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Floppy Baby Syndrome: A Comprehensive Review of the Chromosomal Abnormalities and Gene Mutations

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Abstract

Floppy infant syndrome, sometimes referred to as rag doll syndrome, is a term that is used to define an infant that presents with decreased muscular movements or poor muscle tone that affects the limbs, the trunk and the cranio-facial musculature. The decreased muscle tone and generalized weakness, also referred to as hypotonia, can lead to a delay in milestones being reached and other developmental delays. Depending on the underlying causative agent of floppy infant syndrome, the level of hypotonia will differ and therefore, the actual delay in achieving milestones will also be delayed. Calculating the exact incidence of floppy infant syndrome proves to be a challenge as there are chromosomal disorders, genetic disorders, neurometabolic disorders, etc., that all lead to a variable degree of hypotonia in an infant. The common factor amongst these types of disorders is that the hypotonia improves with age but will initially cause a delay in achieving milestones and other developmental delays. Depending on whether the hypotonia is specific to the limbs or more generalized, the clinical manifestations of the hypotonia will also vary. The examination of a hypotonic infant is very significant in the sense of the signs the infant will present with and the tests that are conducted. The 'U' posture evidentially shows the weakness in the muscles in the neck region - the flaccidity in the muscle tone causing the infant to fall over the examiner's palm in such a distinctive manner. The treatment of floppy infant syndrome focuses on investigating the underlying cause that is leading to the presentation of floppy infant syndrome. In many of the disorders - Smith-Magenis syndrome, Fragile X syndrome, Cri du Chat syndrome - the hypotonia seems to disappear with age. In other syndromes, such as Down syndrome, the hypotonia may become less pronounced but be present in later age as well.

Keywords: *Central Hypotonia; Floppy Infant Syndrome; Inborn Metabolic Errors; Chromosomal Disorders; Neonatal Hypotonia; Poor Muscle Tone*

Introduction

One of the most difficult tasks the general pediatric neurologist is asked to undertake is the evaluation of the hypotonic child [1]. Sometimes compared to a rag doll, a 'floppy infant' is a term used to define an infant that presents with poor muscle tone, affecting the limbs, trunk and the cranial-facial musculature [2]. Floppy infants are typically seen as exhibiting poor control of movement, delayed motor skills and hypotonic motor movement patterns [3]. There is a vast majority of factors that lead to the development of hypotonia in an infant - some being genetic in nature while others are metabolic, or due to acute or chronic illnesses Due to the substantially large list of causes that can cause hypotonia in an infant, the diagnosis of hypotonia in the first year of life is a common diagnostic and management challenge for pediatricians and neonatologists [4]. The consequences of floppy infant syndrome range from hip dislocations, arthrogryposis, flexion deformity of all limbs, to respiratory and feeding difficulties [5]. In the process of evaluating floppy infant syndrome and attempting to narrow down to the primary cause of floppy infant syndrome (FIS), it is imperative to, firstly, determine whether the cause of FIS is peripheral or central. Overall, central hypotonia is more common than peripheral hypotonia amongst FIS infants [4]. Based on research, central hypotonia accounts for 60% to 80% of cases of hypotonia, whereas peripheral hypotonia is the cause in about 15 - 30% of cases [6].

Due to the lack of large population-based studies having been conducted, the true incidence of floppy infant syndrome amongst the neonates is hard to dictate. As the causes of floppy infant syndrome differ to a varying extent, to ascertain any sort of numerical information as to which cause is most likely to prevail requires a level of analysis that has not yet been conducted. On long-term follow up, cerebral palsy and mental retardation turn out to be the 2nd most common causes of FIS [7]. Cerebral palsy and mental retardation are just a couple of the immense list of causes of floppy infant syndrome. A treatable cause of floppy infant syndrome can be attributed to an inborn error of organic acid metabolism due to defective activity of the enzyme beta-methylcrotonyl CoA carboxylase [8]. Furthermore, floppy infant syndrome could be secondary to a connective tissue disorder or it could be a non-specific sign in any acutely ill child [9]. Depending on the underlying cause of floppy infant syndrome, the symptoms would vary, accordingly, and the treatment - if any present - would also differ. Majority of the causes of floppy infant syndrome tend to be secondary to a genetic or chromosomal syndrome such as Prader-Willi syndrome, Sotos syndrome, Cri du Chat syndrome, etc [3]. In an infant younger than 6 months of age who has signs and symptoms such as constipation, listlessness, poor feeding, weak cry and a decreased gag reflex, infant botulism should be suspected [10].

