CLINICAL QUIZ (p51) ANSWER

What is the Diagnosis?

Our patient is diagnosed with Neurofibromatosis type 1 (NF1). He fulfils three of the seven NIH criteria for NF1.

1. He has 18 café au lait spots (CAL) >15 mm in size and some smaller CAL spots of ~1 cm over trunk, buttocks, posterior thigh and extremities. The largest CAL is of 6 cm over the back of the left leg, and another similar one over the front of the left leg.
2. He has mild freckling in the right axillary region and over the inguinal areas.
3. He has more than two neurofibromas.

Regarding the genetic diagnosis, a variant (c.4267A>G, p.(Lys1423Glu)) is identified in the *NF1* gene. He is therefore both clinically and genetically diagnosed to have NF1.

An interesting point to note is that the MRI finding revealed two focal T1W isointense and T2W hyperintense lesions up to 5 mm in size at bilateral basal ganglia. These unidentified bright objects (UBO) were at first a great concern to the clinicians. Upon discovering the UBO on MRI, clinicians were at first worried it could be a malignant or inflammatory lesion in the brain, which they suggested further investigations and frequent monitoring for our patient. Upon the genetic confirmation of NF1, clinicians were less worried about the UBO, as UBOs has well known association with NF1. Hyperintense lesions on T2-weighted MRI images of the brain, predominantly located in the basal ganglia, the brainstem and cerebellum, are frequent findings in patients with NF1. A study analysed MRI scans of 31 children with definite diagnosis of NF1 according to the NIH criteria, high-intensity lesions on T2-weighted images were present in 86% of the patients.[1] These lesions typically appear at around 3 years old, with increasing number and size until 10-12 years old, and then decrease or even disappear at later years. Common locations include basal ganglia, thalami, dentate nucleus of cerebellum and brainstem. Generally, these lesions do not cause neurological symptoms, but they have been correlated with learning disabilities.[2]

The genetic diagnosis helped ease the clinicians' and the family's anxiety as UBO in the context of NF1 has a much better prognosis compared to a UBO in other health context. Thus, the confirmation of NF1 by genetic analysis helped bring great relief to the patient and his family.

What is Neurofibromatosis?

Neurofibromatosis has two recognised types: NF1 (previously known as von Recklinghausen disease on generalised neurofibromatosis) and NF2 (previously known as either central or bilateral acoustic neurofibromatosis).

Neurofibromatosis 1 is an autosomal dominant disease that affects multiple systems, primarily involving the skin and the nervous system. It affects 1 in 3500 individuals and is usually recognised at birth when cutaneous manifestations are apparent.[3] Some features may be age-related thus may not present until later in life. Despite the marked clinical variability of NF1, most children with NF1 do well in their growth and development.

To establish the diagnosis of NF1 according to the National Institute of Health (NIH) Consensus Development Conference, at least 2 features out of the following 7 are required:[4]

1. Six or more cafe-au-lait spots (CLSs) equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients;
2. Two or more neurofibromas of any type or 1 plexiform neurofibroma;
3. Freckling in the axillary or inguinal regions;
4. Optic glioma (optic pathway glioma);
5. Two or more Lisch nodules (iris hamartomas);

6. A distinctive osseous lesion, such as sphenoid wing dysplasia or cortical thinning of the cortex of long bones, with or without pseudoarthrosis; and
7. A first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria.

Café-au-lait spots are usually the initial clinical manifestations of NF1, and tend to increase in number and size during early childhood. Skin folds freckling and dermal neurofibromas, which may grow in puberty. Plexiform neurofibromas, which are found in 25% of individuals, may result in disfigurement if on the face, trunk or extremities.[5] Orthopaedics conditions such as tibial dysplasia and pseudoarthrosis also affect 2-3% of NF1 children.[6] Optic gliomas may be present in up to 15%, one third of them may be symptomatic resulting in visual loss, proptosis, hydrocephalus or precocious puberty.[7] Due to the variable multi-system involvement of NF1, periodic multidisciplinary monitoring is needed to minimise risk of complications.

Although NF1 is mostly clinically diagnosed, molecular technology can detect 95% of the mutations.[8] With the increasing readiness of genetic testing, it is very useful in uncertain cases such as those with some features but not fulfilling the clinical diagnostic criteria.

