CASE REPORT

Multiple Lentigines Syndrome Complex (LEOPARD Syndrome) with Chiari I Malformation

EYL Kan, IYC Wong, SPC Lau, WC Lee

1Department of Radiology, Kwong Wah Hospital, 2Department of Diagnostic Radiology, and 3Department of Paediatric and Adolescent Medicine, Tuen Mun Hospital, Hong Kong

ABSTRACT

This report is of a patient with multiple lentigines syndrome complex (LEOPARD syndrome), a complex dysmorphogenetic disorder, with Chiari I malformation and hydrocephalus. In this patient, the cerebellar tonsillar descent was mild but craniovertebral dysplasia manifesting as shortened clivus, platybasia, and small posterior fossa was evident. This patient provides evidence for the possible existence of craniovertebral abnormality in this rare disease entity.

Key Words: Arnold-Chiari malformation; Hydrocephalus; LEOPARD syndrome; Platybasia

INTRODUCTION

Multiple lentigines syndrome complex, or LEOPARD syndrome, is a cardiocutaneous syndrome that is hypothesised to be of neural crest origin. Gorlin et al introduced the acronym ‘LEOPARD’ in 1969 to recall the main features of the disorder, which include multiple lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth, and deafness. Since 1969, numerous reports of this syndrome have been published in the literature, but there has been only one report describing the association of LEOPARD syndrome with Chiari I malformation. This report is of a patient with LEOPARD syndrome, with the diagnosis supported by genetic studies showing features of Chiari I malformation. The cerebellar tonsillar descent was mild, but craniovertebral dysplasia manifesting as shortened clivus, platybasia, and small posterior fossa was evident. The findings concur with the current notion that the basic structural abnormality of Chiari I malformation is a developmentally small posterior fossa. This patient provides evidence for the possible existence of craniovertebral abnormality in this rare disease entity and might provide insight into the underlying pathogenesis of this poorly understood genetic disease.

CASE REPORT

An 8-year-old Chinese girl was referred to the paediatric clinic following the discovery of multiple café-au-lait patches by her family physician. She was born at full term after an uncomplicated pregnancy. She had macrocephaly since birth, but was otherwise healthy. Her paternal grandmother also had multiple café-au-lait patches.

At examination, her developmental age was appropriate. She was of an average stature and showed no dysmorphic features. Her head circumference was above the 97th percentile. Five café-au-lait patches were noted over her trunk and lower limbs. Cardiovascular, respiratory, and neurological examinations revealed no abnormalities. An electrocardiogram showed left axis deviation, whilst the echocardiography was normal. Her hearing test was normal. Subsequent genetic study detected mutation at the PTPN11 gene and confirmed the diagnosis of LEOPARD syndrome.

Magnetic resonance imaging (MRI) showed mild hydrocephalus. The cerebellar tonsil was triangular in shape and low lying, located 2 mm below the foramen magnum. There was flattening of the clivus with an
LEOPARD Syndrome with Chiari I Malformation

increased basal angle (140°), mild dorsal angulation of the odontoid, crowding at the foramen magnum, and an increased angulation at the cervicomedullary junction (Figure 1). Quantitative measurements of the posterior fossa were obtained from the midline sagittal T1W image using methods similar to those employed in previous studies (Figure 2).3,4 The length of the basisphenoid, measured from the top of the dorsum sellae to the sphenoccipital synchondrosis, was 14.2 mm. The length of the basiocciput, measured from the synchondrosis to the basion, was 20.5 mm. The length of the clivus, equivalent to the total lengths of basisphenoid and basiocciput, was 34.7 mm. The tentorial angle, the angle between the Twining’s line and the tentorium cerebelli, was 63.6°.

