

The Diagnostic Value of Congenital and Nevoid Cutaneous Lesions Associated with Autism Spectrum Disorders in Indian Children- A Case-Control Study

Abstract

Background and Aims: Cutaneous lesions are the defining features of several neurocutaneous syndromes like neurofibromatosis1(NF1), tuberous sclerosis complex (TSC), and Sturge Weber syndrome to name a few. With this background, we explored the possibility of identifying congenital and nevoid cutaneous markers that may help in the early recognition of autism spectrum disorders (ASD) in Indian children. The objective of this study was to measure the strength of association between congenital and nevoid cutaneous lesions and ASD among Indian children. **Methods:** A case-control study was conducted from January 2018 to June 2018. 132 children (18 months-16 years of age) with ASD and equal number of age and sex-matched children without autism were studied. Diagnosis of ASD was based on DSM-5 criteria. All the children were examined for cutaneous lesions with special attention to nevoid and congenital conditions. The strength of association was measured using the diagnostic odds ratio (OR). **Results:** The prevalence of congenital and nevoid lesions were higher in ASD group (OR = 3.12, $P = 0.0001$). Among them, pigmentary mosaicism of hyperpigmented type (OR = 2.76, $P = 0.02$) and café-au-lait macules (CALMs) (OR = 2.40, $P = 0.001$) were the most prevalent with hyperpigmented pigmentary mosaicism showing a higher association with autism. Atypical CALMs (OR = 2, $P = 0.09$) were also more prevalent in the ASD group though not statistically significant. **Conclusion:** The presence of hyperpigmented pigmentary mosaicism and CALMs warrant closer surveillance by the caregivers and physicians for evolving features of autism. Larger multicentric studies are required to validate these findings.

Keywords: Autism, congenital and nevoid lesions, Diagnostic value

Introduction

Autism spectrum disorders (ASD), a neurodevelopmental condition is on the rise in pediatric population in Western and Asian countries including India.^[1,2] Recent estimated prevalence of ASD in India ranges from 0.15% to 0.23%.^[3,4]

Several genes are associated with ASD, including *NRXN1*, *SHANK1*, *SHANK3*, and *PTCHD1*.^[5] A recent study has identified the RAS/mitogen-activated protein kinase (RAS/MAPK) pathway to be involved in ASD.^[6] Several syndromes linked to this pathway are associated with café au lait macules (CALMs). The cutaneous markers are an integral part of the diagnostic criteria of neurofibromatosis 1 (NF1) and tuberous sclerosis complex (TSC). Similarly, ASD is

a neurodevelopmental disorder associated with cutaneous lesions. The dermatological associations in ASD are increasingly recognized in the form of syndromes with dermatological manifestations, tactile dysfunction, nutritional and hormonal problems.^[7] With this background, a case-control study was done to measure the strength of association between congenital or nevoid cutaneous lesions and ASD in Indian children which may be of value in the early recognition of the condition and thereby help in early intervention.

Methods

The study was carried out over a period of 6 months from January 2018 to June 2018 in the departments of Dermatology, Developmental Pediatrics, Child and

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Adolescent Psychiatry and Pediatric Neurology at a tertiary care hospital in south India after approval by the Institutional Review Board and Ethics Committee. The objective of the study was to identify the congenital and nevoid cutaneous manifestations associated with ASD and to determine their strength of association.

There are no published studies on the prevalence of diagnostic congenital and nevoid cutaneous lesions associated with ASD. In this situation, we opted to base our sample size calculation on CALMs, a common neurocutaneous marker. CALMs are seen in 10-20% of the normal population.^[8] Based on this, taking the prevalence of CALMs to be 20%, the sample size calculation was done on the premise that to be of diagnostic value, the magnitude of the association needs to be fairly large [diagnostic odds ratio (OR) of 4 or more]. Considering P_0 , the exposure among controls to be 0.2, the sample size was calculated to be 128 in order for the OR to be 4 with type 1 and type 2 errors taken as 0.05 and 0.2 respectively.