FIS is not a condition that solely follows an inheritance pattern as it can also be acquired. An example of an acquired case of hypotonia in an infant would be through honey ingestion, resulting in botulism toxicity in an infant [11]. Various maternal drugs can also lead to the causation of infantile hypotonia - FIS. An important correlation between maternal use of medication throughout the pregnancy and floppy infant syndrome is the use of benzodiazepines [12]. Long-term use of benzodiazepines during a pregnancy an increased for the fetus to develop floppy infant syndrome [13]. Furthermore, acute use of diazepam, especially intramuscularly or intravenously, during labor may be enough to produce FIS are required during labor, the maternal dose should be the lowest effective dose, as high doses can cause FIS [14].

FIS has been implicated in several different types of syndromes following on a continuum from genetic to acquired. Despite the primary causative agent/disorder of FIS, the classic symptoms leading to the diagnosis of FIS remains fairly constant - focus on the hypotonia of the infant. Based on some research evidence, 50% of patients who have hypotonia are diagnosed by history and physical examination alone [15]. Figure 1 provides a visual image on the categorization of the various causes that could lead to the development of floppy baby syndrome. Due to broad category of disorders and causes of floppy baby syndrome, FIS acts more as an umbrella term under which central and peripheral hypotonia both reside.

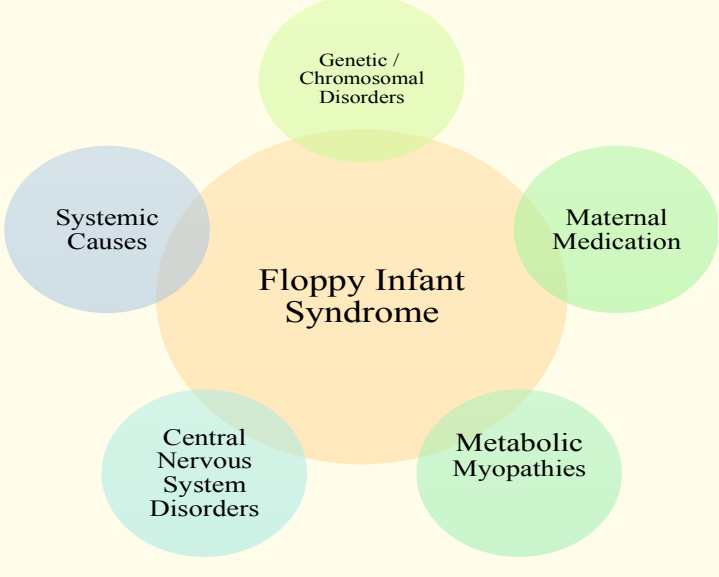

Figure 1: *Categorization of the various causes of FIS.*

The examination of a hypotonic infant is very significant in the sense of the signs the infant will present with and the tests that are conducted. Clinical evaluation includes a detailed neurologic assessment examining tone, strength and reflexes [3]. Most hypotonic infants demonstrate a characteristic posture of full abduction and external rotation of the legs as well as a flaccid extension of the arms [2]. In a case report presented by Leyenaar, Camfield and Camfield (2005), the 5-month-old infant girl made no attempts to roll over, rarely moved her legs and made no attempts to push with her feet when held upright. In this case, there a definite amount of flaccidity and hypotonia present in the infant girl, which was the key point for her parents taking her to the family physician [16]. The variability of hypotonia is on a continuum such that it can be limited to the upper and lower extremities, involve the trunk, present with other dysmorphic features (height, weight and head circumference) or it could involve all. It should be noted that the amount of hypotonicity that is visible in the presenting infant will vary depending on the primary insult that led to the development of floppy infant syndrome. Furthermore, it may very well be possible that in severe cases of hypotonia, there are developmental delays, along with delays in reaching milestones. A floppy infant often lies with limbs abducted and extended [3]. Congenitally dislocated hips may also occur in in hypotonic infants and this is evidence of chronic in utero hypotonia, predisposing the infant to assuming the 'frog leg' position when laying supine [17]. There are several other signs that would be present in chronic in utero hypotonia, such as reduced respiratory efforts in utero that may be manifested as a bell-shaped thorax and pulmonary hypoplasia, and impaired swallowing may cause oligohydramnios [3,17].

