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Minor Physical Anomalies in Children with Autism Spectrum Disorders

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Abstract

Objective—There is clinical heterogeneity among the autistic spectrum disorders (ASD). The presence of dysmorphology (minor physical anomalies; MPAs) is one possible tool for defining a clinically relevant subset in ASD. This study expands on Miles and Hillman's (2000) classifications by using photographs to identify a subgroup with significant dysmorphology among children with ASD, typical development (TYP), and developmental delay (DD).

Method—Children with ASD, DD, and TYP between 2 and 5 years old were part of the CHARGE study. Pediatric specialists blinded to group classified photographs based on the number of MPAs present: “dysmorphic” if >3 and “nondysmorphic” if <3 MPAs.

Results—Photographs for 324 children were included. Significantly more children with ASD were classified as dysmorphic compared to TYP children ($p=0.007$). In children with ASD, seizures were more prevalent in those rated “dysmorphic” ($p=0.005$). Frequencies were similar between ASD versus DD ($p=0.19$) after removing those with known syndromes.

Conclusion—Photographic assessment can be used to detect generalized dysmorphology in children who are often difficult to examine. This has clinical relevance, as children with multiple MPAs can be identified through the use of photographs and prioritized for investigation of brain abnormalities and underlying genetic conditions.

Keywords

autism; dysmorphology; minor physical anomalies

Introduction

Children with autism spectrum disorders (ASD) are a heterogeneous group who vary in their levels of functioning, associated medical conditions, prognosis, and response to medical and behavioral interventions. This variability hinders our ability to identify homogeneous subgroups for study of potential causes of and treatments for ASD. Contrary to Kanner's (1943) early description of children with autism who are “free of obvious defect,” many investigators have recognized that children with autism have increased rates of minor physical anomalies (MPAs) compared to typically developing or sibling controls (Campbell

et al., 1978; Links *et al.*, 1980; Walker, 1977). A MPA arises from a genetic or environmental disruption during early fetal development that affects structural development (Smalley *et al.*, 1988). While the presence of a single MPA is not uncommon in the general population, the greater the number of MPAs present in an individual, the higher the risk of associated medical problems and genetic conditions (Leppig *et al.*, 1987). *Multiple* MPAs are more common in individuals with major disruptions in embryogenesis, and 90% of babies with 3 or more MPAs have a major malformation compared to 3% of those with 1 MPA (Marden *et al.*, 1964).

Higher rates of autism are found in children with identified physical anomalies such as Mobius sequence, CHARGE (Coloboma, Heart anomalies, choanal Atresia, Retardation of growth and development, Genital anomalies, Ear anomalies) syndrome, Goldenhar syndrome, and *in utero* thalidomide or valproate exposure, which lead to the suspicion that there is a common disruption at 4-6 weeks gestation based on the involvement of ocular and otic structures that develop during this period (Miller *et al.*, 2005). Rodier *et al.* (1997a) studied the frequency of individual MPAs and found that posterior rotation of the ear was more common in children with autism compared to the general population, as well as compared to children with developmental delays (DD). Mixed results have been found for anomalies such as a high-arched palate and hypertelorism.

Miles and Hillman (2000) developed a classification system based on the number of MPAs present in order to identify useful subgroups among children with ASD. Children with ASD who were dysmorphic (6 or more MPAs) and/or microcephalic were defined as having “complex” autism and were more likely to have genetic syndromes, structural abnormalities in brain structure, seizures, and low IQ (Miles *et al.*, 2005). The remaining children were considered to have “essential” autism, without evidence of an early embryological insult. The Autism Dysmorphology Measure (ADM) (Miles *et al.*, 2008) was designed to efficiently screen for complex autism without the need for a complete unclothed examination and also included height, which is routinely obtained at pediatric visits. Reliability was established through the evaluation of photographs of each child. No other studies have evaluated the utility of the Miles and Hillman classification system, which incorporates the presence of multiple MPAs, to evaluate children with ASD compared to both DD and general population controls. We undertook this study of children with and without ASD to determine whether the classification of Miles and colleagues would distinguish between ASD and TYP, to assess whether a higher number of MPAs would be associated with seizures or low IQ in a population-based sample, and to evaluate whether the prevalence of MPAs would distinguish DD from ASD in a unique population of well-characterized children with confirmed developmental diagnoses. In addition, we also hypothesized that photographic analysis is a useful method for a generalized dysmorphology assessment.

