SSBP Syndrome Sheets

Coffin-Lowry Syndrome

The Coffin–Lowry syndrome (CLS) (MIM 303600) is a syndromic form of X-linked dominant (Nishimoto et al., 2014) mental retardation characterized in male patients by psychomotor retardation, growth retardation, and various skeletal anomalies. The condition was for the first time independently described by Coffin et al. (1966) and Lowry et al. (1971) and definitively distinguished by Temtamy et al. (1975), who proposed the eponym appellation 'Coffin–Lowry syndrome'. Confirmation of the suspected X- linked mode of inheritance was forthcoming with the mapping of the disease locus to Xp22.2 by Hanauer et al (1988), with the subsequent isolation of the causal gene, *RPS6KA3* (Trivier et al., 1996).

Genetics and molecular biology

The *RPS6KA3* gene encodes a growth factor regulated serine-threonine protein kinase, Rsk2 (alternate names: p90^{RSK2}, MAPKAPK1B, ISPK-1), which acts at the distal end of the *Ras*- Erk1/2 signalling cascade. Mutations in the *RPS6KA3* gene are extremely heterogeneous and lead to premature termination of translation and/or to loss of phosphotransferase activity of the RSK2 protein. For the vast majority of mutations so far reported, no consistent relationship has been observed between specific mutations and the severity of the disease (Delaunoy et al., 2006). However, expression of some features was found to be associated with particular truncating mutations in a few patients (Nakamura et al., 2005).

Incidence / Prevalence

On the basis of the experience of the researchers, a prevalence rate of 1:50 000 to 1:100 000 may be reasonable. Approximately 70–80% of probands have no family history of CLS. This high incidence of sporadic cases may be attributed to genetic selection that occurs against hemizygous males and heterozygous females who are mentally retarded. Molecular studies have further revealed that two-thirds of cases arise from new mutations (Delaunoy, 2006).

Physical features and natural history

The typical facial aspect in adult male patients includes a prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares. Orodontal findings include typically a high narrow palate, a midline lingual furrow, hypondontia, and peg-shaped incisors. Skeletal malformations appear progressively in most patients and may include delayed bone development, spinal kyphosis/scoliosis, and pectus carinatum or excavatum. The extent of kyphoscoliosis may be such that it causes severe chronic restrictive lung disease (Venter et al., 2019). Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges.

Uncommonly associated manifestations include epileptic seizures and sensorineural hearing loss, which can be profound. Stimulus-induced drop episodes, with onset typically from mid- childhood to the teens

(unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness), and cardiac involvement, usually in the form of mitral valve dysfunction, are often present. Reduced total brain volume, with a particular effect on cerebellum and hippocampus, has been reported in some patients. Affected newborn males often show only hypotonia and hyperlaxity of joints. However, broad, tapering fingers may also be present at birth. The typical facial appearance is usually apparent only by the second year of life and shows progressive coarsening thereafter with increasing prominence of the glabella and protrusion of the lips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly. The age of walking is delayed, and difficulties in ambulating may persist with a clumsy gait.

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance to quite marked facial dysmorphism. Ventriculomegaly has been observed in several affected males and females.

Although accurate information is not available the paucity of reports of older affected males suggests that their life expectancy is reduced in contrast to that of females who can survive well into old age. Reported causes of death in affected males include myocarditis, pneumonia and inhalation during a convulsion. Several males have succumbed to complications following general anaesthesia for correction of orthopaedic problems or dental extraction (Hanauer & Young,2002, Hunter, 2002).

Behavioural characteristics

Cognitive deficiencies in CLS male patients are prominent, but markedly variable in severity, including between siblings. However, the vast majority of patients are severely affected, with IQ scores ranging from moderate to profound (between 15 and 60). Very mild cases of the disease have been reported, with in particular in a few families only non-syndromic mental retardation (Field et al., 2006). Delay in speech acquisition is particularly common with most reported males having a very limited vocabulary. Despite the limited verbal abilities, the communication skills are good and affected individuals are usually cheerful, easy going, and friendly.