To demonstrate a stated of decreased tone to confirm the presence of hypotonicity, an infant is suspended in prone position with the examiner's palm underneath the chest (horizontal suspension) [3]. Upon suspension in the examiner's palm, the infant will assume a 'U' posture as it will present with the inability to lift his/her head up and thus, will fall to create a 'U' [3,16]. The 'U' posture evidentially shows the weakness in the muscles in the neck region - the flaccidity in the muscle tone causing the infant to fall over the examiner's palm in such a distinctive manner. Another very characteristic sign that is seen in hypotonic infants upon examination is referred to as the 'scarf sign' [16]. The 'scarf sign' is performed by grasping the infant's hand while he/she is laying supine and pulling it across the chest as far as it will go without significant resistance [1]. In a normal infant, the muscle tone resists this maneuver and thus, the elbow can be brought to the midline of the baby's chin and chest, however, in the hypotonic infant, the elbow can easily be brought well beyond the midline before encountering resistance [1,18]. The 'scarf sign' test measures the appendicular tone in the shoulder and is somewhat sensitive to the gestational age of the infant, the degree of laxity of the ligaments and the state of alertness of the child.[1]The decreased muscle tone is also visible in something that is referred to as the 'pull to sit' [18]. The 'pull to sit' maneuver is performed by grasping the supine infant's hands and gently pulling them to a sitting position [1]. There would be an excessive head lag that would be evident in the 'pull to sit' maneuver [19]. The 'pull to sit' maneuver tests axial tone of the neck and back and appendicular tone of the shoulder and arms and also tests strength to some extent because the normal response from the infant being tests is to resist the pull on the arms and shoulder [1]. By the age of 3 months, there should be no head lag present [20]. The examiner will also go ahead and perform a test that is referred to as the vertical suspension test in which the examiner will pick up the infant by holding him/her under the arms. The hypotonic infant tends to slip through the examiner's hands, and the maneuver is a test of the appendicular tone but can also give some indication of head control (axial) as well as strength because the normal infant provides some resistance in the shoulders when being lifted [1]. Alongside all the physical examinations that occur to test the muscle tone of the infant, it is imperative that the examiner take a very extensive history that looks prenatal, natal and postnatal complications that may have been present [21].

Through this paper, we will be discussing the general categorization of the various causes of FIS and further focusing on specific syndromes within each of the categories. Figure 1 is a visual representation of the categorization of the expanded nature of what leads to the presentation of hypotonia - FIS - in an infant. Through extensive analysis of literature, this paper aims to present an accurate representation of the various causes of FIS while also looking into the possibility of treatment options, such as rehabilitation techniques.