Methods

Participants were part of the CHARGE (Childhood Autism Risks from Genetics and the Environment) Study, an ongoing population-based case-control investigation with subjects sampled from three strata: children with ASD (autism or PDD-NOS/Pervasive

Developmental Disorder-Not Otherwise Specified), children with developmental delay (DD) but not ASD, and children selected from the general population. Children included in the study: a) were between the ages of 24 and 60 months, b) lived with at least one biologic parent, c) had a parent who spoke English or Spanish, d) were born in California, and e) resided in the catchment areas of a specified list of Regional Centers in California. Children with ASD were identified through Regional Centers, which provide case management services to children with eligible developmental disorders across socioeconomic levels and racial/ethnic groups, as well as through the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute clinic. No further exclusions were made based on genetics, family phenotype, or other characteristics, with the exception of children who had visual, hearing or motor impairments that precluded standardized developmental assessment. General population controls were frequency-matched to the projected distribution in ASD children of age and sex. Hence, the male:female ratio is skewed toward males in the control group. This study was approved by the institutional review boards of the University of California in Davis and Los Angeles and the Committee for the Protection of Human Subjects, which serves the California Human Health and Services agencies. Informed consent was obtained prior to participation.

The ASD group included children with a diagnosis of autism or PDD-NOS confirmed using the Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur *et al.*, 2003) and the Autism Diagnostic Observation Schedule (ADOS) (Lord *et al.*, 2003). Final autism case status is defined as meeting criteria on the communication, social interaction, and repetitive behavior domains of the ADI-R with onset prior to 36 months and scoring at or above the total cutoff for autism on the ADOS module 1 or 2. Children classified with PDD-NOS did not meet full criteria for autism on both ADI-R and ADOS, but did meet criteria on either the communication or the social interaction domain of the ADI-R prior to 36 months and were within 2 points of the cut-off on the other domain and met autism spectrum criteria on the ADOS module 1 or 2. All study clinical assessment personnel have attained research reliability on the ADI-R and the ADOS.

Cognitive function was measured using the Mullen Scales of Early Learning (MSEL) (Mullen, 1995). Sub-domains are based on a mean T-score of 50 (SD 10) and include visual reception (problem solving), fine motor, receptive language (comprehension), and expressive language (language production). The Early Learning Composite (ELC) is an age-standardized score generated from the 4 subscales above, with a mean of 100 (SD 15). Adaptive function was assessed by parent interview using the Vineland Adaptive Behavior Scales (VABS) (Sparrow *et al.*, 1984). Children in both the DD and general population control groups were screened with the Social Communication Questionnaire (SCQ, Rutter *et al.*, 2003) and in this study subset, all had scores less than the cut-off of 15. Children classified as DD had scores less than or equal to 70 on the MSEL and scores less than 70 on VABS, which correspond to more than 2 standard deviations below the mean. Children classified as typically developing (TYP) were those who were recruited from the general population who had standard scores above 70 on MSEL and above 69 on VABS. The clinic visit also included medical and family histories obtained by trained physicians, which provided information about the presence of seizures. Head circumference was obtained

using disposable paper tape measure placed above the supraorbital ridge and around the occipital prominence at the largest circumference. Microcephaly was defined in a similar manner used by Miles *et al.* (Miles *et al.*, 2000), with head circumference $\geq 2\%$ on Nellhaus charts (Nellhaus, 1968) considered microcephalic. Standing height was also obtained, with the same definition of short stature (height $\leq 10\%$ for age and gender on CDC growth charts) (Kuczmarski *et al.*, 2002) used by Miles (2008). Regression status was defined using the ADI-R and the Early Development Questionnaire (EDQ) (Ozonoff *et al.*, 2005). Children with loss of language (ADI-R question 11 = 1) or social skills (ADI-R question 25 = 1, or 3 losses reported in EDQ Part 3 questions A3-4 and B1-5) were defined as regressive for this analysis; the other ASD children were classified as early onset cases. Bilingual and bicultural staff is engaged in all activities involving contact with participants.

