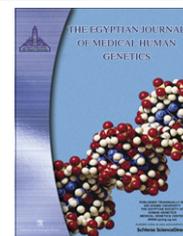




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CASE REPORT

Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) in an Egyptian child with premature loss of teeth, and café au lait skin patches

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Abstract A female, 26 months old with features supporting the diagnosis of neonatal progeroid syndrome was presented. She had prenatal and postnatal growth failure, generalized lipoatrophy except for fat pads in the suprabuttock areas, triangular face, pseudohydrocephalous, sparse scalp hair and eyebrows, prominent scalp veins, greatly widened anterior fontanels, and moderate mental retardation. The patient had also some features not reported previously as premature loss of milk teeth, large mouth, atrophic gums, protruded lower jaw, and café au lait skin patches on lower limbs. Nail dystrophy was also detected. She had local depression of the left parietal bone on CT brain, white matter demyelination in MRI brain, and high level of cholesterol.

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1. Introduction

The neonatal progeroid syndrome (NPS), or Wiedemann-Rautenstrauch syndrome (WRS) is a very rare genetic

disorder. It represents complex symptoms with an unknown cause and pathogenesis [1]. It characterizes a premature aging syndrome in which several features of aging are apparent at birth, therefore allowing their grouping as a neonatal progeroid condition [2].

In 1977 Rautenstrauch and Snigula reported on two sisters with a progeria like syndrome [3]. In 1979 Wiedemann described two unrelated males with the same condition [4]. In 1981 Devos et al. [5] described another affected child whose parents were double first cousins, and in 1988 Rudin et al. [6] reported on a single affected child. After that more patients were described [7]. Martin et al. [8] described neuropathological studies and suggested that WRS is a form of sudanophilic leucodystrophy. Longevity of these patients is unknown. Here we report an Egyptian child with WRS who is still surviving at 26 months.

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2. Case report

A 26 month old female child, first in order of birth of consanguineous parents, pregnancy was uncomplicated with no oligohydramnios or drug intake by the mother. Maternal and paternal ages were 23 and 32 years, respectively. Her weight at birth was 1.5 kg, and she was full term.

The patient was referred to the Genetics Clinics, Pediatric Hospital, Ain Shams University complaining of large head since birth with no history of convulsions, and no family history of similarly affected family member.

The patient had moderate mental retardation and delayed motor and mental development as she could not walk or grasp and transfer objects from hand to hand. Her weight was 8.5 kg (< 3rd percentile), her length was 77 cm (< 3rd percentile). The skull circumference was 46.5 cm, (at 25th percentile).

The patient had craniofacial disproportion which gives a pseudohydrocephalic appearance with wide anterior fontanel and dry sparse scalp hair. There was prominent large forehead with longitudinal depression on the left parietal bone and visible dilated veins. The face was triangular, ears were low set with small ear lobule, eyebrows were sparse with long eyelashes, nasal bridge was depressed, and filtrum was long. The mouth was large with protruded tongue, atrophic gums, and remnants of decayed upper central incisors (premature falling of teeth 3 months after their appearance). There was also protruding lower jaw. The patient's voice was very low and weak. There was slight hirsutism on the lateral sides of the face (Figs. 1, 2 and 3). The neck was short. Both hands and feet were relatively large with long fingers and toes, with no loss of subcutaneous fat over them. There was clinodactyly of little fingers and medial deviation of 4th and 5th toes. The nails were dystrophic in both feet especially over big toes, with apparent veins over lower limbs. One café au lait patch oval in shape, 3 cm in its longitudinal diameter was also present over the lateral aspect of right leg with less defined patches over both legs and toes (Fig. 4).

There was a generalized lipoatrophy except for fat pads in the suprabuttock areas (Fig. 5). The skin was very thin, shiny and dry.



Figure 1 Demonstrates facial features with large mouth and tongue.



Figure 2 Demonstrates scanty scalp hair, low set ears, and relative prognathism.



Figure 3 Demonstrates atrophic gums.



Figure 4 Demonstrates one café au lait patch over the lateral aspect of right leg, other less well defined patches over right leg and toes, and dystrophic nails.



Figure 5 Demonstrates 2 pads of fat on suprabuttock regions.



Figure 6 Demonstrates generalized bulge with apparent lobulations on the anterior abdominal wall.

Chest and cardiac examinations were free. By inspection of the abdomen, there was a generalized bulge with apparent lobulations on the anterior abdominal wall (mostly distended loops of intestine). Umbilicus was shifted downward and flat (Fig. 6). Neurological examination was free. Echocardiography and abdominal ultrasonography were free. Cholesterol level was high with normal triglycerides. Complete blood picture was normal apart from low hemoglobin level (7.7 g/dl). Serum Ca, P, and alkaline phosphatase were normal. T4 and TSH were also normal.

Non contrast CT brain demonstrated focal depression of the left parietal bone. MRI brain was done at the age of 6 months with no abnormality detected. It was repeated at the age of 2 years where it demonstrated patchy areas of high T2 and FLAIR signals affecting both deep periventricular white matter regions, indicating white matter hypomyelination. Karyotype was normal.

3. Discussion

We report a 26 month old child with features of premature aging in favor of the diagnosis of WRS. These features

included intrauterine and postnatal growth failure, old looking face, mental retardation, pseudohydrocephalous, craniofacial disproportion, large anterior fontanel, prominent scalp veins, sparse scalp hair and eye brows, sunken eyes, low set ears, and reduced subcutaneous fat except in the suprabuttock regions, relatively large hands and feet with long fingers and toes. The same features were reported previously [4–10]. In our patient the abdomen appeared large and prominent as was reported once before [11].