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity , depression, psychotic behavior including schizophrenia) have been described in a few female carriers. Epilepsy may occasionally develop. Stimulus-induced Drop Episodes (SIDE) may occur in response to unexpected auditory of tactile stimulus (Rojnueangnit et al, 2013)

Available guidelines for behavioural assessment/treatment/management

There is no specific treatment. Sensorineural hearing deficit should be addressed very early to improve the development and quality of life of the patients. Treatment for individuals with CLS who experience drop attacks includes medications such as valporate and clonazepam or selective serotonin uptake inhibitors. If stimulus-induced drop episodes occur with great frequency, use of a wheelchair may be required to prevent falling and injury (Hunter, 2005).

Useful Websites

U.S. National Library of Medicine (NLM), Genetics Home Reference: https://ghr.nlm.nih.gov

References

1. Coffin G.S., Siris E. & Wegenkia L.C. (1966) Mental retardation with osteocartilaginous anomalies.*Am J Dis Child* **112**, 205–213.
2. Delaunoy JP., Dubos A., Marques Pereira P. & Hanauer A. (2006) Identification of novel mutations in the RSK2 gene (RPS6KA3) in patients with Coffin-Lowry syndrome. *Clin Genet* **70,** 161-6.
3. Field M., Tarpey P., Boyle J., Edkins S., Goodship J., Luo Y. *et al*. (2006) Mutations in the RSK2(RPS6KA3) gene cause Coffin-Lowry syndrome and non syndromic X-linked mental retardation. *Clin Genet* **70**, 509–515.
4. Hanauer A. & Young ID. (2002) Coffin-Lowry syndrome: clinical and molecular features. *J MedGenet* **39**, 705–713.
5. Hunter AG. (2002) Coffin-Lowry syndrome: a 20-year follow-up and review of long-term outcomes. *Am J Med Genet* **111**, 345–355.
6. Hunter AG. Coffin-Lowry syndrome; in Cassidy S, Allanson J (eds): *Management of Genetic Syndromes*, 2nd edn. Hoboken, NJ: Wiley-Liss, 2005; 127–138.
7. Lowry B., Miller J.R. & Fraser F.C. (1971) A new dominant gene mental retardation syndrome. *AmJ Dis Child* **121**, 496–500
8. Nakamura M., Magata T., Mori M. & Momoi M.Y. (2005) RSK2 gene mutations in Coffin-Lowry syndrome with drop episodes. Brain Dev **27**, 114–117.
9. Nishimoto HK, Ha K, Jones JR, Dwivedi A, Cho HM, Layman LC, Kim HG. (2014). The historical Coffin-Lowry syndrome family revisited: identification of two novel mutations of RPS6KA3 in three male patients. Am J Med Genet A **164A**(9): 2172-9.
10. Rojnueangnit K, Jones JR, Basehore MJ, Robin NH. 2013. Classic phenotype of Coffin–Lowry syndrome in a female with stimulus-induced drop episodes and a genotype with preserved N-terminal kinase domain. Am J Med Genet Part A **164**A:516– 521.
11. Temtamy S.A., Miller J.D. & Hussels-Maumenee I. (1975) The Coffin-Lowrysyndrome: an inherited faciodigital mental retardation syndrome. J Pediatr **86**, 724–731.
12. Trivier E., De Cesare D., Jacquot S., Pannetier S., Zackai E., Young I., et al. (1996) Mutations in the kinase Rsk-2 associated with Coffin-Lowry syndrome. Nature **384**, 567-70.
13. Venter F., Evans A., Fontes C., Stewart C. (2019). Severe restrictive lung disease in one of the oldest documented males with Coffin-Lowry Syndrome. J Investig Med High Impact Case Rep **7**, 1–3.

André Hanauer, June 2010, revised Stewart Einfeld, 2015,
Revised Navin Dadlani & Stewart Einfeld, June 2019

Reviewed Stewart Einfeld, June 2023

The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation