Unusual association of diseases/symptoms

Overlap syndrome: a diagnostic dilemma

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Summary

We report an interesting case of a young patient who came with a concern for missing teeth and lack of hair on scalp and body. Examination revealed complete absence of teeth, absence of eyebrows, eyelashes and hair over scalp. He was short-statured, had hyperextensible joints and hyperelastic skin, protuberant lips and many other anomalies such that the overall pattern of defects was not recognisable. A wide array of investigations involving the dental and medical faculties were done; however, the final diagnosis could not be reached, since it appeared to involve features of more than one syndrome, thus the name 'overlap syndrome'.

BACKGROUND

The word syndrome is derived from Greek and literally means 'a running together'. The term syndrome has been applied to collections of signs, to groups of symptoms and to a mixed assortment of signs and symptoms.¹ Opitz *et al*² has distinguished casual or true syndrome from false syndromes such as coincidental, associational and symptomatic syndromes.

Many a times, clinicians are faced with a complex syndrome, that is, 'those groups of heterogeneous disorders with overlapping characteristics that are difficult to separate into specific conditions',³ where several anomalies are observed in the same patient such that the clinician does not recognise the overall pattern of defects from searching the literature, nor from consultation with most learned colleagues in the field.

We report an interesting case of a patient who came with complete absence of teeth in the oral cavity (complete pseudo anodontia), short stature, alopecia, absence of eyebrows, eyelashes, protuberant lips, hyperextensible joints, hyperelastic skin and several other anomalies such that the overall pattern of defects was not recognisable.

CASE PRESENTATION

A young patient came with a concern of absence of teeth and scalp and body hair. The patient gave a history of parental consanguineous marriage, his father marrying his maternal first cousin. The patient was the youngest of four siblings, rest being sisters. He was the only one affected. No other relative from the maternal or paternal side showed expression of the defect even in a minor form.

The mother gave no history of consumption of alcohol, intake of drugs, exposure to eruptive or infectious diseases. There was no history of forceps delivery.

General examination

The patient was conscious, cooperative and alert. He had a normal gait and posture but was short-statured (height 146.5 cm, weight 33 kg. Temperature, pulse 88/min and blood pressure 110/70 mm Hg) at the time of examination

were within normal limits. There was no evidence of pallor, icterus, cyanosis or clubbing.

He had a long trunk compared with his lower extremities, narrow, drooping shoulders, which could not be approximated fully (figure 1). The skin over the body was hyperelastic, smooth, dry, devoid of hair and showed variable scarring. The scars were more prominent on the pretibial regions, where they resembled 'cigarette paper scars' surrounded by multiple smaller pigmented atrophic scars. Also seen were two prominent 'cerebriform' scars on the forearm (figure 2).

Figure 1 Full frontal view.

Figure 2 Forearm.

The hands were short and pudgy, with marked hyperli-
nearity of palms. The fingers were short and stout, with
hyperextensible metacarpophalangeal and interphalangeal
joints (figure 3).

The nails over the extremities showed increased subun-
gal tissue with slight curving in mediolateral dimensions.

Maxillo-facial examination

Skull: Resembled an inverted triangle. It had a brachy-
cephalic appearance. There was absence of hair over the
scalp (patient was wearing a wig at the time of examin-
ation). Frontal and parietal bossing was also evident.

Scalp: Showed numerous brownish, irregular, slightly
pitted scars, most of them centrally located (figure 4).

Face: Had a puffy appearance and the lips were coarse,
protuberant and everted (figure 5).

Eyes: Showed pronounced supraorbital ridges, hypertelo-
rism. The upper eyelids had excessive soft tissue, while the
lower eyelids were thin and atrophic with horizontal fis-
sures radiating from the medial angle of the eye. There
was marked absence of eyebrows and eyelashes (figure 5).

Nose: Was broad based, with a depressed bridge and flared
anterior nares (figure 5).

Figure 3 Left hand.

Figure 4 Scalp.

Ears: Were inserted obliquely into the head. Depressions
in front of the ears were evident.

Neck: Showed firm goitre which moved with degluti-
tion.

The patient could apparently touch the tip of the
tongue to the nose (figure 5).

Intraoral examination

It revealed complete anodontia, broad, flat alveolar ridges
and shallow vestibules (figures 6 and 7). The mucosa over
the ridges was pale, atrophic with smooth, globular eleva-
tions along the ridges, probably implying that the teeth
were present within the bone. The maxillary arch showed
prominent rugae, shallow palate, while the mandibular
arch had a lingual frenum attached close to the alveolar
crest. Intraoral examination also revealed excessive
mucosal folds in the buccal mucosa which were pale in
appearance.

Figure 5 Extraoral frontal view.

Figure 6 Intraoral maxillary view.