Discussion

Before analyzing the various etiology's leading to the development of FIS, differentiation between central and peripheral causes of hypotonia needs to be established. Central causes, both acute and subacute, are more common than are peripheral disorders [3]. Acute

causes of FIS include perinatal hypoxia, sepsis, meningitis, birth trauma, intracranial hemorrhages, intoxication, drug withdrawal, inborn errors of metabolism and acquired metabolic disturbances of glucose, calcium and electrolytes [22]. Central hypotonia is generally the result of global brain dysfunction. In central hypotonia, the site of the lesion is typically above the original of the cranial nerve nuclei or anterior horn cells - such as in the brain, brainstem or the spinal cord [20]. The key to appropriately differentiate between whether the cause of hypotonia in FIS is due to a central or peripheral cause is by conducting a proper neurological examination. Infants who do not track visually, fail to imitate facial gestures, or appear lethargic are more likely to have cerebral causes [17]. Clues of central hypotonia would be history of brain insult, seizures, dysmorphic features, abnormal head size, persistence of primitive reflexes and normal or increased reflexes [20]. Most cases of neonatal hypotonia are of central origin [17]. Central hypotonia does not worsen with time, although if static it may become increasingly apparent when compared with tone in healthy children [3,20,23]. Peripheral causes of hypotonia, on the other hand, include abnormalities in the motor unit, peripheral nerve, neuromuscular junction and muscle, cranial nerve nuclei, or anterior horn cell [20,23].

Whether it be a central cause of hypotonia or a peripheral, it is immensely important that a proper history has been obtained. Furthermore, the conduction of appropriate examinations, such as the neurological examination, would need to occur in order for the cause of hypotonia to be confirmed. If the hypotonic infant is alert, responds appropriately to his surroundings, and shows normal sleep-waking cycles, the hypotonia is most likely due to involvement of the peripheral nervous system or the spinal cord [17]. As mentioned earlier, there are specific signs that are looked for during the physical examination of the infant. Signs such as the 'pull and sit' maneuver, the 'vertical suspension' test, the 'U' posture and the 'scarf sign' all indicate hypotonicity in the infant. The flaccidity of the muscle tone is prevalent in these tests as the infant's muscles are unable to maintain resistance and rigidity that would be necessary to maintain posture, as seen in a normal infant. When it comes to investigating for peripheral hypotonia, the characteristic features that would allow localization of the problem to the motor unit would be the absence of features of central hypotonia, the absence of reflexes and convincing weakness [1]. This suggests that the investigation of hypotonia in an infant focus on examining for a central cause for the hypotonia. Once it has been determined that there is no central cause for hypotonia, an investigation is conducted, evaluating the presence of any peripheral causes, thus, the confirmation of a peripheral hypotonia is based on the diagnosis of exclusion. Overall, despite the cause of hypotonia being central or peripheral, the underlying physical examination signs that are being looked for are similar.

Genetic/chromosomal syndromes

Because majority of the causes that lead to FIS are genetic or chromosomal in origin, there is the possibility of going through with genetic testing in order to understand whether or not the infant would present with the underlying cause that could eventually lead to FIS. Vast majority of the genetic/chromosomal syndromes that ultimately cause FIS as a symptom, can be tested for through karyotype testing, FMR1 test or Array CGH [3]. An analysis of three clinical series showed that chromosomal disorders accounted for 31% of the elucidated diagnosis (CNS anomalies were present in 13%, myopathies in 5%, congenital myotonic dystrophy in 4%, spinal muscular atrophy in 2%, muscular dystrophy in 2% and inborn errors of metabolism in 3%) [24]. Chromosomal and genetic disorders are the largest contributors to the production of floppy infant syndrome and because of their inheritance pattern, some of these disorders may also be seen in other members of the family as well. As mentioned previously, chromosomal and genetic syndromes tend to cause central hypotonia.

As mentioned previously, there is a vast array of chromosomal and genetic syndromes that lead to the development of floppy infant syndrome. Figure 2 represents a small demographic of chromosomal, genetic and metabolic syndromes that lead to the causation of hypotonia in an infant - FIS. It should be noted that there are more syndromes than mentioned in figure 2 for the sake of simplicity, our focus will be on determining the underlying pathophysiology in each of the syndromes portrayed in figure 2 that lead to the development of FIS in an infant. Aneuploidy, microdeletions and sub-telomeric cryptic deletions can present with hypotonia as a prominent feature in early life [2].