Photographs of face (frontal and profile) and hands were evaluated by at least 2 of 3 clinicians (2 geneticists and 1 pediatrician) blinded to group status. Miles and Hillman (2000) created three categories based on a complete unclothed dysmorphology exam. The “phenotypically normal,” or “nondysmorphic” category included children with fewer than 3 MPAs. Children with 3-5 MPAs were considered “equivocal.” Children with 6 or more MPAs were classified as “phenotypically abnormal,” or “dysmorphic.” Because a comprehensive physical assessment was not feasible, we relied on photographs of only face and hands, and modified the Miles and Hillman categories to “nondysmorphic” for ≤ 3 MPA and “dysmorphic” for ≥ 3 MPA. Disagreements in ratings were resolved by group consensus.

Chi-square and Fisher's exact tests were used to compare the frequencies of nondysmorphic vs. dysmorphic status comparing the ASD, TYP, and DD groups. The chi-square test was also used to compare ASD children with and without regression and seizure history. Mullen and Vineland scores were not normally distributed, with a skew toward lower scores, so the Wilcoxon rank-sum test was performed. All analyses were carried out using STATA version 9 (StataCorp, 2007).

Results

Photographs for 358 children were reviewed. Eight photographs were removed due to poor picture quality or inability to see the entire face. One subject dropped out of the study before group assignment (ASD, DD, or TYP) could be determined. Nine children in the DD group scored in the “typical” range on either the MSEL or VABS (MSEL > 70 , VABS ≥ 70), and were therefore excluded as not meeting criteria for DD. Also excluded were eleven children who entered the study in the ASD group but did not meet criteria for ASD after study evaluation and 5 children who entered the study as general population controls but did not have typical development based on MSEL or VABS scores. Twenty-six children (22 DD, 4 ASD) had known genetic syndromes associated with ASD or DD, and analyses were conducted with and without this group.

The average age for the entire group ($n=324$) was 43.2 months (range 24-69 months) and 83.3% were males. Forty-seven percent of children were White, 30% were Hispanic, 6% were Asian, 4% were African-American, and 13% were multi-racial children. The ASD group included 149 children, 63 children comprised the DD group, and 112 children were in

the TYP group. Table 1 includes demographic data by group status. The TYP group was slightly younger than the other 2 groups. The DD group had greater representation of females and children of Hispanic descent and fewer parents who had a college degree. Only 33% of Hispanic families in this study had parents with a college degree. For families of other ethnicities (White, Black, Asian, etc.), at least 58% completed college. The greater representation of Hispanic families in the DD group suggests that Hispanic ethnicity is a marker of lower levels of post-secondary educational completion in this sample and these families are more likely to use the Regional Centers as their primary diagnostic resource.

In the ASD group, 17.4% children were dysmorphic and by definition 82.6% were nondysmorphic (see Table 2). Significantly more ASD children were dysmorphic compared with the TYP group ($p=0.007$), where 5.4% were dysmorphic and 94.6% were nondysmorphic. Head circumference was available for 114 ASD children and 101 TYP children. Two children in the ASD group were microcephalic and were both already rated as dysmorphic. None of the TYP children were microcephalic, so frequencies were the same when considering “complex” (dysmorphic and/or microcephalic) status. We compared the ASD group to the entire DD group, as well as to the DD group excluding known syndromes. The complete DD group showed a higher prevalence of dysmorphic ratings compared to ASD ($p<0.01$) and had the highest frequencies of dysmorphic (47.6%) ratings (ASD: 17.4%, TYP: 5.4%), although no common clinical phenotype was identified in this dysmorphic group. Microcephaly was present in 15 DD children, and all but 2 were dysmorphic. Twenty-four (38%) of the DD group and 4 ASD children had known syndromes (Table 3). When these 26 children with known genetic syndromes were excluded from analysis, the non-syndromic/idiopathic DD group was still more likely to be classified as dysmorphic (25.6%) compared to the non-syndromic/idiopathic ASD group (16.6% dysmorphic), although this difference was not statistically significant ($p=0.19$).