Provisional diagnosis

Following a detailed history and examination, our provisional diagnoses were:

- ▶ Ectodermal dysplasia (hypohydrotic) associated with either:
 - Goitre
 - Hypoparathyroidism
 - Rickets
- ▶ Ehlers-Danlos syndrome
- ▶ Cartilage hair hypoplasia
- ▶ Mucopolysaccharidosis
- ▶ Combination of two or more syndromes.

INVESTIGATIONS

A wide array of investigations were done starting with oral radiographic examination, general skeletal survey, histopathological examination. The patient was also referred to the endocrine, skin, haematology, ophthalmology and ears, nose and throat departments for further investigations.

Oral radiographic examination

Intraoral periapical radiographs (IOPA) were not possible due to shallow vestibules.

Figure 7 Intraoral mandibular view.

Orthopantomograph (figure 8) revealed multiple unerupted, teeth in both the jaws, and hypoplastic maxilla and mandible. The other bones of the maxillofacial complex were also hypoplastic, namely the zygomatic bones, the condyles, malar bones and other bones of the facial complex.

Occlusal radiographs

A maxillary and mandibular occlusal radiograph was taken. They revealed the complete set of primary and secondary teeth one behind the other (figure 9). They were hypoplastic with rudimentary pulp chambers and root formation, and were covered by a thin alveolar cortex.

General radiographic skeletal survey

It was carried out to rule out any general skeletal involvement. Included in the survey were radiographs of lateral skull (figure 10), which showed normal outer and inner tables with thickening in the frontal region, normal sella tursica, small facial bones and cranial vault, hypoplastic maxilla and mandible with unerupted teeth. Soft tissue shadows of enlarged tongue, lips and submandibular region were also evident.

Postero-anterior chest, showed subdiaphragmic bullae and hyperinflated lung fields, tubular heart and well-formed clavicles; however, hand and wrist and pelvis with both hip joints radiographs showed no abnormality.

Blood investigations

Routine and other blood investigations showed no abnormality.

Histopathological investigations

A punched biopsy from the left cheek was taken.

Haematoxylin and eosin stain

Showed pink homogeneous peri-appendageal deposits.

Special stain (periodic acid Schiff stain) was done to test for glycogen deposits.

Showed atrophic epithelium with subepithelial hyalinisation, few dilated sweat ducts and hair follicles surrounded by faintly periodic acid Schiff (PAS) +ve hyaline material (figure 11).

Inference

Tissue showed some kind of mucopolysaccharide deposits, probably some kind of collagen disorder.

Endocrine investigations

Ruled out thyroid and parathyroid disturbance.

Ophthalmic investigations

Fundoscopy examination was normal; however, slit-lamp illumination showed stromal dystrophy, subepithelial opacities in a lattice pattern, prominent corneal nerves with decreased sensations, suggestive of amyloid deposits in the cornea due to a collagen disorder.

ENT investigations

Revealed no abnormality in the ears, nose or throat. Indirect laryngoscopy also proved to be non-suggestive.

Figure 8 Orthopantomograph.

DIFFERENTIAL DIAGNOSIS

Many a times, clinicians are faced with a syndrome, where several anomalies are observed in the same patient such that the clinician does not recognise the overall pattern of defects from searching the literature, nor from consultation with most learned colleagues in the field.

In the present case, it was concluded that the patient had manifestations of more than one syndrome, that is, possibly an overlap syndrome or an associational syndrome.

The patient had some form of ectodermal disturbance as well as a connective tissue disorder and thus instead of one single diagnosis, our differential diagnoses included a variant of ectodermal dysplasia with either:

- ▶ Ehlers-Danlos syndrome
- ▶ Mucopolysaccharidoses
- ▶ Cartilage hair hypoplasia.

Ectodermal dysplasia (ED)

It is a hereditary disorder associated with defective ectodermal structures and their accessory appendages. There

are two basic forms of ED,⁴ the hidrotic and the hypohidrotic types, though Nelson has classified it into five categories and atleast 121 subtypes, which are inherited through all Mendelian modes.⁵

Our patient presented with many characteristic features of ED such as absence of scalp hair, eyebrows, eyelashes and hair over the whole body, smooth dry skin, frontal bossing, depressed nasal bridge, thick protruding lips and ears, complete anodontia (albeit clinically), short stature, hypohidrosis, supplemented by a histological picture showing decreased sweat glands.^{6,7}

However, features not fitting into the ED picture were:

- ▶ Presence of almost all teeth, though impacted (pseudo anodontia), rather than absence of some or all tooth germs as seen with ED.
- ▶ Absence of hyperkeratosis of palms and soles.
- ▶ Absence of flexural eczema.

Ehlers-Danlos syndrome

It constitutes a heterogenous group of generalised connective tissue disorders with skin fragility, skin hypermobility and joint hyperextensibility. Genetic and biochemical studies have defined more than 10 types and the molecular basis of several of them has been identified.⁸

Figure 9 Maxillary and mandibular occlusal views.

