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A neurocutaneous phenotype with paired hypo- and hyperpigmented macules, microcephaly and stunted growth as prominent features

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ABSTRACT

Neurocutaneous disorders represent a heterogeneous group of conditions affecting the skin (with pigmentary/vascular abnormalities, hamartomas or tumors) and the central and peripheral nervous systems. In recent years, besides the well-known neurocutaneous diseases (e.g., the different forms of neurofibromatosis, tuberous sclerosis complex, Sturge-Weber syndrome and mosaic pigmentary/hamartomatous disorders), new distinctive syndromes have been characterized, extending our knowledge on the spectrum of these conditions. The concurrent presence of pigmentary abnormalities (both of the hypo- and hyperpigmented type), and primary microcephaly has not been commonly reported.

We report on a 4.5-year-old girl with primary microcephaly, who had in addition moderate to severe developmental delay, behavioral and stereotypic abnormalities and a cutaneous pattern of paired hypo- and hyperpigmented lesions variously distributed over the body, particularly on the trunk. Failure to thrive and mild facial dysmorphic features were also present. To our knowledge, this complex malformation (neurocutaneous) phenotype has not been previously reported.

1. Introduction

Neurocutaneous disorders are hallmarked by the (non casual) concurrent involvement of *skin* [e.g., congenital pigmentary, hamartomatous or vascular anomalies] and *nervous system* [e.g., intellectual delay, behavioral disturbances, epileptic seizures, and brain malformations] (Ruggieri and Praticò, 2015). The different forms of neurofibromatosis, tuberous sclerosis complex, Sturge–Weber syndrome and mosaic pigmentary/hamartomatous disorders represent the most frequent and well-characterised neurocutaneous diseases; however, recently, new phenotypes have been characterised and included in the spectrum of this group of conditions (Ruggieri and Praticò, 2015; Happle, 2014).

The association between cutaneous lesions and microcephaly has not been commonly reported. Cutaneous pigmentary disorders are classified as hypo- or hyperpigmented and include a large number of heterogeneous conditions, which can occur as genetic or acquired disorders (Ruggieri and Praticò, 2015; Happle, 2014).

Microcephaly is defined as a head circumference of two standard deviations (SDs), approximately the 3rd percentile, below the mean for age and sex. Microcephaly (small head) and microencephaly (small brain) are terms used interchangeably since head circumference grows under the forces (i.e., the molecular information) of the brain, and therefore a diminished skull content usually leads to a small head (Alcantara and O'Driscoll, 2014).

We report on a 4.5-year-old girl with a cutaneous pattern of hypo- and hyperpigmented areas variously distributed over the body, particularly on the trunk, and primary microcephaly with moderate to severe developmental delay and behavioral and stereotypic anomalies. Along with microcephaly and cutaneous anomalies, the girl presented with failure to thrive and mild facial dysmorphic features. To our knowledge, as a whole, this complex malformation (neurocutaneous) phenotype has not been previously reported.

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2. Case report

A girl was first referred to the clinical unit at the age of nine months for a diagnostic work-up regarding her psychomotor delay and stunted growth. She was the second child of healthy, unrelated Italian parents. At the time of gestation the mother was 28 years old and the father was 31 years old. The girl's older sister was diagnosed with retinoblastoma at the age of 8 months and died at the age of 12 months. The youngest brother was healthy and presented a skin appendix on his left little finger. In the paternal family two cousins were affected by Down syndrome and bifid spine, respectively. In the maternal line, three cousins presented moderate cognitive delay.

During the proband pregnancy, the mother denied having infectious diseases or drug or alcohol consume and claimed to have felt normal fetal movements. The girl was born at 37 weeks of gestation. She had a birth weight of 2210 g, a birth length of 45 cm and a head circumference of 32 cm (all below the 3rd percentile). As reported by the parents, her motor development was within the normal range during the first six months, but she showed failure to thrive, slow growth in head circumference, precocious closure of the skull sutures and she had multiple hypo- and hyperpigmented spots mainly in the trunk. She started to walk at the age of 18 months; lallation was attained at the age of 14 months. When she was first admitted to hospital, at the age of 9 months, her weight was 5.9 kg, height was 62.5 cm, and her head circumference was 38.5 cm (all below the 3rd percentile). Routine laboratory investigations were normal, including IGF-1 level, tests for hypothyroidism, LDH, sialotransferrin, VLCFA, plasmalogens and 7-dehydrocholesterol, as well as thoracic and pelvic X-rays, and full ophthalmologic evaluations. A kidney ultrasound showed a cyst (filled with fluid) 1.2 cm in diameter.

