**MORFAN Syndrome: A Rarity but a Reality!**

**Gourab Roy, Sumit Sen, Shreya Poddar**

From the Department of Dermatology, Institute of Post Graduate Medical Education and Research and SSKM Hospital, Bhowanipore, Kolkata, West Bengal, India

Address for correspondence:
Dr. Shreya Poddar,
Flat No. 202, Rukmani Apartments, Near Chowk Thana, Jhauganj, Patna - 800 008, Bihar, India.
E-mail: shreyapods@gmail.com

**Abstract**

Acanthosis nigricans (AN) describes clinically hyperpigmented skin, which most commonly affects the flexural areas such as axilla, groin and neck. It is usually a benign condition associated with obesity, insulin resistance, and hyperinsulinemia; endocrinopathy; or malignancy, in particular, gastrointestinal adenocarcinoma. It can also occur in association with various genetic syndromes involving various organ systems. Few such known syndromes are Berardinelli-Seip syndrome, Alström syndrome, Leprechaunism, and Bardet-Biedl syndrome. MORFAN syndrome, which associates mild mental retardation, pre- and post-natal overgrowth, remarkable facies and diffuse and widespread AN, is a rare entity.

**KEY WORDS:** Acanthosis nigricans, MORFAN syndrome, pre and post-natal overgrowth

**Introduction**

Acanthosis nigricans (AN) is a common dermatosis first described by Santi Unna and Monath Pollitzer in 1890. It is characterized by thick, hyperpigmented, verrucous plaques distributed at typical sites including mucous membranes. AN is associated with multiple etiologic factors including direct autosomal transmission, genetic abnormalities, medication, malignancy, and endocrinological abnormalities.

MORFAN is the acronym for a rare syndrome (M = Mild mental retardation, O = Pre and postnatal Overgrowth, RF = Remarkable Facies, AN = Acanthosis Nigricans). Exact diagnostic criteria for MORFAN is lacking. Till date, only three cases have been reported worldwide.

To the best of our knowledge no case has been reported from Asian subcontinent till date. Here, we report a case of a 10-year-old female fitting with the phenotypical features of MORFAN and give a comprehensive review of the other three similar cases [Table 1].

**Case History**

A 10-year-old Hindu girl, second issue, born out of non-consanguineous marriage presented to our OPD with complaints of gradually progressive, diffuse, velvety, blackish plaques over the neck, anterior part of the chest, bilateral cubital fossa, axilla, knuckles of fingers, and toes since 4 years of age. The intertriginous areas were affected the most [Figure 1]. The patient also complained of gradual weight gain and obesity since the same duration.

There was no history of similar signs or symptoms in her elder female sibling or any near or distant family members. Her mother was hypothyroid. According to her mother, she was delivered prematurely at 34 weeks of gestation by normal vaginal delivery with a birth weight of 2.5 kg. She did have some respiratory distress for which she was given mask ventilation. There was no history of convulsion/seizure during her infancy or childhood. She had a history of suffering from recurrent respiratory infections and hypocalcemia during her childhood days.

Patient’s mother took medical advice at 18 months of age for delayed developmental milestones. The child started standing with support at 3 years of age. The eruption of first tooth of the patient took place at 4 years of age. She started speaking mono and bi syllables at 5 and 6 years of age, respectively as noticed by her mother. Since last 2 years, the girl was often seen muttering to herself. Her mother also noticed that she could not compete socially or intellectually with children of her own age and hence underwent psychometric...
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The patient had started menstruating at 9 years of age. She has no control over her bladder. She was sent for Tanner breast staging that supported the impression of precocious puberty. She has been admitted to special education school for the last one and half years.

General examination revealed that her vitals were within normal limits. Anthropometric measurements revealed her weight to be 54 kg (>97 percentile) and height was 5 feet and 2 inches (>97 percentile). She also had large flat feet and large palms.

Mucocutaneous findings revealed diffuse, blackish, velvety pigmentation over the neck, anterior chest, bilateral cubital fossa, axilla, knuckles of fingers, and toes [Figure 2]. Oral and genital mucosa were not affected. Hair and nails were within normal limits.

She had characteristic facial features with large, flat nose with depressed bridge of the nose. Her eyes were large, prominent, and protruding. She had puffy everted lips, large low lying ears, fleshy tongue with dental caries, and mixed dentition.