Subsequently, 132 consecutive children between 18 months to 16 years of age diagnosed with ASD by DSM-5 criteria^[9] were included in the study. The cases were recruited from the departments of Pediatric Dermatology, Developmental Pediatrics, Child and Adolescent Psychiatry, and Pediatric Neurology and the diagnosis of ASD was made by the concerned specialists. For the control group, next available eligible person i.e. of same age and gender, but without autism were enrolled. Hence 132 age and gender-matched children attending the pediatric dermatology out-patient department during the same period were recruited as controls and were examined for the presence of any congenital or nevoid conditions and findings recorded. Informed consent from the parents/guardians was taken for both the groups.

Demographic details, history, and clinical findings were noted. All the children were examined for the presence of any cutaneous lesions, both congenital and acquired. The findings were recorded in a standardized proforma. Syndromic associations, if present, were also noted.

Congenital and nevoid hyperpigmented lesions were categorized as (1) pigmentary mosaicism and (2) circumscribed hypermelanosis. Pigmentary mosaicism included the seven archetypical patterns described by Kromann *et al.*^[10] and segmental hypermelanosis. The latter included hyperpigmented macules in a segmental pattern as described by Alan Taieb *et al.*^[11] and quadrangular and flag like hyperpigmented lesions present from birth with a sharp midline cut off and serrated lateral borders as described by Torchia *et al.*^[12] Congenital dermal melanocytosis, café-au-lait macules, and nevus spilus were grouped under circumscribed hypermelanosis.^[13] CALMs with irregular margins and ragged borders were defined as atypical as per published criteria.^[14]

Hypopigmented lesions, present since birth, occurring in a Blaschko-linear pattern including those previously

classified as hypomelanosis of Ito were included under pigmentary mosaicism as suggested by Kromann *et al.*^[10] Other types included flag-like hypomelanotic nevus which is described as a form of pigmentary mosaicism presenting as a unilateral patch of variable shape (oval or angulated) that, if large and close enough to the midline, appears in a block-like fashion.^[12] Nevus depigmentosus was further classified as focal, segmental, and generalized.^[15]

Congenital lesions that could not be categorised into any of the described entities were labelled as 'congenital and nevoid hyper or hypomelanosis - not categorised. Diagnostic ORs were calculated and Fisher's exact test was used to determine statistical significance.

Results

Demography

Among 132 cases, male to female ratio was 3.5:1 and mean age was 4.7 years while among controls, male to female ratio was 3.7:1 with a mean of 4.9 years (range in both the groups -18 months to 16 years).

Dermatological manifestations

The prevalence of pigmentary mosaicism and nevoid lesions seen in patients and controls is shown in Table 1. Congenital and nevoid lesions, including syndromes associated with autism were seen in 94/132 cases (71.2%), and in 61/132 controls (46.2%), (OR = 2.87, $P = 0.0001$). when the syndromes were excluded, OR was 3.12 with a P value of 0.0001. [Table 1]

Among cases, congenital and nevoid hyperpigmented lesions (75/132, 56.8%) were more prevalent than congenital and nevoid hypopigmented (10/132, 7.6%).

Among the controls, congenital and nevoid hyperpigmented lesions were seen in 43/132 (32.6%), and in the hypopigmented category in 10/132 (7.6%).

The prevalence of congenital and nevoid hyperpigmented lesions was higher among cases (75/132) than controls (43/132) (OR = 2.72, $P = 0.0001$).

Congenital and nevoid hyperpigmented lesions

Pigmentary mosaicism

Pigmentary mosaicism of the hyperpigmented type was seen in 20/132 (15.2%) children with ASD versus 8/132 (6.1%) among controls (OR = 2.76, $P = 0.02$).

The patterns of pigmentary mosaicism seen in cases and controls is shown in Table 2. The patterns seen among cases were Blaschko-linear [Figure 1] in 12 children (60%) and segmental [Figure 2] in 8 children (40%) with ASD. The most common sites in patients with the Blaschko-linear pattern were lower limbs (8), followed by face (3), and trunk (1). The segmental lesions were most often found on lower limbs (5), followed by trunk (2), and upper limbs (1).