Physical examination, at the age of 3 years, showed the girl to be in fairly good general conditions. The girl's weight was 9 kg and her height was 82 cm (<3rd percentile) with a head circumference of 43.5 cm (remarkably below the 3rd percentile). Her face was little in size, with telecanthus, epicanthal folds, rounded nasal tip, thin lips, medially sparse eyebrows and a triangular chin [Fig. 1]. A cutaneous dimple was present in the elbows bilaterally. We could count twenty-two hypopigmented macules (0.3–1 cm in diameter), oval-shaped, some with regular and irregular margins, mostly localized on her back and to a minor degree on her chest arranged in a somewhat phylloid pattern [Fig. 2]; hypopigmented macules were also present on the thighs (sized 5 × 0.5 cm). Hyperpigmented macules (café-au-lait macules) were prevalently localized on the lower abdomen in a block-like pattern at the level of right hypochondriac region [Fig. 3]. Three of the hyperpigmented macules showed a polygonal aspect, were 4 × 3 cm in size and presented sharp edges, and two of them slightly crossed the midline. In the same area, interplaced with the largest macules, were some small hyperpigmented spots (0.1 × 0.3 cm). Isolated hyperpigmented patches were also observed: three small patches (0.5 cm)

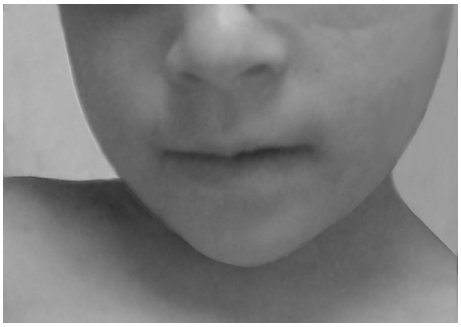

Fig. 1. Photograph of the patient, at the age of 3 years, showing thin lips and a triangular chin.

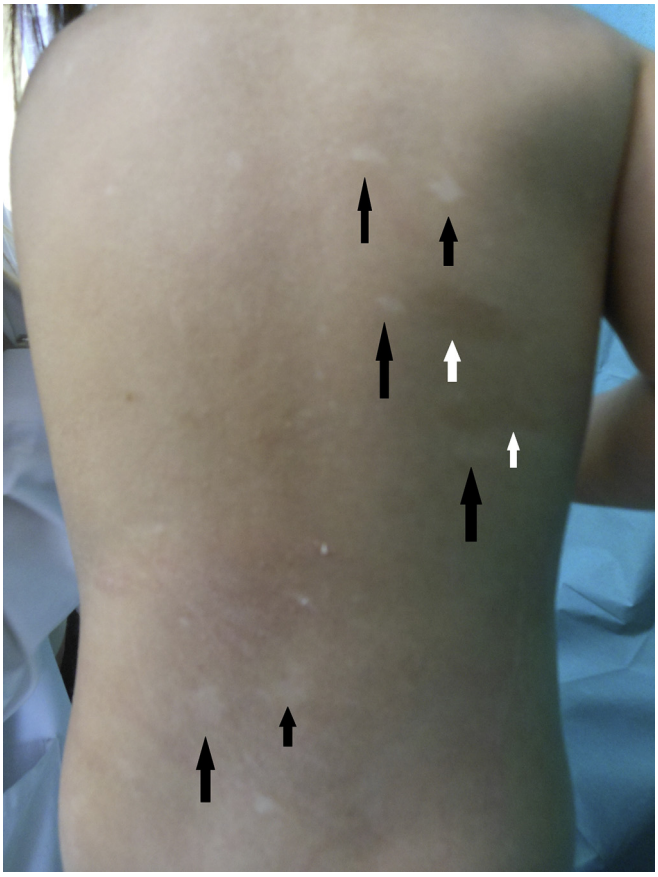

Fig. 2. The patient at 4 years of age. Hypopigmented macules (0.3–1 cm in size, black arrows), which were oval shaped with regular and irregular edges, together with larger hyperpigmented macules (white arrows), can be observed on the back.

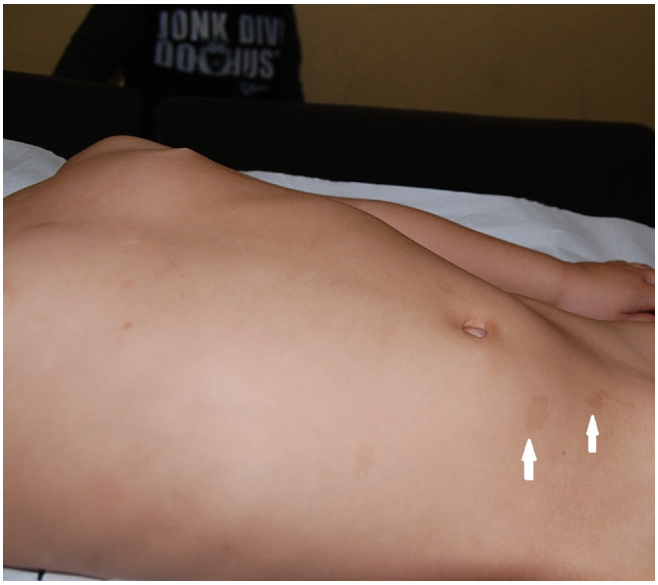

Fig. 3. The patient at 4 years of age. The lower part of the abdomen shows hyperpigmented macules in a block-like pattern at the level of right hypochondriac region in a segmental pattern (see white arrows).