RESEARCH PAPER

Dysmorphism in Non-Syndromic Autism: *A Cross-Sectional Study*

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Received: May 01, 2016;
Initial review: May 19, 2016;
Accepted: January 24, 2017.

Objective: To determine the effect of association of dysembryogenesis (manifested by presence of dysmorphic markers) on the developmental profile of autistic children. **Methods**: 26 autistic children were classified into complex autism (if they had specific dysmorphic markers) or essential autism (in the absence of dysmorphic markers) using the Miles Autism Dysmorphology Measure (ADM). The developmental abilities (Griffith's Mental Development Scales) and the clinical severity (Childhood Autism Rating Scale) of both groups were compared. The prevalence of dysmorphic markers was also determined in 140 non-autistic controls. **Results**: Children with complex autism had poorer development (General Quotient 29.4 *vs* 34.0, *P*=0.06) and earlier onset of autistic symptoms (18 *vs* 24 mo, *P*=0.05). Dysmorphic markers were significantly more in autistic children compared to normal children (27% *vs* 10%, *P*=0.002). **Conclusions**: Dysembryogenesis may contribute to the clinical heterogeneity of autistic children.

Keywords: *Complex autism, Development, Essential autism, Outcome*.

Published online: February 02, 2017. PII:S097475591600035

A variety of genetic and environmental insults are implicated in the causation of autism [1-3]. Dysmorphic features are more common in children with autism and other psychiatric illnesses compared to the normal population [4,5]. Dysmorphic markers are well recognized indicators of genetic or environmental insults during the first trimester, and thus may be considered as markers of disturbances during embryogenesis [6]. Miles, *et al*. [7] developed the Autism Dysmorphology Measure (ADM) to detect specific dysmorphic markers in children with autism. Their subsequent studies showed that 20% of autistic children have complex autism (dysmorphic markers present). Complex autism has a lower male to female ratio, poorer developmental outcome, poorer response to therapy and increased incidence of seizures [8].

This study was done to compare the clinical presentation and developmental abilities of children with complex autism and those with essential autism.

Methods

This cross-sectional study was done on a group of children with autism, diagnosed using the Diagnostic and Statistical Manual -IV edition, TR (DSM-IV TR) between 1 February, 2013 and 30 November, 2013. Autistic children with no identifiable syndromes and with no deficits in vision and hearing who visited the Developmental Paediatrics Unit of a tertiary referral hospital in southern India were invited to participate in the study. Informed consent was taken from the parents of all participants and the study was approved by the Institutional Review Board. The children were examined and syndromes were ruled out on the basis of characteristic clinical features in consultation with the Geneticists. The common syndromes which are known to be associated with Autism are Tuberous Sclerosis, Neurofibromatosis, Down syndrome, Angelman syndrome, and Fragile X syndrome. There were five children who were suspected to have a genetic syndrome – one child was screened for Fragile X, one child had a peripheral blood karyotype and the other three had both Fragile X screening and Peripheral blood karyotype. All five were negative for the tests which were done. Of a total of 30 children who were recruited, only 26 children completed the detailed neurodevelopmental assessment and were finally recruited into the study. Presence of dysmorphic markers was assessed using the Autism Dysmorphology Measure (ADM). Twelve body regions are assessed and coded as normal (if there are no dysmorphic markers) or abnormal (if dysmorphic markers are present). An algorithm is then used to classify the children as having complex autism (if dysmorphic markers are present) or essential autism (in the absence of dysmorphic markers) [9]. The developmental level was assessed using the Griffith's Mental Developmental Scales-Extended Revised (GMDS-ER), and the severity of

autism was assessed using the Childhood Autism Rating Scale – Second Edition (CARS-2). The GMDS has five subscales – locomotor, personal social, hearing and speech, eye-hand coordination and performance. The performance on each of the subscales is estimated by the Sub-quotient (SQ). The General quotient (GQ), which is the composite of all the sub-quotients, is used as the indicator of the child's overall developmental abilities. GQ and SQ of less than 76 (less than 2 SD) are considered abnormal.

One hundred and forty normally developing children with no chronic or neurologic disorders, who visited the General paediatrics OPD were examined using the ADM to determine the prevalence of dysmorphic markers in the normal population. The data was analyzed using SPSS. In view of the small sample size, statistical significance was determined using the Wilcoxon – Rank sum test. Fisher exact test was done to determine the association between the dichotomous variables.

RESULTS

Twenty six autistic children (24 boys) ranging between 24-111 months (mean age: 55 months) were recruited. Seven children (27%), of whom two were girls, had dysmorphic features and were classified as complex autism. There were no significant differences in the demographic details or perinatal risk factors between the complex autism and essential autism groups (***Table* I**). Development assessment was done in 23 children (assessment of three children could not be completed due to their restlessness); all were developmentally delayed.

TABLE I CLINICAL CHARACTERISTICS IN CHILDREN WITH AUTISM

	Complex autism (n=7)	*Essential autism (n=19)*
*Age at admisson	58 (36-108)	46 (24-111)
Males	5 (71.4)	19 (100)
*Father's age	39 (29-48)	35 (29-51)
*Mother's age	31 (19-40)	28 (20-37)
Antenatal complications	3 (43)	6 (32)
Prematurity	1 (14)	3 (16)
Low birth weight	0	3 (16)
Delayed cry at birth	3 (43)	4 (21)
Neonatal jaundice	5 (71)	6 (32)
Social or language regression	3 (42)	12 (63)
*Age at onset, mo	18 (5-24)	24 (12-48)[#]
*General quotient	29.4 (21.9-41)	34.0 (18.1-71.6)
*CARS-2 score	32 (29-36)	31(27-36)

**Values in median (range); [#]P=0.05.*

Comparison between the two groups (***Table* I**) showed that children with complex autism were more developmentally compromised in all domains (significantly in the locomotor and language domains). However, the severity of autism did not show statistically significant difference between the two groups (***Table* I**). One child with complex autism (1/7) and four children (4/19) with essential autism had seizures. Among the 140 controls (78 boys), only 14 (10%) had dysmorphic markers, which was significantly lower (P=0.002) than in autistic children.

DISCUSSION

This cross-sectional study compared two groups of autistic children based on the presence of dysmorphic markers and found 27% with dysmorphism, which is similar to previous reports [8]. Similar to a previous study [8], we found that children with complex autism are distinct from those with essential autism in that they are more developmentally compromised, and have an earlier onset of regression of their language and social milestones. However, unlike the previous study, the children with complex autism in our study did not have an increased incidence of seizures. Like other Western studies [10,11], we too observed that dysmorphic features were more prevalent in autistic children compared to normal controls.

The major limitations of our study are the small sample size, and the short duration of follow-up. The eventual developmental outcomes in the two groups could not be conclusively ascertained. Fountain, *et al*. [12] reported that autistic children who have poor developmental abilities at the initial presentation are likely to remain low functioning and significantly compromised at 14 years of age. Therefore, it is likely that long term follow-up may also reveal significant differences between complex autism and essential autism children. These findings could be because insults to the fetal brain during early development, which may manifest as dysmorphic features, could contribute to the heterogeneity of autism.

In addition to documenting the proportion of autistic children with complex autism, this study also shows that Autism Dysmorphology Measure, which was formulated for the Caucasian population, is a feasible tool to systematically evaluate the presence of dysmorphic features in Indian children with autism. Studies with larger sample sizes and long term follow up are needed to further elucidate the role of dysembryogenesis in the pathogenesis and developmental outcome of autism.

WHAT THIS STUDY ADDS?

- Children with complex autism are likely to have an earlier onset of autistic features and more developmental delay than children with essential autism.

Acknowledgements: Mrs. Reeba Roshan, Mrs. Miriam Rainu Kuruvilla and Ms. Rachel Beulah (psychologists) for their assessment of the children in this study.
Contributors: SMZ: assessed for dysmorphism, collected the data, prepared the manuscript; SPO: reviewed and revised the manuscript; CSP, HG, LG: did the developmental assessments.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th ed. Arlington, VA American Psychiatric Association; 2013.
2. Betancur C. Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. Brain Res. 2011;1380:42-77.
3. Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiol Camb Mass. 2002;13:417-23.
4. Compton MT, Walker EF. Physical manifestations of neurodevelopmental disruption: are minor physical anomalies part of the syndrome of schizophrenia? Schizophr Bull. 2009;35:425-36.
5. Aldridge K, George ID, Cole KK, Austin JR, Takahashi TN, Duan Y, *et al*. Facial phenotypes in subgroups of prepubertal boys with autism spectrum disorders are correlated with clinical phenotypes. Mol Autism. 2011;2:15.
6. Aase JM. Diagnostic dysmorphology. New York: Plenum Medical Book Company; 1990
7. Miles JH, Takahashi TN, Hong J, Munden N, Flournoy N, Braddock SR, *et al*. Development and validation of a measure of dysmorphology: Useful for autism subgroup classification. Am J Med Genet A. 2008;146A:1101-16.
8. Miles JH. Dysmorphology Training (ADM) Manual, University of Missouri, 1-10-08 edition. Available from: *https://depts.washington.edu/dbpeds/Dysmorphology%20Training%20Manual%201-10-08%20(2).pdf* .
9. Miles JH, Takaashi TN, Bagby S, Sahota PK, Vaslow DF, Wang CH, *et al*. Essential versus complex autism: definition of fundamental prognostic subtypes. Am J Med Genet A. 2005;135:171-80.
10. Ozgen H, Hellemann GS, Stellato RK, Lahuis B, van Daalen E, Staal WG, *et al*. Morphological features in children with Autism spectrum disorders: A matched case–control study. J Autism Dev Disord. 2011;41:23-31.
11. Links PS, Stockwell M, Abichandani F, Simeon J. Minor physical anomalies in childhood autism. Part I. Their relationship to pre- and perinatal complications. J Autism Dev Disord. 1980;10:273-85.
12. Fountain C, Winter AS, Bearman PS. Six developmental trajectories characterize children with autism. Pediatrics. 2012;129:e1112-20.