The Journal of Medical Research

Case Report

JMR 2022; 8(4):129-131
July- August
ISSN:2395-7565

www.medicinearticle.com
Received:21-07-2022
Accepted:10-09-2022

Case Report: Fortuitous discovery of a white matter signal abnormality in the context of Leopard syndrome

Jennifer Nyangui Mapaga[1], Mikel Martinez[2], Philomène Kouna Ndouongo[1]

[1] Neurology department, University Hospital of Libreville, Gabon

[2] Neurology department, Hospital Center of DAX, France

Abstract

Multiple Lentigines syndrome is an autosomal dominant inherited disorder of variable expressivity also known by the acronym LEOPARD syndrome. A rare disease with multiple congenital anomalies, mainly characterized by skin, facial and cardiac anomalies. Other malformations can be encountered, in particular cerebral and dysmorphic. We report the case of a 40-year-old female patient known for a Leopard syndrome, who in the context of bilateral hypoacusis, the cerebral MRI carried out finds a lesion in flair hypersignal at the asymptomatic left occipital level, we do not note any evolution of this lesion after 10 years this could correspond to "unidentified shiny object: OFU". In conclusion, LEOPARD syndrome is a disease with a multi-systemic involvement, the discovery of a lesion corresponding to an OFU" is possible.

Keywords: Leopard Syndrome, Genetics, OFU.

INTRODUCTION

Leopard syndrome (LS) is an autosomal dominant disorder, first described in 1936 by Zeisler and Becker [1]. It was Gorlin *et al* who introduced the acronym LEOPARD as the name of the syndrome in 1969 [2]. The acronym LEOPARD groups together the different anomalies observed: L for *"multiple lentigines"*; E for *"electro-cardiographic conduction abnormalities"*; O for *"ocular hypertelorism"*; P for *"pulmonary stenosis"*; A for *"abnormalities of genitalia"*; R for *"retardation of growth"* and D for *"deafness"* [2]. This mnemonic acronym is however restrictive, since the seven groups of anomalies are rarely combined in the different observations and do not account for many other frequently encountered malformations, in particular cerebral and dysmorphic [3]. Approximately 200 patients have been reported worldwide, but the true incidence of SL has not been evaluated [4,5]. We report the case of a 40-year-old female patient known to have Leopard syndrome, in whom an asymptomatic left occipital flair hypersignal lesion did not evolve after 10 years consistent with OFU.

CASE REPORT

A 40 year old female patient who has had Leopard syndrome diagnosed for over 15 years. The syndrome was discovered during a family screening, the mother is a carrier of Leopard syndrome, the brother and sister are also affected. The patient is active and has no psychomotor developmental delay. She has no children, but her brother has two children, one of whom is affected, and her sister has a daughter who is also affected. Our patient has cardiomyopathy treated with beta-blockers for 9 years. For the past two weeks, she has presented with bilateral hypoacusis for which she was referred to an ENT specialist who found a moderate bilateral hearing loss on audiogram. It is in this context that a brain magnetic resonance imaging (MRI) will find a 6 mm round T2 Flair hypersignal lesion in the left occipital lobe, without contrast after gadolinium injection (Figure 1). There is no diffusion or echogradient sequence abnormality. This lesion is asymptomatic, the neurological examination does not reveal any particular abnormality, the cranial pairs are normal. No hemi- or quadranopsia was noted on examination. At the skin level, lentigines were noted in the entire skin integument and in the conjunctival and labial mucous membranes, which were already known in the context of her disease. Ten years later, the patient remains neurologically asymptomatic, and the lesion has not evolved on several MRI scans. She is currently wearing a hearing aid for the hearing loss and is on beta-blocker for the cardiomyopathy.

***Corresponding author:**
Dr. Jennifer Nyangui Mapaga
Neurology department, University Hospital of Libreville, Gabon
Email: jenica45@yahoo.fr

