SSBP Syndrome Sheets

Lowe Syndrome

Lowe syndrome was first described in 1952 by Dr. Charles Lowe (Lowe et al., 1952). Other names for Lowe Syndrome include cerebrooculorenal syndrome, Lowe oculocerebrorenal syndrome, oculocerebrorenal syndrome, oculocerebrorenal syndrome of Lowe, phosphatidylinositol-4,5-bisphosphate-5-phosphatase deficiency, and OCRL1 syndrome. Lowe syndrome is often referred to medically as oculocerebrorenal syndrome because of the three main organ systems involved (eyes, brain, and kidneys).

Genetics

Lowe syndrome is caused by a mutation or alteration to the OCRL gene on the X chromosome. This gene is responsible for coding an enzyme that helps to regulate the production of certain cells, of which seem to impact primarily the retina, brain, and kidneys (Bökenkamp & Ludwig, 2016; Loi, 2006). The exact mechanism that leads to these three organ systems being primarily affected is not yet known. The OCRL gene has been found to highly expressed in the human hypothalamus, pituitary and other endocrine tissues, areas known to play a role in growth regulation. It is suspected that absence of this gene contributes to the short stature seen in LS and that this may be amenable to growth hormone therapy in future treatment developments (Sena et al., 2022).

A diagnosis of Lowe syndrome is most often confirmed through an enzyme deficiency analysis, usually done by taking a small skin sample. It can also be diagnosed clinically and through DNA analysis (Lewis, 2001). Diagnosis can occur before or after birth. Female carriers of the gene causing Lowe syndrome can be tested, as they usually show changes in the lens of their eye from the age of 10, which can be identified by an ophthalmologist (Röschinger et al., 2000). Carrier status can also be identified through DNA analysis and family history.

Differential Diagnosis

Generalized congenital infections, such as Rubella, are associated with a combination of congenital neonatal-onset cataracts, hypotonia, and kidney dysfunction and should also be considered as a differential diagnosis. There are also a number of different rare genetic conditions that affect similar organ systems to Lowe syndrome, resulting in overlapping symptomology. Overlapping and distinguishing features of other genetic conditions can be found on Gene Reviews (Lewis, 2001).

Prevalence

Lowe syndrome is a rare genetic condition with an estimated prevalence of 1 in 500,000 individuals (Bökenkamp & Ludwig, 2016). It is believed to occur worldwide. Because the condition is X-linked, it primarily affects males. As females have two X chromosomes, it is extremely rare for girls to have Lowe syndrome because both copies of the X chromosome would need to be affected.

Clinical and Physical Phenotype

Vision

Cataracts are present at birth in nearly all cases of Lowe syndrome (Sena et al., 2022). In addition, infantile glaucoma occurs in approximately half of individuals with Lowe syndrome, where there is too

much pressure in the eye, causing eyes to become enlarged or appear bulging (Kruger et al., 2003; Loi, 2006; McSpadden, 2000).

Kidney Function

Affected males have varying degrees of proximal renal tubular dysfunction of the renal Fanconi type. In a survey of clinical symptoms by the Lowe Syndrome society, 55.4% of individuals were reported to have kidney calcification, and 21.9% to have renal stones (Sena et al., 2022). Progressive renal tubular injury is thought to eventually lead to chronic kidney disease and end-stage renal disease for many individuals between the second and fourth decades of life.

Facial Characteristics

Elongation of the face is sometimes a feature of Lowe syndrome. Prominent forehead, deep-set eyes, high-arched palate, and fair complexion are also common.

Oral Health

Dental problems are common in LS and are reported by approximately half of parents (Sena et al., 2022). There is often a delayed eruption of adult teeth and overcrowding in the mouth. Teeth will often have white spots due to thin enamel and excessive calcium deposits (Harrison et al., 2000). Cysts can appear in the mouth and gums, leading to infection. Despite the high prevalence of dental problems reported in LS, parents report difficulties accessing dental appointments and supporting dental hygiene at home (Lowenstein et al., 2023).

