Abstract
We present the case of a 3-year old girl with clinical manifestations typical of XP-CS, an extremely rare combination of Xeroderma Pigmentosum and Cockayne Syndrome. She had a swelling above the upper lip and multiple brown spots on her face, neck, arms and back. She was globally delayed, deaf, dumb and photophobic. MRI brain showed mild cerebral atrophy and bilateral demyelination. De Sanctis Cacchione variant (dSCS) and Rothmund Thomson syndrome (RTS), which were among the differential diagnosis were ruled out upon careful evaluation. Supportive treatment was given and regular checkups were recommended to monitor the progression of the disease but our patient did not show up for the follow up. This report shows that the diagnosis of XP-CS can be based on clinical features and MRI findings when the genetic testing is not available.

Keywords: Xeroderma Pigmentosum-Cockayne Syndrome complex (XP-CS), Xeroderma Pigmentosum (XP), Cockayne Syndrome (CS)

Introduction
Xeroderma Pigmentosum-Cockayne Syndrome Complex (XP-CS) is an exceedingly rare genetic syndrome that exhibits the clinical features of two autosomal recessive diseases, Xeroderma pigmentosum (XP) and Cockayne Syndrome (CS) and paradoxically an XP genotype. First described as a distinct clinical entity in 1974, it has only 43 reported cases in the literature. Based on gene mutation, four complementation groups have been identified for XP-CS: XP-B, XP-D, XP-F and XP-G. The molecular defect in XP-CS is persistence of the TFIIH complex at the sites of DNA damage that subsequently impairs DNA synthesis and transcription. XP-CS follows a progressive deteriorative course like CS. Clinically, the patients have a marked susceptibility to acute sunburns after minimum exposure, facial freckling, increased risk of skin cancer and pigmentedary changes that are characteristic of XP. The neurological and somatic features are CS-like and include growth failure, intellectual disability, delayed development, sensorineural hearing deficit, progeria, failure to thrive, and severe cachexia characterized by deep-set eyes. The neuroimaging reveals brain atrophy, ventriculomegaly, tigroid demyelination and microcephaly, findings also characteristic of CS. Here, we report a case of a 3-year-old girl presenting with clinical features strongly suggestive of XP-CS complex. However, the genotype could not be established owing to a lack of availability of molecular testing.

Case Report
A three-year old female child, born of consanguinity, presented to the Paediatrics Department in May 2017 at Civil Hospital, Karachi with complains of swelling just above the upper lip for the past one month. There was also a history of dark brown spots persisting from the third day after birth and involuntary movements from the third month of life. The swelling was only present above the upper lip, and did not increase in size. Most of the brown spots were confined to the face and neck, but there were some also present on the arms and back. As stated by the mother, these spots appeared after even minimal exposure to sunlight. Initially they were light in colour but gradually became darker and then disappeared after several weeks. The child was globally delayed, and did not achieve any of the normal developmental milestones.

On examination, the child was found to be photophobic, deaf and dumb and had dysmorphic features. Large ears, microcephaly, short stature, deep set eyes and prominent maxillae were noted. Anthropometric measurements showed that her weight was nine kilograms and height was seventy-seven cm (both less than the tenth centile), mid upper-arm circumference was eleven cm (normal), and occipital-frontal circumference was 39 cm (less than the fifth centile). Multiple hypo and hyper pigmented macules were visible on the face and forearms. The skin of the sun
exposed parts of the body was dry and scaly. The respiratory, abdominal, cardiovascular and CNS examination were unremarkable. Prenatal history and antenatal history were unremarkable. Feeding difficulties were present from birth and family history was not contributory. The child was not vaccinated. The basic laboratory investigations were all normal.

Xeroderma pigmentosum-Cockayne syndrome complex, De Sanctis Cacchione variant (dSCS) and Rothmund Thomson syndrome (RTS) were among the differential diagnosis until further investigations were carried out. The pelvic ultrasound revealed normal uterus and ovaries according to the age of the patient. Ophthalmologic evaluation showed salt and pepper retinal pigmentation, and mild optic disc atrophy. Brainstem evoked response audiometry revealed bilateral sensorineural deafness. MRI scan of the brain demonstrated mild, generalized cerebral atrophy which was more pronounced in the temporal lobes, and bilateral dysmyelination especially in the corona radiata. Due to unavailability of testing, UV exposure of cultured fibroblasts and further DNA studies could not be performed. The MRI findings, and the clinical presentation when correlated were highly suggestive of Xeroderma Pigmentosum-Cockayne Syndrome Complex. The patient was managed by giving Moxifloxacin eye drops, antibiotic eye ointment, topical Vitamin A eye drops, artificial tears, SPF-80 sunscreen, and sunglasses were prescribed. An excisional biopsy of the upper lip swelling revealed no malignancy. The patient was called for a follow up visit but did not show up. Informed consent was taken from the parents of the patient to reproduce her case in this report.

Discussion

Xeroderma pigmentosum-Cockayne syndrome is a rare clinically overlapping genetic disorder characterized by somatic and neurological abnormalities of Cockayne syndrome and skin and eye manifestations of Xeroderma pigmentosum. In making the diagnosis for
this patient, the clinical features were evidently indicative of Cockayne syndrome. In a previously published review article by Nance and Berry, it was stated that the diagnosis of CS should rest on two major findings: growth failure and neurological dysfunction with predominant white matter involvement. Moreover, at least three other minor features ought to be present including cutaneous photosensitivity, progressive pigmentary retinopathy or cataract, optic disc atrophy, miotic pupils, sensorineural hearing loss, dental caries and a characteristic physical appearance. Our patient did not display signs of miotic pupils or cataracts, but all other features were present. XP was established by skin hypersensitivity to sunlight, and the development of freckling and pigmentary changes. In a case study reported in Pakistan, 4 out of 7 members of a family had similar features characteristic of XP, ocular manifestations being more prominent, and were also diagnosed using clinical findings only since diagnostic tests were not available in our setting. The patient was reevaluated for de Sanctis-Cacchione syndrome (dSCS), which had been in the differential diagnosis. However, majority of the characteristics (general appearance, normal genitalia, type of neurological dysfunction) were typical of CS rather than dSCS. The absence of the characteristic facial rash also excluded RTS as the diagnosis. The hallmark radiological findings in XP-CS patients include intracranial calcifications, brain atrophy and tigroid demyelination; two of these are present in the index case. Calcifications are often not present in young children, and develop later on. A review of 43 cases of XP-CS showed that hearing loss was present in 86% of 21 patients, whereas short stature was present in 33 out of 34 patients. Low weight was also very common, just as is seen in our case. Delayed development is also a hallmark feature in XP-CS patients. The patients severely affected did not progress beyond the level of an infant while those mildly affected were able to walk and attend school. Although XP harbours skin malignancies, they are not commonly seen in XP-CS. However, two cases highlight XP-CS patients who developed skin malignancies very early in life indicating that our patient may also be at an increased risk and hence, exposure to UV light should be minimized. Most XP-CS patients die early in childhood, with the severely affected dying younger than the mildly affected ones. Literature highlighted the occurrence of XP-CS in three brothers in Pakistan, showing that it may cluster in families and the diagnosis here was also established using clinical background only. The treatment of XP-CS is mainly symptomatic and supportive. Avoidance of UV light, the use of sunscreens/protective eyewear, eye ointments, hearing aids, special education for delayed development and physical therapy to prevent restriction of movement is beneficial. All of this was advised to our patient. MRI should be repeated at intervals, and regular follow ups are necessary to monitor complications like malignancies, liver disease, kidney disease and hypertension. However, our patient failed to show up for a follow up visit.

**Conclusion**

XP-CS is a progressive genetic disorder that manifests with symptoms similar to XP and CS. This report shows that in the absence of availability of molecular studies because of low socioeconomic standing or a lack of resources in underdeveloped countries like Pakistan, MRI and clinical symptoms combined maybe used to establish a diagnosis of XP-CS. This report also emphasizes on a pressing need for more clinical trials to be done on such patients to better understand treatment modalities and disease process.

**Consent:** Informed consent was obtained from the parents of the patient to reproduce her case in this report.

**Conflict of Interests:** The authors declare that they have no conflict of interests.

**Disclaimer:** The manuscript has not been published previously and is not under consideration for publication in any other journal.

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