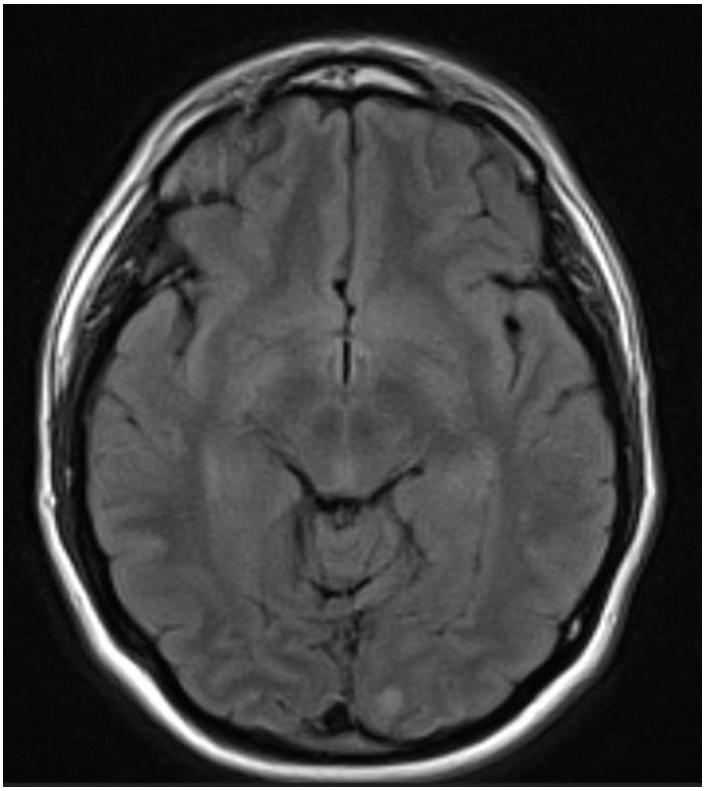

Figure 1: T2 flair hypersignal in the left occipital area

DISCUSSION

LEOPARD syndrome (LS), or multiple lentigines syndrome is an autosomal dominant genetic disorder with high penetrance and variable expressivity [1]. Within the group of so-called "neuro-cardio-facial-cutaneous" (NCFC) syndromes, LS is probably the second most common disorder after Noonan syndrome (NS) [6]. However, LS is probably underdiagnosed or misdiagnosed because many of its features are benign and the correct diagnosis may be missed in the absence of lentiginosis. LEOPARD syndrome can be inherited from an affected parent, as in our observation. It may be due to a new genetic change in a person with no family history of the disease. No epidemiological data are available on gender predominance. There is speculation about a slight preponderance of males [7]. In 1976, Voron *et al* proposed minimal criteria for the diagnosis of LEOPARD syndrome: at least two of the following features must be present: Other skin abnormalities, structural or electrocardiographic cardiac abnormalities, genitourinary abnormalities, endocrine abnormalities, neurological abnormalities, cephalofacial dysmorphia, short stature, skel *et al* abnormalities. If lentigines are absent, a diagnosis of LEOPARD syndrome can be made if the patient has at least 3 features mentioned above and has an immediate relative with the defined diagnosis [8]. Neurological abnormalities such as psychomotor delays, which are usually present in 30% of cases, and nystagmus can be found [9]. Imaging (CT scan or brain MRI) may reveal cerebral atrophy, budd chiari syndrome, syringomyelia, agenesis of the corpus callosum. Arterial abnormalities (extremely elongated and tortuous left vertebral artery and basilar artery) may be present [10]. The so-called "neuro-cardio-facial-cutaneous" syndromes (NCFC), are still called RASopathies by other authors, as these diseases affect the RAS signaling pathway. Brain MRI in these conditions may show acquired and structural abnormalities in the posterior fossa (hemorrhage, vermis hypoplasia) and in addition, may show an increased incidence of cerebral white matter abnormalities, cortical lesions and corpus callosum [10]. In addition, lesions called OFU are described, these lesions are in T2 hypersignal and they affect the myelin. They are frequently reported in Neurofibromatosis type 1 (NF1). OFU affect 48% of children and adolescents in NF1. The exact nature of these lesions remains unclear, histological analysis has shown that OFU result from vacuolization or spongy alteration of the white matter caused by intra myelin edema [11]. Studies report a spatial distribution most commonly found in the gray matter followed by the thalamus and cerebellum, with the brainstem being least involved. Variations in the size and number of OFU during the first decades of life have been described. They are rare in people over 20 years old [12]. Nevertheless, studies show no reduction in OFU during the first decade of life, and even show a tendency for these lesions to increase, especially in the younger years. However, after the first decade, although some lesions remained unchanged, most lesions disappeared or decreased in size [13]. The presence of OFU can be confused with neoplastic lesions and can often multiply the need for further investigations despite the asymptomatic nature of the lesions as in our case. The presence of OFU is often correlated with neuropsychological disorders especially if they are in the basal ganglia and in particular in the vicinity of the thalomo-striate region. It is therefore supposed that the presence of OFU would not be asymptomatic MRI images but would on the contrary be involved in the pathophysiology of the learning disorders observed in NF1 in particular, but this remains debated [14]. Molecular diagnosis of Leopard syndrome can provide more information and is essential for the differential diagnosis. In 95% of cases, it is related to mutations in the protein tyrosine phosphatase non-receptor type 11 (PTPN11) gene and more rarely to mutations in the BRAF and RAF genes. The PTPN11 gene encodes the SHP2 protein, which has phosphatase-like activity on phosphorylated tyrosine residues [8,15-17]. The treatment of SL is preventive: regular cardiological follow-up; reduction of intensive physical exercise; use of betablockers, calcium channel blockers, amiodarone recommended symptomatically in some cases [8,18,19].