Height was available for 112 of the ASD children, 101 TYP children, and 50 DD. In ASD and DD children, dysmorphic children were more likely to have short stature. Four percent of the non-dysmorphic ASD children were shorter than the age-appropriate 10th percentile using the CDC growth charts compared to 35% of the dysmorphic ASD children ($p<0.001$). In the DD group, 15% of the non-dysmorphic children had short stature compared to 42% of the dysmorphic children ($p=0.04$).

Among children with ASD, there was no difference in mean or median cognitive scores between children considered dysmorphic versus nondysmorphic (mean Early Learning Composite Standard Scores (ELC) 64 vs. 62.1; median ELC 52 vs. 55, see Table 4) but the distributions for both groups were skewed toward the lower end. Thirty-four percent of the entire ASD group scored at the bottom of the test (ELC=49) and 53% scored >3 standard deviations below the mean (ELC<55). Since the data were skewed, Wilcoxon rank-sum tests were performed on ASD children; results did not show any statistically significant differences in MSEL or VABS scores based on dysmorphology status (see Figure 1 and Table 4), although a greater percentage of the dysmorphic ASD children ($n=15$; 58%) scored lower than 3 standard deviations below the age-standardized means on the ELC and sub-domains of the MSEL compared with nondysmorphic ASD children ($n=59$; 48%). For the sub-domain T-scores, age-standardized means are 50 with a 10 point standard deviation, so

extremely low scores (>3 standard deviations below the mean) are 20 or below. A higher percentage of dysmorphic ASD children scored 20 on the visual reception, receptive language, and expressive language sub-domains (reported in Figure 1). However, these differences were not statistically significant based on chi-square tests.

In the ASD group, seizures were reported more frequently in children considered dysmorphic (11.5%) compared to those considered nondysmorphic (2.4%) ($p=0.005$) (Table 4). Four children in the ASD group had previously identified syndromes (Table 3), comprising 8% of the dysmorphic group and 2% of the non-dysmorphic group ($p=0.08$). However, since comprehensive genetic testing was not obtained for every individual, these percentages may underestimate the prevalence of genetic syndromes. Gender, family status (simplex vs. multiplex), and regression did not differ in children with ASD according to dysmorphology status determined from photographic assessment (Table 4), with loss of social and/or language skills occurring in 42-43% ($p=0.94$) in both ASD subgroups.

Discussion

We have shown, in a large population-based sample of children aged 2-5 years, in whom dysmorphic features were assessed, that 1) dysmorphology is more common in those with ASD as compared with TYP, 2) dysmorphic children with ASD are more likely to have seizures, should be followed for medical and genetic conditions, and may represent a group with early embryonic origins, and 3) dysmorphology status determined from photographs in children with ASD is a useful tool.

Our results support other studies that document higher frequencies of MPAs in children with ASD compared with typically developing children (Campbell et al., 1978; Rodier et al., 1997b; Tripi et al., 2007; Walker, 1977) and replicate the work of Miles *et al.* (2005) using their classification system. Seventeen percent of ASD children were dysmorphic in our sample, which is comparable to Miles' dysmorphic (16%) and complex (20%) groups. Only 2 children with ASD were microcephalic, and they were both dysmorphic, so head circumference did not add additional predictive value in this sample. While most studies compare against a typically developing control group, we add to the literature by also including a DD control group, which displayed the highest frequency of dysmorphic ratings although after children with known syndromes were removed, there was no significant difference in dysmorphic ratings between idiopathic DD and idiopathic ASD.

Miles' classification system revealed a higher frequency of seizures in dysmorphic children with ASD (Miles *et al.*, 2005), a finding confirmed in our population-based sample: we found 11% of dysmorphic children had a parentally reported history of seizures compared to only 2% of those considered nondysmorphic. Of note, Miles' study reported higher rates of seizures (17% essential; 39% complex) and this may be due to differences in age of participants, since the Miles study included older children and adults. The CHARGE study consisted of children between the ages of 2 and 5 years, which catches only the early peak when seizure disorders commonly occur in ASD (the later period for seizure onset in ASD is after 10-12 years) (Volkmar, 2005). The higher rate of seizures in children with dysmorphic features may be due to malformations of cortical development, which represent altered

neuronal migration or abnormal brain structure/function during early development (Wong, 2008), the origins of which could be environmental or genetic insults.