What is the Molecular Genetics behind NF1?

The *NF1* gene encodes for the protein neurofibromin, a tumour suppressor. Pathogenic mutations in *NF1* cause reduced neurofibromin function, thus resulting in excess cell proliferation.

50% of the NF1 patients have de novo mutation, which means the mutation is not inherited from either parent. It is an autosomal dominant condition. An individual with known pathogenic NF1 mutation has 50% chance passing down the variant to his/her offspring in each pregnancy. Prenatal diagnosis is possible, but it cannot predict the clinical outcome of offspring who inherited the variant due to marked variability.

Due to the high penetrance of NF1, clinical manifestations will be expected in individuals who carry the mutation. In individuals who are mosaic for an NF1 mutation, they may have localised signs, or "segmental neurofibormatosis". The mutant gene may be transmitted to their offspring if the germ cells are affected.

What is the Management of NF1?

NF1 patients are usually mildly affected, but the presence of plexiform neurofibromas may result in serious complications. The lifelong risk of malignancy may be increased, with malignant peripheral nerve sheath tumours representing the most common neoplasm (5-10%).[6] Other malignancies include pheochromocytoma, rhabdomyosarcoma, leukaemia, and brain tumours such as optic gliomas. Short stature and macrocephaly may also be related to NF1. Neurofibromas in the gastrointestinal tract may cause obstruction or bleeding. Seizure may occur in 6-7% of cases.[6] Non-ossifying fibromas of long bones may cause fractures. Scoliosis is also present in 10-30% of NF1 cases, which may lead to decrease pulmonary functions.[6] Hypertension occurs in 4% of NF1 cases due to essential hypertension, pheochromocytoma, renal artery stenosis, or aortic stenosis.[6] NF1 is also associated with intellectual disability and ADHD, speech problems may occur due to velopharyngeal insufficiency. Approximately one-third of NF1 develop serious complications. Due to the marked variability, it is impossible to determine the prognosis after establishing a diagnosis of NF1.

Therefore, the management of NF1 requires a multidisciplinary approach due to its multi-organ involvement. The aim of management is both early detection and treatment of complications as they occur. Regular clinical evaluation is needed and should include: examining the skin for new neurofibromas and progression of lesions and plexiform neurofibromas; checking the child's blood pressure yearly for hypertension secondary to renal artery stenosis, aortic

stenosis, and pheochromocytoma; evaluating neurodevelopment progress - MRI may be needed to detect optic gliomas; ophthalmology testing yearly; evaluating for any skeletal changes such as scoliosis, tibial dysplasia, limb deformities; checking for signs of learning disabilities and attention-deficit/hyperactivity disorder, and also reviewing the effects of puberty on the disease.

To conclude, the management of NF1 is not limited to multi-disciplinary care by paediatricians, clinical psychologists, psychiatrists, orthopaedics and surgeons; it also requires life-long regular monitoring and care.

Acknowledgments

We would like to express our gratitude to the patient and his family for their contribution. Informed consent was obtained for publication.

References

1. Rosenbaum T, Engelbrecht V, Krölls W, et al. MRI abnormalities in neurofibromatosis type 1 (NF1): a study of men and mice. Brain and Development 1999;21:268-73.
2. Cutting LE, Koth CW, Burnette CP, Abrams MT, Kaufmann WE, Denckla MB. Relationship of cognitive functioning, whole brain volumes, and T2-weighted hyperintensities in neurofibromatosis-1. J Child Neurol 2000;15:157-60.
3. North KN. Neurofibromatosis 1 in childhood. Semin Pediatr Neurol 1998;5:231-42.
4. National Institutes of Health Consensus Development Conference statement: neurofibromatosis. Bethesda, Md., USA, July 13-5, 1987. Neurofibromatosis 1988;1:172-8.
5. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in South East Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 1989;26:704-11.
6. Viskochil D. Neurofibromatosis type 1. In: Cassidy SB, Allanson JE, eds. Management of Genetic Syndromes. Hoboken, NJ: John Wiley & Sons Inc; 2005:369-84.
7. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr 1989;114:788-92.
8. Messiaen LM, Callens T, Mortier G, et al. Exhaustive mutation analysis of the NF1 gene allows the identification of 95% of mutations and reveals a high frequency of unusual splicing defects. Hum Mutat 2000;15:541-55.