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Case Report

Café Au Lait Spots: What is the Diagnosis If It Is Not Neurofibromatosis Type I ?

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Abstract Multiple café au lait spots is a common referral indication for assessment of possible syndromal disorder. Neurofibromatosis type 1 (NF-1) is a common disease in paediatric population, which characterised by café au lait spots, intertriginous freckling, neurofibroma, lisch nodules and/or osseous lesions. Plexiform neurofibroma, optic nerve and other central nervous system gliomas are occasionally seen. Legius syndrome is a relatively new disorder that being described in the literature since 2007, which present with NF-1 like features, including café au lait spot, freckles, macrocephaly and learning disability. However, it is not associated with benign or malignant tumours. Therefore, the differentiation between these two entities are important that not only for diagnosis, but also for prognosis counselling and follow up surveillance. Here, we report a child who initially referred for suspected NF-1, who is subsequently diagnosed to have Legius syndrome. Also, we have summarised and compared the clinical features of NF-1 and Legius syndrome, their difference in counselling and surveillance are also being discussed.

Key words Legius syndrome; NF1-like; *SPRED1* gene

Introduction

Neurofibromatosis type 1 (NF-1) is one of the most common neurocutaneous syndrome in paediatric population that presented with multiple café au lait spot. Legius syndrome is a recently reported disease entity that manifested with NF-1 like features. The two diseases may be indistinguishable in early childhood. Here, we reported a 15 years old boy presented with NF-1 features, who was subsequently diagnosed to have Legius syndrome by *SPRED1* gene testing. This is the first reported Chinese case in the literature.

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Case Report

A 15-year-old boy was referred to clinical genetic clinic in July 2016 for suspected NF-1, due to multiple café au lait spots and axillary freckles. He was the first child from a non-consanguineous Chinese couple, born at full term with birth weight of 3.8 kg. Antenatal follow up revealed mild dilated renal pelvis, which was eventually normalised in the postnatal renal ultrasound. Otherwise, he enjoyed good health and normal development. There was no skeletal dysplasia and ophthalmological assessment was normal. He had no neurological symptoms all along. Family history was unremarkable. Physical examination showed mild macrocephaly (head circumference 59 cm, 0.5 cm >97th percentile), multiple café au lait spots more than 6 patches with size more than 1.5 cm. The maximal size was around 8 cm at the longest diameter (Figure 1). There were also axillary and groin freckles but no neurofibroma nor plexiform neurofibroma. There was also no scoliosis or skeletal dysplasia. Examinations of other systems were normal. Based on the clinical diagnosis of NF-1, genetic testing included Multiplex ligation-dependent probe

amplification (SALSA P081-B1/P082-B1 kit) and sequencing of *NF1* gene (reference sequence NM_000267.3) were performed, but no pathogenic variant or copy number change in coding region of *NF1* gene was detected. Since there was no other stigmata of neurofibromatosis type 1 apart from café au lait spots and freckles at his adolescent period, Legius syndrome was suspected. Sequencing of *SPRED1* gene was performed that showed a heterozygous 4 base pair deletion c.1149_1152delAGAG pathogenic variant in exon 7 of *SPRED1* gene. This is a reported mutation in the literature[1] and the diagnosis of Legius syndrome was substantiated. Parental testing showed it is a denovo change.

Discussion

Multiple café au lait spot is a common indication of referral for genetic assessment and counselling. Among the list of differential diagnoses (Table 1A), neurofibromatosis type 1 is one of the most common and well-known cause of café au lait macules. Neurofibromatosis type 1 (OMIM #162200) is an autosomal dominant genetic disorder with incidence of 1 in 3000 live births. The main features include café au lait spot, intertriginous freckling, neurofibroma, lisch nodules and osseous lesions. Learning disability presents in 50% of cases. More serious but less frequent features included plexiform neurofibroma, optic nerve and