This finding has clinical relevance for medical evaluation and treatment, as children with multiple MPAs who can be identified through the use of photographs may therefore be prime candidates for further investigation of brain abnormalities and underlying genetic disorders. Basic genetic testing (high resolution karyotype and fragile X DNA) was recommended for all children with ASD and intellectual disability/mental retardation by the American Academy of Pediatrics in 2007 (Johnson and Myers, 2007), although this is not universally obtained by medical providers in clinical practice, potentially because ASD is a heterogeneous disorder that does not have a single physical phenotype that triggers a physician to suspect an underlying genetic syndrome. In addition, general pediatricians may not be aware of new practice parameters are even less likely to obtain chromosomal microarray (aCGH), which is now considered first-tier testing for individuals with ASD, developmental delay, and multiple congenital anomalies (Miller *et al.*, 2010) since it has higher diagnostic yield than karyotyping. This information is important for non-medical providers as well, since they often diagnose ASD and provide recommendations that are used to guide intervention for educators and physicians.

Routine EEGs are not recommended for all children with ASD, however, our findings suggest that targeted screening in children with increased risk (dysmorphic) may have higher diagnostic yield. In the same manner, more detailed genetic work-up and referral to a geneticist, should be considered in children with ASD and dysmorphic features.

While dysmorphology status assessed from photographs of only face and hands is useful in identifying children with ASD at greater risk for seizure, it did not predict differences in cognitive and adaptive functioning or regression status. While photographic assessment may be a good screening tool for individuals who require further medical investigation, it is not as powerful as a comprehensive in-person dysmorphology examination and is not meant to replace trained experts. However, there are only a limited number of trained dysmorphologists, and the pre-selection of those individuals who are in most need of their services allows for better use of limited resources.

In Miles' sample, dysmorphic children were twice as likely as those with <3 MPAs to have IQ/DQ scores <55. We also found that a greater percentage of dysmorphic and equivocal children with ASD had MSEL scores <55, but this did not reach statistical significance. This lack of association is likely related to the large proportion of children with ASD who scored at the bottom of the MSEL. Another factor involves age of our study sample, which was comprised of children 2-5 years of age. The study carried out by Miles *et al* (2005) examined a broader age range of participants (1-55.9 years). Individuals who are diagnosed with ASD at a young age often are identified because of developmental delay whereas older individuals present with social deficits or unusual behaviors and may have a more variable degree of cognitive impairment. Cognitive functioning in our study was measured using the Mullen Scales of Early Learning, whereas Miles' study used IQ scores for older participants and Vineland (adaptive) scores only for the subjects in the age range we studied.

In Miles' sample, language regression was more common in the nondysmorphic group (43%) compared to 24% of the dysmorphic group ($p=0.02$). We did not find a difference in our ASD sample, with loss of *social and/or language skills* (as reported in the ADI-R and/or EDC) present in 42% regardless of dysmorphology status. Defining regression based on loss of language alone may underestimate the frequency of developmental regression (Hansen *et al.*, 2008). While developmental regression is a documented phenomenon in ASD, we do not yet understand its etiology, and meaningful differences in the characteristics of children with and without regression have not yet been identified (Hansen *et al.*, 2008; Stefanatos, 2008). There do not seem to be differences in prenatal or obstetric complications (Davidovitch *et al.*, 2000; Kurita, 1985; Wilson *et al.*, 2003) or rate of head growth (Bernabei *et al.*, 2007; Webb *et al.*, 2007) in children with and without regression. The similar frequency of regression in the dysmorphic and non-dysmorphic groups is also in line with the studies mentioned above that show no differences in biological or physical characteristics between children who regress and those who do not.

Strengths of our study include the use of a well-characterized sample; all children were evaluated with the same developmental assessments (MSEL and VABS) and the diagnosis of ASD was confirmed with gold-standard measures (ADOS and ADI-R) by trained clinicians. Our sample was population-based (not clinic-based), included over 300 children, and utilized an important control group: children with developmental delay but not autism. Raters were blinded to group status.