Table 1: A comparative tabulation between present case and the previous three reported cases

| Features                          | Present case                                      | Case 1 (Seemanova et al.) | Case 2 (Garg et al.) | Case 3 (Young et al.) |
|-----------------------------------|---------------------------------------------------|---------------------------|----------------------|-----------------------|
| Age/Sex                           | 10 Years/Female                                   | 5 Years/Male              | 6 Months/Female      | 17 Years/Female       |
| Intellectual Disability/Developmental Delay | Mild mental retardation                          | Mild mental retardation   | Slight developmental delay | Mental retardation present |
| Overgrowth                        | Height >97 Percentile                             | Height >97 Percentile     | Height 50 Percentile | Weight 25-50 Percentile |
| Bone age                          | Accelerated                                       | Accelerated               | Consistent with chronological age | Not mentioned |
| Facial features                   | Large eyes, depressed nasal bridge, puffy everted lips, and large feet and palms. | Protruding eyes, puffy eyelids, antimongoloid slant, large ears, retrognathia, macrostomia, and everted lips | Flat forehead with hypertrichosis, slightly united eyebrows, hypertelorism, prominent proptotic eyes, and flat nasal bridge | Dysmorphic facies |
| Oral cavity                       | Macroglossia and dental caries                   | Dental caries             | Macroglossia         | Not mentioned         |
| Hair                              | Curly hair                                        | Dry and Curly hair        | Curly hair           | Not mentioned         |
| Acanthosis nigricans (Pattern)    | Diffuse, Most prominent in intertriginous areas since 4 years of age | Prominent at neck, inguinal areas, axilla, and abdomen since infancy | Present but details not mentioned | Acanthosis nigricans in intertriginous areas since 7 years of age |
| Insulin and glycemic Status       | Normal fasting plasma glucose and insulin levels  | Fasting hypoglycemia, post-prandial hyperglycemia, and normal/decreased plasma insulin levels | Hypoinsulinemic hypoglycemia | Insulin resistance present for which she had been receiving metformin |
| Other features                    | Hypercalcaemia and precocious puberty            | Hyperlipidemia            | AKT2 mutation was identified | Hypothyroidism and ovarian cyst |

Figure 1: A 10-year-old girl of MORFAN syndrome with Acanthosis nigricans. Clinical image of axillary region showing black, velvety plaques.

Figure 3: A 10-year-old girl of MORFAN syndrome with Acanthosis nigricans. Clinical image of axillary region showing black, velvety plaques.
Routine laboratory investigations revealed mild anemia (Hb-10.6 g %). Liver function test, renal function test, fasting lipid profile were all within normal limit. Fasting glucose level was 58 mg/dl and fasting insulin level was 7 uIU/ml at the time of presentation. Thyroid profile and early morning cortisol level were within normal levels. Serum calcium level showed mild hypocalcemia (8.3 mg/dl). Radiological bone age revealed an age between 11 to 14 years. USG abdomen, MRI/CT brain revealed no abnormality.

Genetic screening or mutation study could not be done because of lack of facility at our institution. A diagnosis of the rare MORFAN syndrome was made from the clinical findings.

Discussion
MORFAN is a very rare syndrome.

The first case of MORFAN was reported by Seemanova et al. in 1993 of a 5-year-old boy who had mild mental retardation, pre- and post-natal overgrowth, facial anomalies, and AN. They postulated that the patient had a genetic defect in insulin receptors according to his fasting as well as post-prandial glucose and insulin levels, which was perhaps the cause of AN, mental retardation, curly hair, and abnormal facies in this subject.

After 25 years, researchers reported a similar case with hypo-insulinemic hypoglycemia with distinct facies and other features consistent with MORFAN syndrome. Whole exome sequencing revealed a mutation of the AKT2 gene. However, they failed to establish any relation of the mutation to MORFAN syndrome as similar mutations were also noted in other patients with hypo-insulinemic hypoglycemia.

The third reported case was a 17-year-old female with diffuse AN, dysmorphic facies, developmental delay, and insulin resistance for which she had been receiving metformin.

Our patient had diffuse long-standing AN, endomorphic body habitus, subtle facial features, and mild mental retardation consistent with the syndrome, but her fasting and post-prandial glucose and insulin levels were normal at the time of presentation. AN has a multifactorial etiology such as direct autosomal transmission, medications, endocrinopathy, malignancies, and genetic abnormalities. Unfortunately, a genetic screening or mutation study could not be performed. She also had persistent hypocalcemia, precocious puberty, and accelerated skeletal growth.

The genetic and molecular basis of this syndrome still somehow remains a mystery, hence no treatment algorithm also exists apart from symptomatic management. We hope that complete physical, biochemical, and genetic screening is pursued in cases fitting the above phenotype to better identify the syndrome and elucidate its pathogenesis. MORFAN is not a myth but a fact.

Conclusion
MORFAN is an extremely rare syndrome with three cases reported worldwide till date as per data available with an exhaustive search on the internet with keyword MORFAN. No algorithm exists to identify MORFAN as of today and more reports of rare cases such as ours will aid in forming a criterion.

Lack of genetic studies is a drawback in our patient. We report this disorder to increase awareness about the existence of such a rare syndrome.

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 patient understood that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.
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Conflicts of interest
There are no conflicts of interest.

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