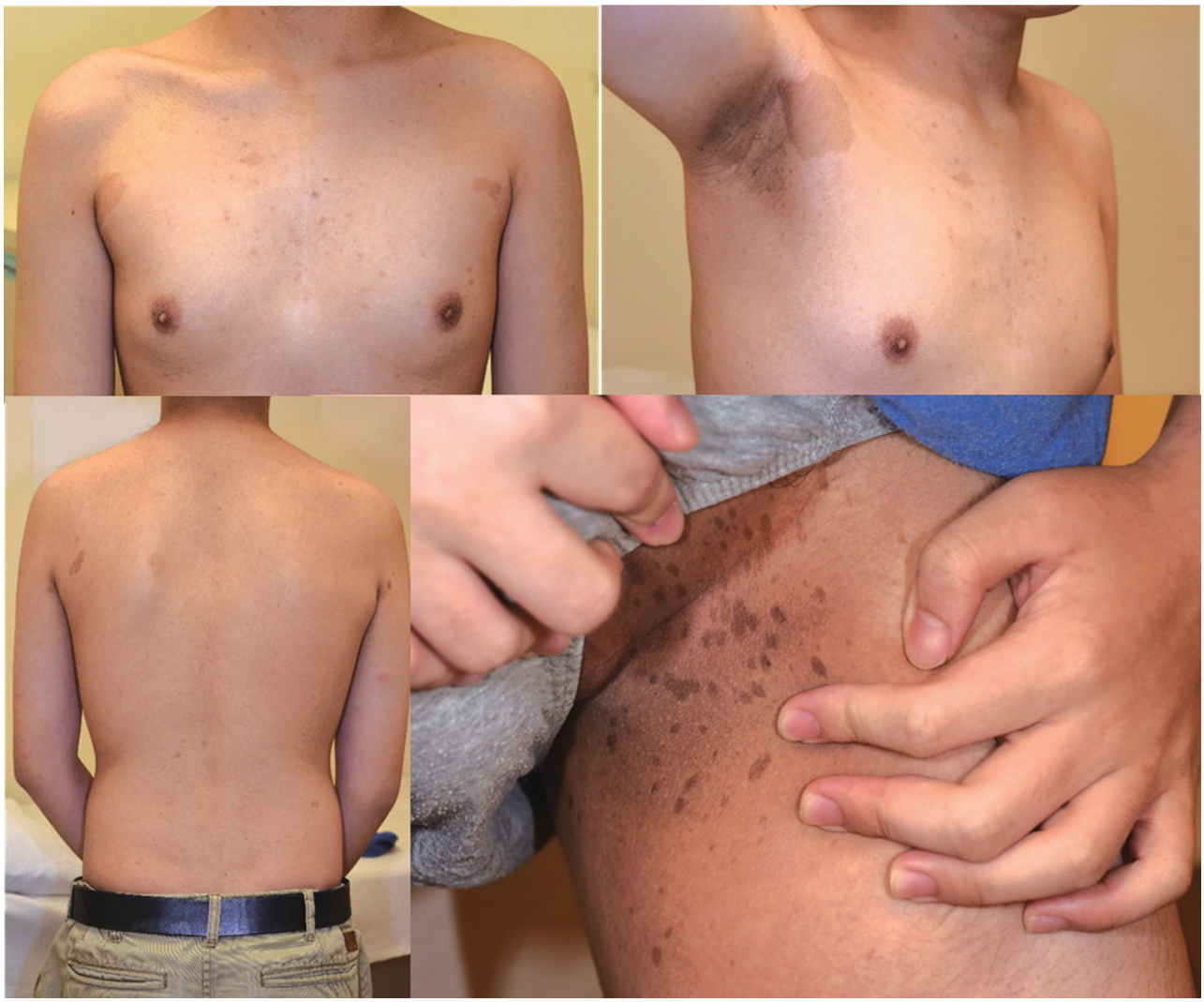

Figure 1 This showed multiple café au lait spots, pigmentary macules and Intertriginous freckling in our patient. There is no neurofibroma, plexiform neuroma or skeletal deformity.

other central nervous system gliomas.[2] Legius syndrome (OMIM #611431) is an autosomal dominant disorder that have many overlapping features with NF-1 particularly cutaneous changes like café au lait spots, with or without intertriginous freckling, intellectual disability and macrocephaly. But there are no non-cutaneous features like neurofibroma, plexiform neurofibroma, optic gliomas, sphenoid wing dysplasia.[3] Also, Legius syndrome is not associated with increased risk of malignancies (Table 1B). Therefore, distinction of the two entities is important in clinical management and counselling of disease prognosis.

Legius syndrome is caused by heterozygous germline pathogenic variant in *SPRED1* gene. *SPRED1* gene is located on chromosome 15q13.2 that encodes a protein spred1 which negatively regulates Ras-MAPK signaling. Mutation in *SPRED1* gene would result in dysregulation of Raf1 kinase activation and downstream Raf-MEK-ERK signaling.[3] As NF-1 is caused by mutation in *NF1* gene that is a key component of same pathway, therefore it would explain the overlapping clinical features between two disease entities.

Studies showed that about 1-4% of individuals with multiple café au lait spots and clinical NF-1 like features have *SPRED1* mutation. Different prevalence in publications is due to the difference in clinical practice like age of testing and availability of genetic testing.

Table 1 Differential diagnoses of multiple café au lait spots and the comparison of clinical features between Neurofibromatosis type 1 and Legius syndrome

(A) Differential diagnoses of multiple café au lait spots

Neurofibromatosis type 1
Legius syndrome
Noonan syndrome
Autosomal dominant café au lait spots
LEOPARD syndrome
McCune Albright syndrome
Hereditary non polyposis colon cancer
Bloom syndrome
Fanconi anaemia
Russell-Silver syndrome
Bannayan Riley Ruvalcaba syndrome
Costello syndrome
Cardiofaciocutaneous syndrome
Tuberous sclerosis complex

(B) Comparison of clinical features between Neurofibromatosis type 1 and Legius syndrome

	NF-1	**Legius syndrome**
Multiple café au lait spots	+	+
Intertriginous freckling	+	+
Neurofibromas	+	-
Plexiform neurofibroma	+	-
Optic gliomas	+	-
Lisch nodules	+	-
Macrocephaly	+	+
Learning disability	+	+ (milder)
Malignant peripheral nerve sheath tumour	+	-
CNS tumour	+	-
Leukaemia	Higher risk than general population	No evidence of increased risk

Distinguishing the two disease entities clinically in early childhood is difficult. But more specific characteristics of NF-1 may evolve when the child grow up. Until now, there is no consensus in the indications for *SPRED1* gene testing. But in the literature, there was a study to demonstrate it is cost effective in testing *NF-1* negative patients after puberty.[4,5] They recommended that *SPRED1* gene test should be considered in NF-1 like individual but without characteristic features of NF-1 at age between 10 and 14 years old.

In summary, we have reported the first molecularly confirmed Legius syndrome in Chinese. In patient with multiple café au lait spots, although NF-1 is the most common cause, alternative diagnosis like Legius syndrome should be considered. Differentiating patient with Legius syndrome from NF-1 is important as NF-1 patients require regular surveillance of the extra-cutaneous manifestations like optic pathway glioma and possible neurological tumours, which would not happen in the patient with Legius syndrome. Therefore, the diagnosis of Legius syndrome may not only avoid unnecessary medical intervention, but it would also relieve the psychological burden of patient and families, who are expecting less serious complications of Legius syndrome as compared with NF-1.

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