CONCLUSION

Leopard syndrome is an autosomal dominant disease that affects multiple organ systems. It may be associated with T2 hypersignal lesions of the asymptomatic white matter called OFU. These lesions can be the cause of a multiplication of complementary examinations, leading to diagnostic errors. They should not be ignored by clinicians.

Conflicts of interest

None declared.

Financial support

None declared.

REFERENCES

1. Zeisler EP, Becker SW. GENERALIZED LENTIGO: ITS RELATION TO SYSTEMIC NONELEVATED NEVI. Arch Dermatol Syphilol. 1936;33(1):109-25.
2. Gorlin RJ, Anderson RC, Moller JH. THE LEOPARD (MULTIPLE LENTIGINES) SYNDROME REVISITED: The Laryngoscope. 1971;81(10):1674-81.
3. Bessis D. LEOPARD syndrome or multiple lentigines syndrome. Images in Dermatology. 2008;(1):16-19.
4. Gorlin RJ, Anderson RC, Blaw M. Multiple lentigos syndrome. Suis J Dis child. 1969;17:652-62.
5. Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigo syndrome. Case report and review of the literature. Suis J Med. 1976;60:447-56.
6. Bentires-Alj M, Kontaridis MI, Neel BG. Arrests along the RAS pathway in human genetic diseases. Nat Med. 2006;12:283-5.
7. D. Bessis. Neuro-cardio-facio-cutaneous syndromes and RASopathies. Images in Dermatology. 2010:122-26.
8. Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome: case report and review of the literature. The American journal of medicine. 1976;60(3):447-56.
9. Porciello R, Divona L, Strano S, Carbone A, Calvieri C, Giustini S, *et al*. Leopard syndrome. Dermatology Online Journal. 2008;14(3):7.
10. Cizmeci MN, Lequin M, Lichtenbelt KD, Chitayat D, Kannu P, James AG, *et al*. Characteristic MR imaging findings of the neonatal brain in RASopathies. American Journal of Neuroradiology. 2018;39(6):1146-52.
11. Szudek J, Friedman JM. Unidentified bright objects associated with features of neurofibromatosis 1. Pediatr Neurol. 2002;27(2):123e7

12. Itoh T, Magnaldi S, White RM, Denckla MB, Hofman K, Naidu S, *et al*. Neurofibromatosis type 1; the evolution of deep gray and white matter MR abnormalities. AJNR Am J Neuroradiol. 1994;15:1513e9.
13. Ferraz-Filho JRL, da Rocha AR, Muniz MP, Souza AS, Goloni-Bertollo EM, PavarinoBertelli EC, *et al*. Unidentified bright objects in neurofibromatosis type 1:Conventional MRI in the follow-up and correlation of microstructural lesions on diffusion tensor images. European journal of paediatric neurology. 2012:42-47.
14. ChabernaudC,Deseille-Turlotte D,Barbier D,Sirinelli D,Cottier JP,Castelnau P Influence of OFU on learning disabilities in NF1. Archives of Pediatrics. 2008;(15): 929-30.
15. Legius E, Schrander-Stumpel C, Schollen E, Pulles-Heintzberger C, Gewillig M, Fryns J, *et al*. PTPN11 mutations in LEOPARD syndrome. J Med Genet. 2002;39:571-4.
16. Digilio MC, Conti E, Sarkozy A, Mingarelli R, Dottorini T, Marino B, *et al*. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. The American Journal of Human Genetics. 2002;71(2):389-94.
17. Al-Olabi L, Polubothu S, Dowsett K, Andrews KA, Stadnik P, Joseph AP, *et al*. Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy. The Journal of clinical investigation. 2018 Apr 2;128(4):1496-508.
18. Sarkozy A, Digilio MC, Dallapiccola B. Leopard's syndrome. Orphanet J Rare Dis. 2008;3(1):13.
19. Tartaglia M, Martinelli S, Stella L, Bocchinfuso G, Flex E, Cordeddu V, *et al*. Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease. The American Journal of Human Genetics. 2006;78(2):279-90.