Figure 10 Lateral skull radiograph.

Figure 11 Photomicrograph of punch biopsy of left cheek.

Our patient presented with hyperextensibility of joints, and hyperelasticity of skin, outward and downward projected ears, ease in touching tip of nose with the tongue (Gorlin's sign), redundant skin folds about eye, epicanthal folds, poor scar tissue formation, pretibial scarring, velvety feel to the skin and tendency for the hands and soles to be redundant.

However, he did not have other features of Ehlers-Danlos syndrome like:

- ▶ Blue sclera, myopia, or strabismus.
- ▶ Diaphragmatic, inguinal or umbilical hernias.
- ▶ Chronic joint dislocations.
- ▶ Rupture of vessels in ecchymotic form.
- ▶ Genu recurvatum, pes planus or scoliosis.
- ▶ Pseudotumours over heels and major joints.

Cartilage-hair hypoplasia (metaphyseal chondrodysplasia, McKusick type)

Described first by McKusick⁹ in 1964. The basic defect is not known but there may be decreased reactivity of some disulphide bonds in hair leading to its abnormal biophysical and biochemical properties.^{10 11} It is an autosomal recessive disorder with reduced penetrance.

Our patient had baldness, absent eyebrows and eyelashes, dwarfism of short limb variety, short and pudgy hands and loose jointedness in fingers, wrist and feet. Chest deformity (pectus excavatum) and classic form of achondroplasia were ruled out by skull, spine and pelvic roentgenograms.

However, he did not have other features of the syndrome like:

- ▶ An intestinal defect (absorptive defect and megacolon).
- ▶ History of viral infections (chicken pox) or other infections such as otitis media or pneumonia.
- ▶ Posterior projection of heel.
- ▶ Ability to fully extend the elbows.

Mucopolysaccharidoses

These are a family of inherited metabolic diseases that result from deficiency of different lysosomal enzymes involved in the degradation of the mucopolysaccharides.¹² Based on clinical and biochemical studies this group of metabolic disorders have been designated, mucopolysaccharidoses I to MPS VII.¹¹ Deficiency of a specific lysosomal enzyme has been demonstrated in each of the MPS disorders. Each has autosomal recessive inheritance, with the exception of Hunter's syndrome MPS II, which has x linked recessive inheritance.

On the basis of typical infiltrated appearance of facies and intraoral mucosa and the histochemical picture of PAS+ve-stained hyaline material, MPS was considered.

However, many characteristic classical features were absent, such as:

- ▶ Mental retardation.
- ▶ Characteristic craniofacial dysmorphism.
- ▶ Stiffness of joints.
- ▶ Corneal clouding.
- ▶ Abundant eyebrows and scalp hairs.
- ▶ Inguinal or umbilical hernias.
- ▶ Hepatosplenomegaly.
- ▶ Recurrent respiratory infections.

OUTCOME AND FOLLOW-UP

Individuals affected by such disorders would require a lifetime of special needs which may include:

- ▶ Dentures at a young age with frequent adjustments and replacements.
- ▶ Special diet to meet dental/nutritional needs.
- ▶ Comfortable, cool environment.
- ▶ Wigs to conceal hair and scalp condition.
- ▶ Carrier identification testing.
- ▶ Osseointegrated dental implants.

DISCUSSION

After considering all the possible syndromes related with the patient's signs and symptoms, it was difficult to delineate it to one particular syndrome and hence we considered it as an overlap of manifestation of a few syndromes.

The process of syndrome delineation is not an academic exercise but actually fosters good patient care. When an unknown syndrome becomes delineated, its phenotypic spectrum, its natural history and its recurrence risk become known, allowing for better patient care and family counselling. We need a team approach to manage this case,¹³ wherein, firstly the impacted, unerupted teeth will be surgically removed, followed by a planned prosthetic treatment of osseointegrated dental implants,¹⁴ to meet his functional and aesthetic needs. We hope we can do justice to this patient and help him lead a careful and better life.

Learning points

- ▶ If there is a positive history of consanguineous marriage between the parents, inform such parents to undergo prenatal diagnosis, as there is more probability of some kind of congenital or developmental disturbance in the offspring (like in this case).
- ▶ Consider edentulous jaws, absence of eyebrows, eyelashes and hair on scalp as a part of spectrum of an ectodermal disturbance.
- ▶ Hyperelastic skin, hypermobile joints, ability to touch the tip of tongue to the nose and skin fragility, may point to the probability of some connective tissue disorder like Ehlers-Danlos syndrome.
- ▶ Typical infiltrated appearance of facies (puffy face) and intraoral mucosa and histochemical picture of hyalinisation may be suggestive of some metabolic disease like mucopolysaccharidoses.

Competing interests None.

Patient consent Obtained.

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