Due to a lack of age-matched reference values of these measurements, a control group of 20 Chinese patients aged 7 to 10 years was selected from MRI studies performed during the previous months. Only images with normal findings were included. The MRI images were studied and the lengths of the basisphenoid, the basiocciput, and the clivus, and the tentorial angle were measured; the mean values were 16.1 mm (SD, 1.6 mm), 27.1 mm (SD, 3.0 mm), 42.8 mm (SD, 3.4 mm), and 42.1° (SD, 5.0°), respectively. The results illustrated that the length of the clivus in this patient was more than 2 standard deviations below the mean, while the tentorial angle was more than 2 standard deviations above the mean, confirming the small size of the posterior fossa. This patient has been referred for neurosurgical assessment.

DISCUSSION

The marked variability in expression of LEOPARD syndrome, in which members of a family can be discordant for many of the features, often leads to difficulty in establishing the diagnosis. The exact aetiology-pathogenesis of the syndrome is unknown, but a mutation in the stem-cell pool of the neural crest in embryonic life has been proposed as a cause of cutaneous and neurological defects. In recent years, the underlying genetic defect associated with the development of this syndrome has been located on chromosome 12 and the responsible gene, PTPN11, was found to be mutated in 88% of patients with the condition.5

Although the problem that most frequently requires medical attention in patients with LEOPARD syndrome relates to cardiac involvement, neurological abnormalities are not infrequent and can be debilitating. Mental retardation occurs in approximately 30% of patients and there are electroencephalograph abnormalities in approximately 15%.6,7 There may also be mild brain atrophy, partial agenesis of corpus callosum, basilar impression, and platybasia.5,8,9,10 The association with Chiari I malformation was first reported in 1995.2
Inferior tonsillar ectopia of more than 5 mm has been the main diagnostic criteria for Chiari I malformation, and cerebellar tonsils that are situated at ‘borderline’ positions (3 to 5 mm below the foramen magnum) may be regarded as pathological if accompanied by other elements of the malformation, such as syringohydromyelia and/or cervico-medullary kinking. However, researchers have demonstrated that these criteria can produce false-negative predictions. Other factors such as crowding of the neural structures within the posterior cranial fossa, their impaction at the foramen magnum, and the configuration of the tonsillar tips have been suggested to better define the severity of Chiari I malformation. Recent morphometric studies have established that in Chiari I malformation, the basic structural abnormality is a small posterior fossa. In addition, the clivus is hypoplastic and the overcrowding in the posterior cranial fossa induces a consistent upward shift of its contents, leading to a significantly steeper tentorium. When compared with the control group, it was found that this patient not only had platybasia and a short clivus, but also an increased tentorial angle. As a result of the low lying cerebellar tonsil at the foramen magnum and the narrowing of the anterior subarachnoid space below the foramen magnum secondary to a retroflexed odontoid process, the cerebral spinal fluid pathway was hindered, leading to mild hydrocephalus.

The fundamental pathogenic entity in Chiari I malformation is believed to be due to the underdevelopment of the occipital somites of the para-axial mesoderm, resulting in a hypoplastic posterior fossa. In LEOPARD syndrome, a mutation in the stem-cell pool of the neural crest has been proposed as a cause of the cutaneous and neurologic defects; research on avian embryos provided evidence that mesoderm and neural crest cells from a given metameric level cooperate in myogenesis and vasogenesis. By affecting the neural crest development, the genetic predisposition in LEOPARD syndrome might also alter the development of mesoderm, resulting in skeletal dysplasia. The reason for occipital and upper cervical predilection is unclear, but the fact that Chiari I malformation is involved in a large number of genetic conditions may suggest that there is intrinsic weakness in the development of these metameres.

In patients presenting with multiple café-au-lait spots, the most commonly associated systemic conditions are neurofibromatosis I and polyostotic fibrous dysplasia. This patient serves as a reminder to the neuroradiologist that this additional association merits special attention. As well as searching for brain atrophy and corpus callosal agenesis, attention should be paid to structures in the posterior cranial fossae, with consideration of the possible association of Chiari I malformation.

REFERENCES