Musculoskeletal

Hypotonia is present after birth (weak muscle tone), which can cause difficulties with feeding and obtaining motor milestones. Seventy-five percent of boys with Lowe syndrome are able to walk independently between the ages of 6 to 13 years old (McSpadden, 2000). Around 28.5%-50% of individuals with Lowe syndrome develop scoliosis (McSpadden, 2000; Sena et al., 2022). Rickets is common in Lowe syndrome and can often lead to bowing of the legs; however, this can often be prevented with medical treatment. Most individuals with Lowe syndrome will usually have a short stature and fall below the 10th percentile for height (Sena et al., 2022).

Low phosphorus levels may occur in approximately 41.6% of individuals, low vitamin D in approximately 70.2%, with frequency of bone fractures reported to be common at approximately 46% of individuals (Sena et al., 2022).

Puberty

Puberty is often delayed in onset, and between 33-47% of males may experience cryptorchidism (undescended testes; Recker et al., 2014; Sena et al., 2022).

Other

Cysts can often appear in the mouth and skin, such as in the gums, buttocks, and low back, which can cause pain and are at risk of infection (Ikehara & Utani, 2016). Seizures occur in approximately 45- 50% of individuals with Lowe syndrome. There is no specific seizure type (Erdogan et al., 2007; Sena et al., 2022).

Development and Cognition

Although most people with Lowe syndrome will eventually be able to walk, difficulties with motor skills often persist, leading to challenges with tasks such as opening doors, using buttons, shoelaces, zips, keyboards, or pens. Dressing and self-care tasks that require coordination can be particularly difficult. Most individuals will require support in adulthood for tasks such as meal preparation (Sena et al., 2022) and will require support from physical therapy and occupational therapy.

Delayed language is evident in early childhood, but most individuals with Lowe syndrome can imitate words by the age of 2 and a half and can talk by the age of 7 (McSpadden, 2000). Most children with Lowe syndrome become toilet trained between the ages of 5 and 13, although this can be challenging due to constipation, which is thought to effect approximately 70% of individuals (Sena et al., 2022).

Almost all affected males have some degree of intellectual disability, with approximately 10-25% in the low to normal range (borderline), 25% in the mild to moderate range, and 50-65% in the severe to profound range of intellectual disability (Kenworthy et al., 1993).

Behavioural Aspects

Currently, there is little research regarding the social characteristics of individuals with Lowe syndrome. However, parents often report that their children enjoy social interaction but have difficulties interpreting social cues and knowing how to respond appropriately.

Research on parent reports of autistic traits found that 7 out of 10 parents reported that their child had autistic traits, and 3 out of 10 had a score suggestive of an autism diagnosis (Oliver et al., 2010). With regard to formal diagnosis, autism diagnosis has been reported in approximately 10% of individuals, and Attention Deficit Hyperactivity Disorder in 8.2% of individuals.

Repetitive behaviour is commonly reported in Lowe syndrome (Sena et al., 2022). In a study comparing the prevalence of parent-reported repetitive behaviours across different rare genetic syndromes, hand stereotypies and lining up behaviours were found to be higher in Lowe syndrome compared to other groups (Moss et al., 2008). Hand stereotypy has been noted in approximately 60% of individuals, on survey-based measures (Sena et al., 2022).

Emotional outbursts have been identified as common in Lowe syndrome, with aggression often being a core feature, including behaviours such as self-injury and destruction of property (Cressey et al., 2019; Sena et al., 2022). The most commonly reported triggers are changes in routine and unmet desires (e.g., wanting something that is not available) (Cressey et al., 2019). Some of these difficulties might be related to impaired cognitive processes such as emotional regulation and executive functioning, as similar links have been found in individuals with other rare genetic conditions (Chung et al., 2022; Rice, Woodcock, and Einfeld, 2018). Preliminary research at the University of Birmingham has found that individuals with Lowe syndrome often have difficulties delaying gratification, supporting that executive dysfunction within emotionally salient contexts likely plays an important role in reported emotional regulation difficulties (Waite et al., 2016).

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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