Table 1: Prevalence of Pigmentary Mosaicism and Nevoid lesions in patients and controls

| Cutaneous Lesions | Cases (n=132) (%) | Controls (n=132) (%) | P | Odds ratio |
|--|-------------------|----------------------|--------|------------|
| Total number of children with pigmentary mosaicism and nevoid conditions | 92 (69.7) | 56 (42.4) | 0.0001 | 3.12 |
| Hyperpigmented lesions | 75 (56.8) | 43 (32.6) | 0.0001 | 2.72 |
| Hypopigmented lesions | 10 (7.6) | 10 (7.6) | 1.00 | 1 |
| Hyper+hypopigmented lesions | 7 (5.3) | 3 (2.3) | 0.33 | 2.40 |
| Pigmentary mosaicism- hyperpigmented type | 20 (15.2%) | 8 (6.1) | 0.02 | 2.76 |
| CALMs | 60 (45.5) | 34 (25.8) | 0.001 | 2.40 |
| Atypical CALMs | 22 (16.7) | 12 (9.1) | 0.09 | 2 |
| Nevus spilus | 1 (0.8) | 0 (0) | 1.00 | - |
| Mongolian spots | 5 (3.8%) | 8 (6.1) | 0.57 | - |
| Pigmentary mosaicism- hypopigmented type | 3 (2.3) | 1 (0.8) | 0.62 | 3.04 |
| Nevus depigmentosus | 14 (10.6) | 12 (9.1) | 0.83 | - |
| Nevoid hyperpigmentation (uncategorised) | 2 (1.5) | 2 (1.5) | 1.00 | - |

Table 2: Types of pigmentary mosaicism seen in cases and controls

| | Total study subjects (264) | Cases (132) | Controls (132) | Odds ratio (P) |
|--|----------------------------|-------------|----------------|----------------|
| Pigmentary mosaicism of hyperpigmented type | 28 | 20 | 8 | 2.76(0.02) |
| Blaschko-linear | 13 | 12 | 1 | - |
| Patchy pattern without midline separation | 3 | - | 3 | - |
| Segmental pattern | 12 | 8 | 4 | - |
| Pigmentary mosaicism of hypopigmented type | 4 | 3 | 1 | 3.04(0.62) |
| Blaschko-linear | 4 | 3 | 1 | - |

**Figure 1: Hyperpigmented type of pigmentary mosaicism along Blaschko's lines (lower limb)**

Eight children (6%) in the control arm had pigmentary mosaicism. The patterns were (i) segmental pattern in 4 (50%), ii) patchy pattern without midline separation in 3 (37.5%), and iii) Blaschko-linear pattern in 1 (12.5%). The sites of involvement were lower limbs in 4 cases, trunk in 2 cases and both trunk and lower limbs in 2 cases.

Café au lait macules

60/132 (45.5%) children in the ASD group and 34/132 (25.8%) in the control group had CALMs (both typical and atypical) [Figure 3a and b] (OR = 2.40, $P = 0.001$). The number of CALMs ranged from 1-4 (median -1) in the ASD group with multiple CALMs (>1) seen in 17 children, while in the control group (excluding NF1), it ranged from 1-3 (median -1) with multiple CALMs in 8 children ($P = 0.09$).

Atypical CALMs were also more prevalent in children with ASD although not statistically significant [22/132 (16.7%) in ASD vs. 12/132 (9.1%) in controls, (OR = 2, $P = 0.09$)].

Mongolian spots

Persistent Mongolian spots were seen in 5/132 (3.8%) children with ASD and 8/132 (6.1%) controls. One each in either group had aberrant lesions. Multiple disseminated lesions were present in 1/5 cases and 2/8 among controls. No associated metabolic disorders were identified in children with extensive Mongolian spots in both groups.



Figure 2: Flag like segmental hypermelanosis

Nevus spilus

Seen in 1 child with ASD over the left buttock while no cases noted in the control group.

Congenital and nevoid lesions- not categorized

2 children each among cases and controls had circumscribed hyperpigmented nevoid lesions- in the “not categorized” category.

Congenital and nevoid hypopigmented and depigmented lesions

Hypopigmented pigmentary mosaicism

Hypopigmented type of pigmentary mosaicism was seen in 3/132 (2.3%) children with ASD all of which were following Blaschko-linear pattern. It was localized to one anatomical site, abdomen, and neck in 2 children, while in the third child it involved the left half of the body involving the left upper and lower limbs and left side of trunk.

It was present in one (0.8%) of the controls, also following Blaschko-linear pattern involving the right lower limb (OR = 3.04, $P = 0.62$).

Nevus depigmentosus

Nevus depigmentosus was seen in 14/132 (10.6%) children with ASD and 12/132 (9.1%) among controls ($P = 0.83$). All lesions were focal among the cases. Among controls 1/11 had a segmental pattern, the remaining had a focal pattern.



Figure 3: (a): Typical cafe-au-lait macule. (b): Atypical cafe-au-lait macule

Combined hyperpigmented and hypopigmented congenital and nevoid lesions

Both hypo and hyperpigmented congenital and nevoid lesions were seen in 7/132 (5.3%) cases and 3/132 (2.3%) controls. Among the 7 cases, nevus depigmentosus and CALMs were seen in 4, CALMs and hypopigmented pigmentary mosaicism in 2, nevus depigmentosus and hyperpigmented pigmentary mosaicism in one child. Among controls, combination of nevus depigmentosus and hyperpigmented pigmentary mosaicism was seen in 2, CALMs and nevus depigmentosus were seen in one child.

Syndromes

2 children in the ASD group and 1 in the control group were diagnosed with TSC while there were 4 cases of NF1 in the control group. No other neurocutaneous syndromes were identified in either group.

Discussion

Studies on the genetic changes prevalent in autism have shown monogenic etiology, copy number variations and polymorphisms. An analysis by David *et al.* found 1031 genes associated with ASD and at least one other related disorder, and a core set of 262 genes unique to ASD.^[16] The implicated networks have been identified at the cellular level for many of these variations based on genetic network analyses and genetic functional studies.^[17] Genetic alterations were identified in 1-25% of the individuals with autism of which FMR1 (fragile X syndrome) was found to be the most common.^[18] The nevoid conditions described in association with ASD include pigmented lesions, congenital nevi, and CALMs. Among them, pigmented lesions (hyper and hypopigmented spots) were reported to be significantly associated with autism.^[19] The present study was done to determine if there is any consistent association of a neurocutaneous marker with ASD, a neurodevelopmental disorder, as it would help in the timely identification of

children at risk and to initiate appropriate behavioral interventions. Neurocutaneous markers could also be used as a screening tool or in questionnaires to parents during their routine physician visit. Awareness of its association among physicians and parents is of paramount importance so as to refer the children early for a formal developmental assessment. Diagnostic odds ratio was used to determine the strength of association. Ratio of odds for exposure among cases to odds for exposure among controls is the diagnostic OR which can range from zero to positive infinity. Values above 1 provide a measure of the strength of association from the context of diagnostic value. A test with a sensitivity of 75% and a specificity of 75% will provide a diagnostic OR of 9. This study was designed to detect an OR of at least 4 which would be equivalent to a sensitivity and specificity of 66% each.