One limitation of this study is that not all children received genetic testing or brain imaging; hence, we were unable to ascertain the true prevalence of genetic syndromes or structural anomalies of the CNS, whereas all children in the Miles studies received comprehensive genetic evaluation, EEG, and brain MRI. Instead, we relied on the medical work-up from the child's health care provider. In addition, ratings were based on standardized photos of the face and hands only: MPAs involving other body areas could not be determined. While this simplification allows for more widespread use, it limits the ability to predict cognitive/adaptive scores, history of regression, or family status. Another limitation was that photographs of parents and/or siblings were not available for analysis.

In conclusion, ASD is a heterogeneous disorder, and one meaningful subgroup includes children with generalized dysmorphology. In this subgroup, an insult during embryological development may contribute to autism risk. Because of their higher risk for seizures, dysmorphic children with ASD should be carefully followed for such abnormal brain activity and would benefit from more detailed genetic evaluation for underlying syndromes. While photographic analysis of dysmorphology in children with ASD can not replace a comprehensive physical examination, it can be a useful and efficient tool to identify individuals with generalized dysmorphology who may be at higher risk for seizures and benefit from more extensive genetic testing. Like the Autism Dysmorphology Measure (Miles *et al.*, 2008), this method of assessing generalized dysmorphology is practical, as it does not require disrobing and photographs may be obtained by a variety of providers, increasing access to information that may guide treatment and increase diagnostic yield of medical investigations.

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Figure 1.

Table 1
Demographic data by group status

	ASD N=149	DD n=63	TYP n=112
Age in months, mean (range) *	44 (25-69)	45 (24-65)	41 (25-61)
Male, % †	87%	69%	76%
Race/ethnicity ^I †			
White, %	50%	37%	55%
Black or African-American,%	1%	10%	4%
Hispanic, %	28%	45%	25%
Asian, %	8%	3%	5%
Native Hawaiian or Other Pacific Islander, %	0	0	0
Multi-Racial, %	10%	6%	12%
Parent with college degree, % †	62%	39%	62%

* ASD vs. TYP, p=0.05

† ASD vs. DD, p 0.05

^I May not add up to 100% due to rounding or missing data.

Table 2
Dysmorphology ratings by group

	DD	ASD	TYP
Dysmorphic % (#)	47.6% (30/63)	17.4% (26/149)	5.4% (6/112)
Nondysmorphic % (#)	52.4% (33/63)	82.6% (123/149)	94.6% (106/112)
Total	63	149	112

ASD vs. DD, $p < 0.001$

ASD vs. TYP, $p = 0.007$

DD vs. TYP, $p < 0.001$

Table 3
Children with syndromes that may cause ASD or DD

Syndrome	Group
Neurofibromatosis-1	ASD (2)
Down Syndrome	ASD (2); DD (13)
Chromosome 22q11.2 Deletion Syndrome	DD (2)
Fragile X Syndrome	DD (2)
Tuberous Sclerosis	DD (1)
Smith-Lemli-Opitz Syndrome	DD (1)
Other genetic syndrome	DD (3)

Table 4
Nondysmorphic vs. Dysmorphic ASD

	Nondysmorphic	Dysmorphic	p-value
History of seizures	2.4% (3/123)	11.5% (3/26)	0.005
Identified syndromes	1.6% (2/123)	7.7% (2/26)	0.08
Male	87.8% (108/123)	84.6% (22/26)	0.7
Multiplex	20.6% (13/123)	15.4% (4/26)	0.5
MSEL Early Learning Composite (IQ)	62.1 (sd 17.8)	64 (sd 20.5)	0.6
ELC<55	48% (59/123)	58% (15/26)	0.4
Receptive language score	28.2 (sd 12.2)	28.6 (sd 13.6)	0.9
Expressive language score	27.3 (sd 10.9)	28.2 (sd 11.4)	0.7
VABS (adaptive)	64.4 (sd 10.4)	66.2 (sd 14.3)	0.5
Regression	43% (53/123)	42.3% (11/26)	0.9