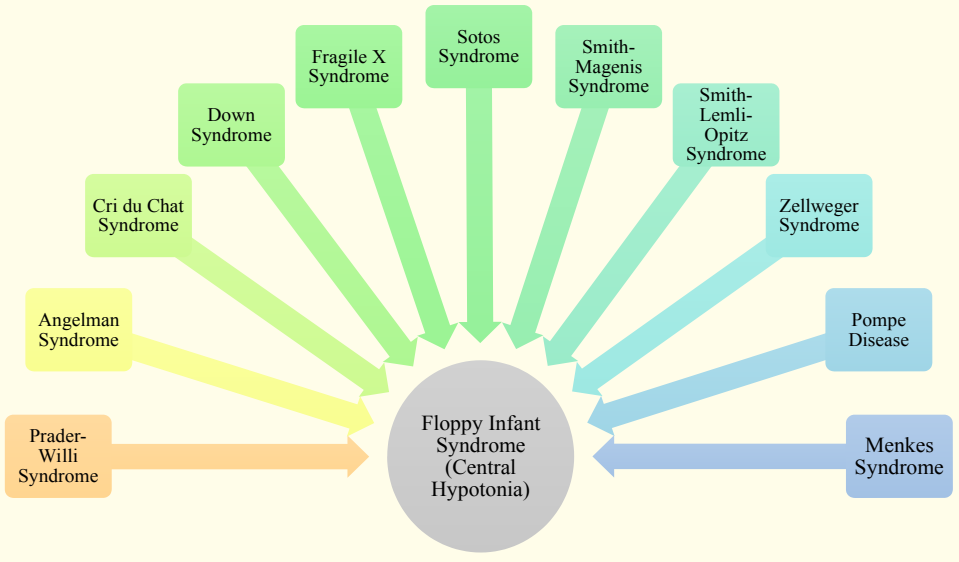

Figure 2: *Introduction to chromosomal/genetic syndromes leading to hypotonia in an infant.*

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is one of the more common causes of severe neonatal hypotonia as it is seen in 1:15,000 newborns [25]. PWS is defined as an imprinting genetic disorder characterized by lack of expression of genes on the paternal chromosome 15q11-q13 region [26]. Majority of PWS cases occur sporadically; however, familial inheritance of PWS has been described frequently, which was referred to as a grand matrilineal inheritance [27]. Deletions account for 70 - 80% of cases, most of which are due to interstitial deletions [28]. The majority of imprinted genes in this region are involved in both RNA and protein processing of neuro-regulators and hormones at the brain level [26]. Infantile hypotonia caused by PWS is a universal finding, causing decreased movement and lethargy with decreased spontaneous arousal, weak cry and poor reflexes, including a poor suck [29]. Children with Prader-Willi syndrome tend to have delayed motor milestones but are generally able to reach ambulatory independence [30]. Towards the first year, hyperphagia appears, resulting in a very significant weight gain with a compulsion to satisfy its food needs [31]. PWS is a syndrome that effects both sexes equally and presents with similar signs such as short stature, hypogonadism, cognitive impairment, and hyperphagia with subsequent obesity [32]. The significant weight gain predisposes the individual for other complications such as diabetes mellitus, dyslipidemia, cardiovascular and respiratory complications but the early onset of obesity explains the morbidity and mortality of these patients [31]. Those diagnosed with Prader-Willi syndrome tend to present with behavioural problems as well such as stubbornness, temper tantrums and obsessive-compulsive behavior. Hypotonia seen in PWS will usually manifest as decreased fetal movements, abnormal fetal position at delivery and increased incidence of assisted delivery or caesarean section, associated with a tendency for intrauterine growth retardation [17,32].