In our study, it was found that there was a significantly higher prevalence of congenital and nevoid conditions in ASD as compared to controls. Among them, hyperpigmented pigmentary mosaicism in Blaschko-linear and segmental patterns and CALMs were significantly associated with ASD. Pigmentary mosaicism of the hyperpigmented type had the highest association with a diagnostic OR of 2.76. The reported prevalence of autism in cases with pigmentary mosaicism varies between 3.8-10% in various studies.^[20,21] In another study published on the clinical profile of 16 cases with linear and whorled nevoid hypermelanosis, autism was reported in one child.^[22] Segmental hypermelanosis is a type of cutaneous mosaicism of the pigmentary system which may appear anywhere on the skin and are typically unilateral with a sharp cutoff at the midline, it may follow a dermatome.^[11] There have been reports of associated neurological involvement, although not specifically that of autism.^[11] In contrast to the studies from West that report an increased prevalence of hypomelanosis of Ito in cases with autism,^[23] in our study pigmentary mosaicism of hypopigmented type was seen in only 2.3% of cases. Although the OR was 3.04, this was not significant. White matter abnormalities in the periventricular and subcortical regions have been associated with severe neurologic abnormalities and delayed language milestones in cases with hypomelanosis of Ito.^[24] In another study, the reported prevalence of autism varied between 1-60% among patients with hypomelanotic skin conditions like oculocutaneous albinism, hypomelanosis of Ito, tuberous sclerosis, Angelman syndrome, and Prader-Willi syndrome.^[25] Pigmentary mosaicism results from either genomic or epigenetic mosaicism. The Lyon-effect, that is random X-inactivation naturally occurring in females is an example of epigenetic mosaicism, while genomic mosaicism is the presence of at least 2 populations of cells which differ in the genome.^[10] Additional tests like karyotyping, FISH, and genetic testing which may have helped in the better categorization of pigmentary mosaicism and understanding of the association with ASD were not done in our study.

Although studies have shown a significant prevalence of ASD in NF1,^[26] the association between isolated CALMs and ASD has not been evaluated in previous studies. In a study reported in 1997 on hospitalized Jewish patients with ASD, the prevalence of CALMs was reported to be 6.7%.^[19] In the present study, nearly half of the children with ASD had CALMs (both typical and atypical). Atypical CALMs, defined as those with irregular and ragged borders by Ben Shachar *et al.*^[14] were also more prevalent in the ASD group. Multiple CALMs were also more prevalent in children with ASD. CALMs are an important diagnostic phenotype of various RASopathies with germline mutations in the RAS/MAPK cascade. The RAS/MAPK pathway was also identified as crucial for controlling pigmentation.^[27] A study by Lauren Weiss showed that approximately 40 percent of individuals with classical RASopathies show significant traits of autism.^[6] The pathway has been implicated in the pathogenesis of non-syndromic forms of ASD as well.^[18]

The prevalence of TSC in patients with ASD in our study was 1.5% and was similar to a study by Fombonne *et al.*, where it's prevalence was 1.1% in a sample of 174 children with ASD.^[28] Additional studies have confirmed this association, with TSC prevalence estimates of 1% to 4% in patients with ASD.^[29-31] Features of ASD are seen in 25% to 50% of those with TSC.^[30] There were no cases of NF1 in the ASD group in our study (all 4 being in the control group), probably because of the small numbers studied. ASD has also been reported in patients with Sturge-Weber syndrome. In a study by Gittens *et al.*, on a cohort of 92 children with Sturge-Weber syndrome, 24% had a diagnosis of ASD, with 45% overall having evidence of social communication difficulties.^[32] No vascular anomalies however were seen in our study in association with ASD.

Among the limitations, skin biopsies were not done from patients with atypical CALMs to confirm the diagnosis. Besides, genetic studies to diagnose specific syndromes were not done, so correlations, if any, between the congenital and nevoid pigmentary abnormalities and associated syndromes in children with ASD could not be identified. As the clinical severity of ASD was not assessed in this study, it could not be correlated with the cutaneous manifestations.

To conclude, in this study, we found a significant association of congenital and nevoid conditions with autism but was not of the magnitude to be of diagnostic value. However, their presence especially that of pigmentary mosaicism of hyperpigmented type and CALMs should alert the physician to look for features of ASD. Large multicentric studies focusing on the association between nevoid lesions and ASD are required to establish if they can serve as diagnostic cutaneous markers for ASD which will then facilitate early identification and management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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