Kugelberg Welander Syndrome (KWS)

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1. Core Definition

Kugelberg Welander Syndrome (KWS), also formally recognized as **Spinal Muscular Atrophy Type 3 (SMA Type 3)**, represents a specific genetic disorder characterized by the progressive degeneration of motor neurons located in the spinal cord and brainstem. This degeneration leads to profound muscle weakness and atrophy, primarily affecting the proximal muscles of the limbs, trunk, and sometimes the bulbar muscles. The underlying cause of KWS is a **genetic mutation**, specifically a deletion or mutation in the **survival motor neuron 1 (SMN1) gene**, which is situated on **chromosome 5q13**. As the mildest form among the classic childhood-onset spinal muscular atrophies, KWS typically manifests with a later onset of symptoms and a slower progression compared to SMA Type 1 (Werdnig-Hoffmann disease) and SMA Type 2.

Individuals with KWS often present with initial symptoms in early childhood, typically between the ages of 18 months and three years, although onset can occasionally extend into adolescence or adulthood. A distinguishing characteristic of KWS is the ability of affected individuals to achieve and maintain independent ambulation for a significant period, distinguishing it from the non-ambulatory nature of more severe SMA types. However, as the disease progresses, many patients may experience a gradual decline in motor function, eventually leading to a loss of the ability to walk and requiring assistive devices or wheelchair use. The severity and rate of progression can vary considerably among individuals, influenced by genetic modifiers such as the number of copies of the SMN2 gene, which plays a compensatory role in SMN protein production.

2. Etymology and Historical Context

The syndrome derives its name from the pioneering work of two Swedish neurologists, **Erik Kugelberg** and **Lisa Welander**, who meticulously described the condition in **1956**. Their observations focused on a cohort of patients who presented with a distinct form of proximal spinal muscular atrophy, characterized by a later onset and a significantly milder clinical course compared to the already recognized severe forms of the disease. These patients maintained the ability to walk for extended periods, a feature that was instrumental in differentiating this subtype from other, more debilitating motor neuron diseases of childhood. The recognition of KWS was a pivotal moment in the classification of spinal muscular atrophies, broadening the understanding of the disease spectrum and highlighting the importance of phenotypic variability.

The broader history of spinal muscular atrophy dates back to the late **19th century**. The earliest systematic descriptions were provided by **Guido Werdnig** in **1891** and subsequently by **Johann**

Hoffmann in **1893**, who independently described the severe infantile form of the disease, now known as SMA Type 1 or Werdnig-Hoffmann disease. These initial descriptions laid the groundwork for understanding hereditary motor neuron diseases. Over the subsequent decades, clinicians and researchers identified intermediate forms (SMA Type 2) and, later, the milder form identified by Kugelberg and Welander. This progressive understanding of clinical heterogeneity culminated in the comprehensive classification system that recognizes SMA Types 0 through 4, with KWS firmly established as SMA Type 3, reflecting its specific clinical presentation and course. The genetic basis of SMA, including KWS, was ultimately elucidated in the mid-1990s with the identification of the **SMN1 gene** on chromosome 5q13, revolutionizing diagnostic capabilities and paving the way for targeted therapeutic development.

3. Genetic Basis and Pathophysiology

The fundamental cause of Kugelberg Welander Syndrome lies in a genetic defect affecting the **survival motor neuron (SMN) gene complex** located on **chromosome 5q13**. Specifically, KWS is primarily caused by a homozygous deletion or a pathogenic mutation in the **SMN1 gene**. The SMN1 gene is responsible for producing a crucial protein known as the **SMN protein**, which is vital for the health and survival of motor neurons. Motor neurons are nerve cells that originate in the spinal cord and brainstem and transmit signals to muscles, enabling movement. A deficiency in SMN protein leads to the progressive degeneration of these critical neurons, resulting in muscle weakness and atrophy.

Adjacent to the SMN1 gene, there is a highly homologous gene called **SMN2**. While SMN1 is the primary producer of full-length, functional SMN protein, SMN2 typically produces only about 10-15% full-length protein, with the majority being a truncated, non-functional version due to a critical nucleotide difference (C to T transition) that affects splicing. However, the number of copies of the SMN2 gene (ranging from 0 to 8 or more) acts as a significant **disease modifier** in SMA. Individuals with KWS generally possess more copies of the SMN2 gene (typically 3 or 4 copies) compared to those with more severe forms of SMA. These additional SMN2 copies allow for the production of a greater amount of functional SMN protein, albeit still insufficient for normal motor neuron function, which explains the milder phenotype, later onset, and slower disease progression characteristic of KWS. Understanding this genetic interplay has been pivotal in developing therapeutic strategies aimed at increasing the production of functional SMN protein from the SMN2 gene.

4. Clinical Manifestations and Disease Progression

The clinical presentation of Kugelberg Welander Syndrome typically involves a gradual onset of motor symptoms, often noticed by parents or caregivers between **18 months and three years of age**, though it can vary significantly. Initial signs often include subtle difficulties with motor skills

that were previously mastered or delays in achieving new ones. Common early symptoms include an awkward gait, frequent falling, and challenges with activities such as climbing stairs, running, or rising from a squatting or sitting position. The muscle weakness is predominantly **proximal**, meaning it affects the muscles closer to the body's core (hips, thighs, shoulders, upper arms) more severely than distal muscles (hands, feet).

As the disease progresses, individuals with KWS may exhibit a characteristic **waddling gait** due to hip girdle weakness, and they often employ a **Gowers' sign** maneuver to stand up, using their hands to "climb up" their legs for support. Muscle atrophy, or wasting, becomes more evident over time, particularly in the affected limb muscles. Other common manifestations include **scoliosis**, a curvature of the spine, which can develop due to trunk muscle weakness and uneven muscle pull. While ambulation can be maintained for many years, a significant number of individuals will eventually experience a progressive decline in their walking ability, ultimately requiring mobility aids such such as walkers, crutches, or wheelchairs, particularly in their teenage or adult years. Unlike more severe forms of SMA, bulbar involvement (affecting muscles for swallowing and speaking) and respiratory difficulties are typically less pronounced in KWS, though severe cases may eventually develop mild breathing compromise, especially during sleep or illness. Deep tendon reflexes are often diminished or absent, and a fine tremor of the outstretched fingers may be observed.

5. Diagnosis and Differential Diagnosis

The diagnosis of Kugelberg Welander Syndrome is primarily established through a combination of clinical evaluation and genetic testing. Clinically, suspicion arises based on the presentation of progressive, proximal muscle weakness, muscle atrophy, and the characteristic motor difficulties, especially in a child who initially achieved independent ambulation. A detailed neurological examination will often reveal diminished or absent deep tendon reflexes, muscle fasciculations (visible muscle twitching), and the absence of sensory deficits, as SMA is purely a motor neuron disorder. Electromyography (EMG) and nerve conduction studies (NCS) may be performed to support the diagnosis by showing evidence of denervation (motor neuron loss) in muscles and normal sensory nerve function, thereby distinguishing it from primary muscle diseases (myopathies) or other neuropathies.

The definitive diagnosis of KWS, like other forms of SMA, relies on **genetic testing** for deletions or mutations in the **SMN1 gene**. This test is highly accurate and is now the gold standard. A common method is quantitative polymerase chain reaction (qPCR) or multiplex ligation-dependent probe amplification (MLPA) to detect the homozygous deletion of exon 7 in SMN1. In cases where only one copy of SMN1 is deleted, sequencing of the remaining SMN1 allele is performed to identify point mutations. Crucially, the number of **SMN2 gene copies** is also typically determined, as this correlates with disease severity and is a critical prognostic indicator, helping to confirm KWS (SMA

Type 3) in the context of the clinical phenotype. Differential diagnosis is important to rule out other neuromuscular conditions that may present with similar symptoms, such as limb-girdle muscular dystrophies, congenital myopathies, metabolic myopathies, and other forms of motor neuron disease.

6. Management and Therapeutic Approaches

The management of Kugelberg Welander Syndrome has undergone a revolutionary transformation with the advent of disease-modifying therapies in recent years. Historically, management was primarily supportive, focusing on symptomatic treatment and rehabilitation to maintain function and improve quality of life. This included regular physical therapy and occupational therapy to preserve muscle strength, prevent contractures, and optimize mobility. Orthopedic interventions, such as bracing and surgery, were often necessary to manage scoliosis and other musculoskeletal complications. Nutritional support and respiratory care, though less critical than in more severe SMA types, were also part of comprehensive management.

Today, the landscape of KWS treatment is dominated by three groundbreaking therapies specifically approved for SMA: **nusinersen** (Spinraza), **onasemnogene abeparvovec** (Zolgensma), and **risdiplam** (Evrysdi). Nusinersen, an antisense oligonucleotide, is administered intrathecally and works by modifying SMN2 gene splicing to increase the production of full-length SMN protein. Onasemnogene abeparvovec is a gene therapy administered as a single intravenous dose, delivering a functional copy of the SMN1 gene to motor neuron cells. Risdiplam is an orally administered small molecule that also modifies SMN2 splicing to enhance full-length SMN protein production. These therapies have demonstrated significant improvements in motor function, stabilization of disease progression, and even attainment of new motor milestones in patients with KWS, particularly when initiated early. The choice of therapy depends on factors such as age, disease severity, patient preference, and regulatory approvals.

7. Prognosis and Quality of Life

The prognosis for individuals with Kugelberg Welander Syndrome is generally more favorable than for those with SMA Type 1 or 2, largely due to its milder and slower progressive nature. Many individuals with KWS maintain the ability to walk into adulthood, though often with increasing difficulty and the eventual need for assistive devices. The life expectancy for individuals with KWS is typically near normal, especially with proactive management of potential complications. However, the quality of life can be significantly impacted by the progressive muscle weakness and its secondary effects, such as pain, fatigue, and reduced participation in daily activities.

Despite the generally good prognosis, continuous medical care, rehabilitation, and psychosocial support are crucial for optimizing outcomes and enhancing the quality of life for KWS patients. The

advent of disease-modifying therapies has dramatically improved the long-term outlook, with treated individuals experiencing a slower decline in motor function, or even improvements, which can delay or prevent the loss of ambulation and reduce the severity of other symptoms. However, even with these treatments, ongoing rehabilitation remains essential to maximize motor potential and manage musculoskeletal issues. Psychological support is also important for patients and families to cope with the challenges of living with a chronic, progressive condition. Access to these advanced therapies, coupled with comprehensive multidisciplinary care, is paramount in enabling individuals with KWS to lead fulfilling and active lives.

8. Current Challenges and Future Directions

Despite the transformative impact of approved therapies, several challenges remain in the field of Kugelberg Welander Syndrome. One significant challenge is the ongoing need for **early diagnosis**. While newborn screening programs for SMA are expanding, universal implementation is still pending in many regions. Early diagnosis is critical, as therapies are most effective when initiated before significant motor neuron damage has occurred, even in a milder form like KWS. Another area of complexity lies in optimizing treatment strategies, including determining the ideal timing, dosage, and combination of therapies, as well as managing the long-term efficacy and safety profiles of these relatively new treatments.

Furthermore, while current therapies address the root genetic cause, they do not fully restore lost motor neuron function or completely eliminate symptoms. Many individuals with KWS, even those on treatment, continue to experience residual weakness, fatigue, and require ongoing supportive care. This highlights the need for research into complementary therapies, such as advanced rehabilitation techniques, muscle-strengthening interventions, and drugs that target muscle health directly. Future directions in KWS research include the exploration of novel therapeutic targets beyond SMN protein production, such as neuroprotection, muscle regeneration, and enhancing neuromuscular junction function. There is also a growing focus on personalized medicine, aiming to tailor treatment approaches based on individual genetic profiles, SMN2 copy number, and clinical response, ultimately striving to improve outcomes and enhance the quality of life for all individuals living with Kugelberg Welander Syndrome.

Further Reading

Kugelberg-Welander disease - Wikipedia
Spinal Muscular Atrophy Information Page - National Institute of Neurological Disorders and Stroke (NINDS)
Spinal Muscular Atrophy - GeneReviews® - NCBI Bookshelf
Spinal Muscular Atrophy (SMA) | Muscular Dystrophy Association
Kugelberg-Welander Syndrome - National Center for Advancing Translational Sciences (NCATS)