Figure 3 represents the pathogenesis of PWS starting from the microdeletion of the paternal 15q11-13 region, leading to the infant having two copies of the maternal chromosome 15. The imprinting genetic disorders leads to a variety of systemic abnormalities. Disruptions in the hypothalamic pathways leads to the presence of central hypotonia which is visible through reduced muscle movements and poor reflexes, weak cry, etc. The presence of infantile hypotonia results in a delay in the motor milestones and the average age of sitting is 12 months and walking is 24 months [33,34]. Furthermore, the hypotonia present in infancy will be much more severe than in adult form, where the hypotonia become more mild. The reduced muscle movements result in a reduced energy expenditure that leads to the obesity that is already occurring due to the increased ghrelin secretion. The increased ghrelin secretion occurs due to reduced satiety control. The increased secretion of ghrelin is why these individuals require strict dietary supervision because an imbalanced diet would result

in an earlier onset of weight gain. The obesity is central in distribution with relative sparing of the distal extremities and even subjects who are not overweight, tend to deposit fat on the abdomen, buttocks and thighs [34]. Furthermore, the disruptions of the hypothalamic pathways result in a decreased secretion of the growth hormone releasing hormone from the hypothalamus that results in a decreased growth hormone secretion from the pituitary gland. The decreased growth hormone secretion results into the short stature presentation in PWS individuals. Birth weight and length are usually within normal limits, but short stature, if not apparent in childhood, is almost always present by the second half of the second decade associated with lack of a pubertal growth spurt [33]. There is also an abnormal level of sex hormones in the notion that there are variable combinations of normal or low luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin B. The abnormal combination of these sex hormones results in gonadal hypoplasia, delayed puberty and infertility, specifically in men.