However some characteristic features reported in patients with WRS are missing in our patient like the presence of neonatal teeth which is considered very helpful in diagnosis [3–5]. However neonatal teeth were not reported in a Turkish patient and in 19 published cases they were not described in 6 of them (31.6%) [1]. In our patient teething was delayed up to one year and teeth were lost one after the other after 3 months of their eruption due to decaying. To our knowledge this finding was not reported before although Hou [12] reported an abnormal dentition.

Receding jaw and microstomia usually reported in patients with WRS [13,14] were not reported in our patient. Instead our patient had small maxilla and protrusion of lower jaw most probably this prognathism is relative.

Ocular manifestations include, cloudy cornea with congenital glaucoma, other dermatological manifestations like dermatitis/acrodermatitis enteropathica reported in some patients [15] were not reported in our patient. However a large well defined café au lait and other less defined café au lait patches were also reported in legs of our patient.

Feeding difficulties reported in many patients with WRS [7] were not reported in our patient where in spite of high caloric nutrition, the increase in weight was not satisfactory and she was underweight and anemic.

Skeletal findings reported in some WRS patients including scoliosis characteristics of a neuromuscular curve [16], osteoporosis with loose joints, camptodactyly/joint contracture [12], and congenital hip dysplasia [17] were not reported in our patient. However our patient should be followed up regularly as these findings may represent progression.

In our patient cholesterol level was high with normal triglycerides. In two patients reported previously the triglyceride levels were high [6,18]. Other endocrine and lipid abnormalities including hypothyroidism due to a partial organification disorder [15] or persistent hyperthyrotropinemia, growth hormone deficiency, very low insulin-like growth factor I levels with delayed bone age reported in some patients [12] were not reported in our patient.

CT of the brain demonstrated focal bony depression of the left parietal bone which was not reported previously. MRI of the brain demonstrated white matter hypomyelination at the age of 2 years which was not detected at the age of 6 months. Sudanophilic leucodystrophy was reported previously in patients with WRS by Devos et al. [5]. However findings like Dandy walker malformation and ventriculomegaly, basal ganglia calcification reported in some patients [12], and agenesis of corpus callosum reported in other patients [17] were not reported in our patient.

Patients with WRS usually have short life expectation [16]. The disease is usually lethal by 7 months. Our patient is 26 months and is still living. Also Hoppen et al. [9] reported two siblings with the syndrome at age 5 and 12 years and on rare occasions patients had survived into teens and 20s [19].

Our patient was the product of consanguineous marriage which supports an autosomal recessive inheritance. The same was also reported by Arboleda et al. [2] as the syndrome was reported in sibs from unaffected parents and without consanguinity. This also supports the possibility of homozygosity mapping as a good approach to find the causative gene [9,20].

The etiology of WRS remains unknown. Several studies analyzing telomere length and lamin A gene had not revealed any alterations. However, mutations in LMNA had been reported in several other atypical progeroid syndromes. Based on these observations, several hypotheses could be withdrawn concerning the etiology of WRS. The study of genes associated with lamin A metabolism, such as Zmpste24, and the metabolic pathways associated with insulin, such as protein kinase B or AKT, are of particular interest. WRS characteristics were believed to indicate that the discovery of the gene and the metabolic pathway associated with this syndrome will most likely lead to new knowledge about the physiopathology of human aging [2]. However mutations in Lamin A/C (LMNA) gene were not found in four WRS patients, and in particular, G608G mutation (GGC > GGT transition) which is associated with most cases of Hutchinson–Gilford progeria (OMIM 176670). These findings suggest that WRS represents a distinct progeroid entity that may be caused by recessive mutations of a different gene [21].

Increased chromosomal breakage and the presence of basal ganglia calcification after early childhood suggest that DNA repair defects are involved in the pathogenesis of this disorder. LMNA, ERCC8, or ZMPSTE24 gene mutations could not account for the disorders in these patients. Thus this rare disorder represents a complex of symptoms with unknown cause and pathogenesis, and more than one disease may account for the clinical variability of WRS [12].

Terminal restriction fragment (TRF) length to evaluate whether the patient's premature aging process is accompanied by shortening of telomere length in her cultured fibroblasts was studied. Mean TRF of 13.5 kb found in the patient's fibroblasts was not shortened as compared to that of normal fibroblasts. These results differ from those observed in Hutchinson–Gilford progeria [22]. Jäger et al. [23] reported that lack of cellular differentiation capacity in WRS patients may be responsible for the clinical appearance and symptoms of this rare disorder. Karyotype was normal in patients with WRS [12] as was found in our patient.

Ultrasound examination can be a useful tool in prenatal diagnosis of this rare syndrome.

During pregnancy growth retardation particularly in the biparietal diameter and abdominal diameters but not in the femoral length can be detected through serial ultrasound scans [13].

To conclude WRS represents a complex of symptoms and signs with an unknown cause and pathogenesis. Variability in the phenotype of WRS is clear, however the phenotype remains distinct enough to allow a secure diagnosis [14]. This case is a contribution to the exact description of that extremely rare syndrome. We hope to facilitate establishing the major and minor criteria to help the differential diagnosis in difficult cases because of heterogeneity. We have to discuss if the WRS really represents a separate genetic entity within the group of premature aging syndromes. Long term follow up of patients with WRS should provide information relative to their ultimate psychomotor development.

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