths of this study include our strategy of sampling from all children with NF1 referred to the neurofibromatosis clinic, not only those referred for specific neurocognitive or

social–emotional concerns. This provided us with a more representative sample of the general population of individuals with NF1. However, given that about half of our families completed and returned the questionnaires, it remains possible that the most severely affected individuals were in fact the ones from whom questionnaires were received, and we do not have the ability to determine specifically the differences between responders and non-responders. Additionally, we had the ability to evaluate several factors previously shown to relate to social functioning in children with NF1, specifically the role of ADHD symptomatology. Moving forward, a larger prospective approach including criterion-standard quantitative measures of social cognition and formal diagnosis of ASD would strengthen our findings. Additionally, incorporating larger samples of clinical and healthy comparison groups is important, as some of our null findings may have reflected limited power. There are many neurocognitive, social information processing, and emotional factors involved in social competence, and expanding upon this study by evaluating more of these will probably provide additional clarity in understanding the social impairments present in individuals with NF1.

To summarize, we found that in our population of children with NF1, ASD-related symptoms were common, with approximately one-third being at risk for clinically significant/functionally impairing levels of these symptoms. The number of children with NF1 with symptom levels generally associated with ASD was higher than previously described in NF1 and much higher than the general population. These raised levels of symptoms were not explained by disease severity or by comorbid externalizing or internalizing behavioral disorders. However, there was a high level of comorbidity between certain ADHD and ASD symptoms, particularly relative to social awareness and motivation. The results of this study imply the need for increased screening for the presence of impairments in social cognition in children with NF1. Further, this presents an opportunity to consider novel targets for intervention studies aimed at improving peer relationships and socialization in this population of patients.

SUPPORTING INFORMATION

Additional material and supporting information may be found in the online version of this article.

Table S1: Individual item group means and response percentages for the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS).

Table SII: Individual item group means and response percentages for the Social Responsiveness Scale (SRS).

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