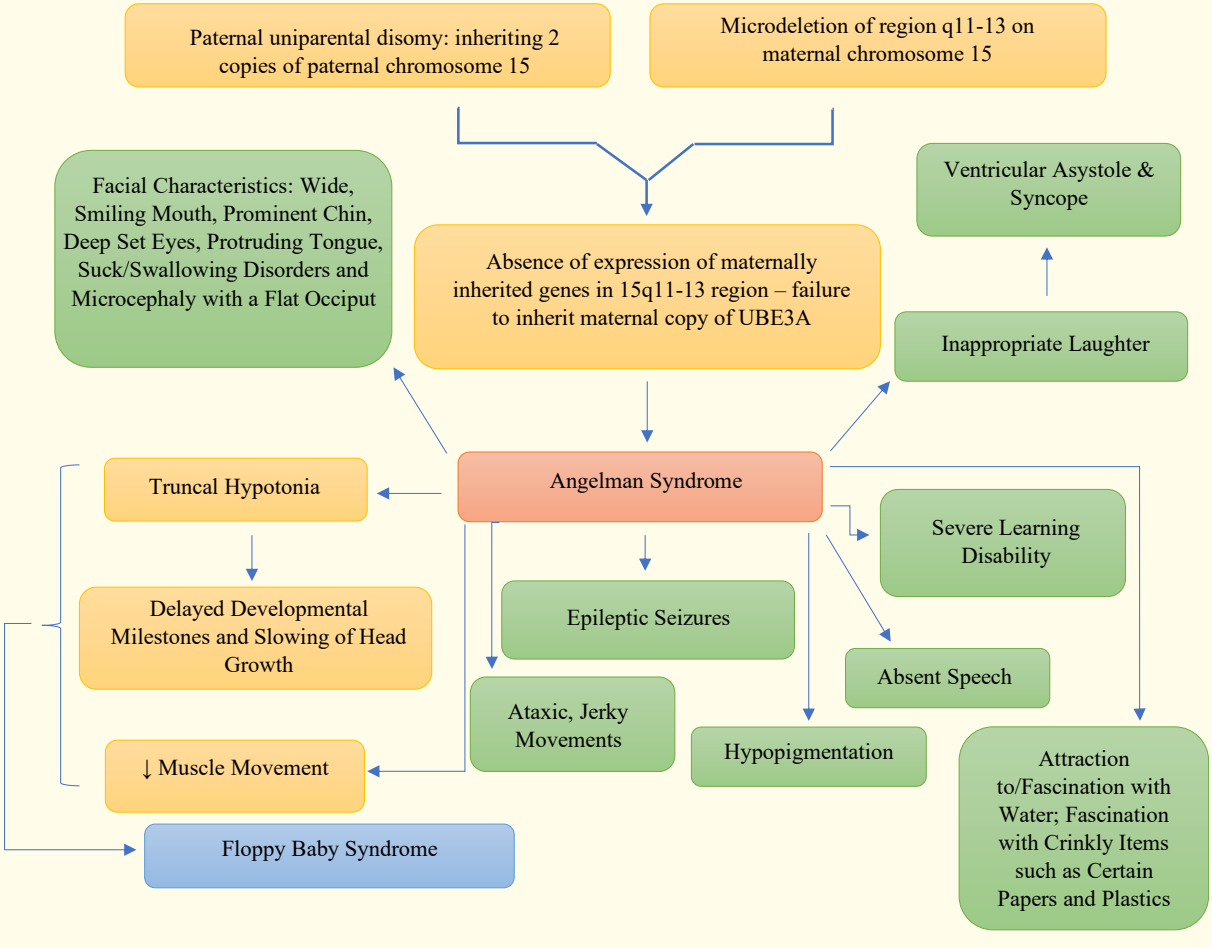

Figure 3: *Pathogenesis and clinical findings of Prader-Willi syndrome.*

Hypogonadism presents differently in males and females. It is manifested as cryptorchidism, scrotal hypoplasia (small hypopigmented, and poorly rugated) and sometimes a small penis in males, and by hypoplasia of the labia minor and clitoris in females [34]. As presented in figure 4, the hypogonadism is hypothalamic in origin and gonadotrophins, oestrogen and testosterone are generally deficient [35]. Alongside hypogonadism, there is also abnormal puberty development. While pubic and axillary hair may develop early or normally, the remainder of pubertal development is delayed and usually incomplete [34]. Figure 3 also depicts the behavioral issues, developmental

delay and mental retardation that presents in varying degrees amongst individuals. Individuals with PWS also present with distinct facial characteristics such as almond shaped palpebral fissures, narrow nasal bridge, thin upper lip, downturned mouth and narrow bifrontal diameter.

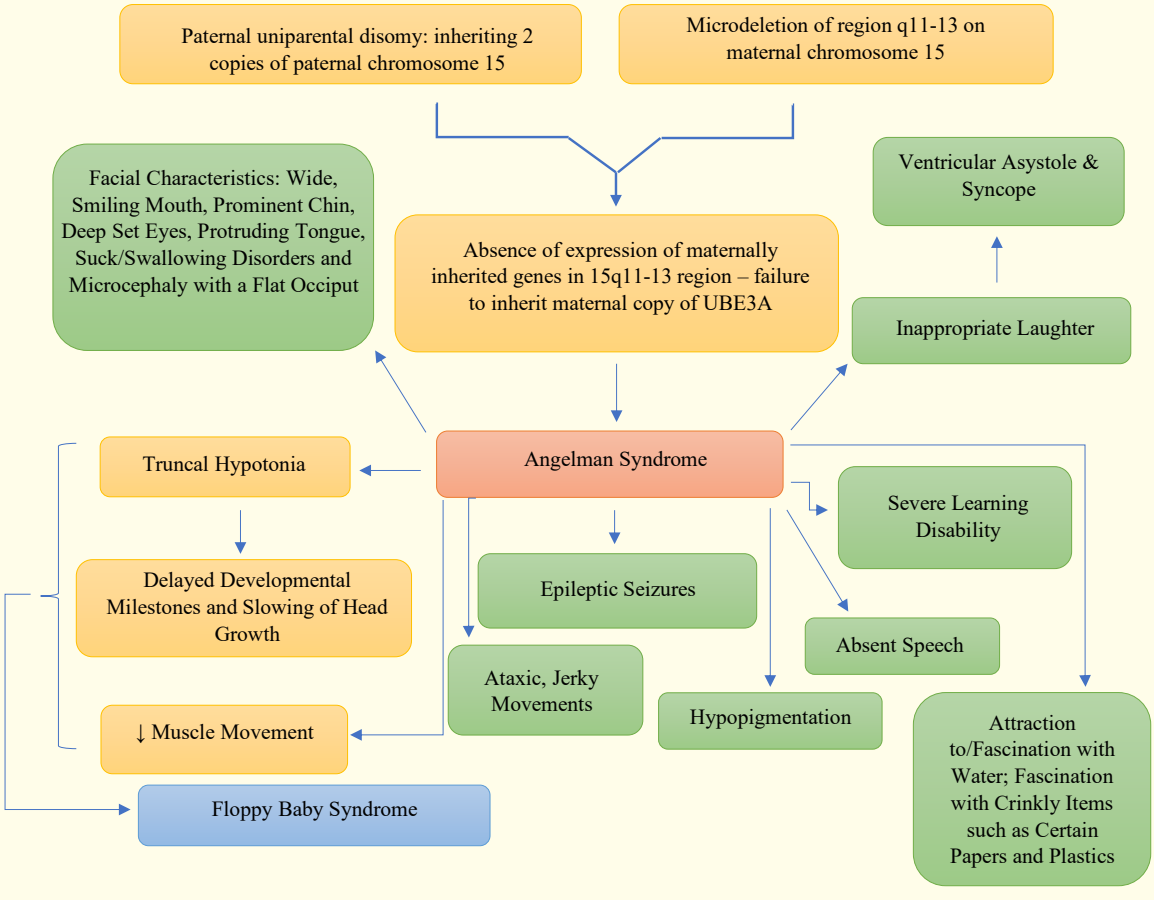

Figure 4: *Pathogenesis and clinical findings of Angelman syndrome.*

Treatment of PWS is multi-systemic. Generally, after the first year of life, strict dietary supervision and physical activity plans should be initiated to reduced cardiovascular and respiratory disorders that are the leading causes of death [31]. The treatment for PWS becomes one that is focused on hormonal therapy, specifically growth hormone. Results of growth hormone treatment improve growth, increase lean body mass and reduce fat mass and there is also some evidence of improvements in respiratory function and physical activity [36]. Since the pituitary gland and the gonads are normal but the problem is under stimulation, treatment with pituitary gonadal hormones can improve secondary sex characteristics [35]. Currently, there is no cure for Prader-Willi syndrome, but several of the problems associated with the condition, as mentioned above, can be managed effectively if treatment is started early [36,37].

Angelman syndrome

Prader-Willi syndrome was associated with the lack of expression of genes on the paternal chromosome 15 q11.2-11.3. Angelman syndrome is the exact opposite in the sense that it is associated with the lack of expression of genes on the maternal chromosome 15 q11.2-11.3. Angelman syndrome was originally known as the 'happy puppet' syndrome due to the inappropriate laughter of patients [38]. The known genetic causes of Angelman Syndrome (AS) are maternal deletion of chromosome 15q11-q13, paternal chromosome

15 uniparental disomy (UPD), UBE3A mutation and an abnormality of the imprinting process, termed imprinting defect [39]. The most common genetic mechanism giving rise to Angelman Syndrome, occurring in approximately 70 - 75% of patients, is an interstitial deletion of chromosome 15q11-q13 region and most of these deletions occur de novo and are of maternal origin in contrast to the 15q11-q13 deletions observed in Prader-Willi syndrome which are of paternal origin [40]. The common deletion can be detected by FISH analysis and by methylation analysis therefore, in the presence of a maternal deletion, only the paternal unmethylated pattern will be detectable [38]. In general, those with deletion have a more severe phenotype, and those with UPD and imprinting defects a less severe phenotype [41]. In most tissues, UBE3A appears to be expressed from both alleles but, in the brain, the paternally derived UBE3A gene is silenced, and only the maternally inherited copy is active [42,43]. The UBE3A deficiency impairs synapse formation and experience-dependent synapse remodelling [44].

The clinical features reported in patients with Angelman syndrome were severe learning disability, epileptic seizures, ataxia, absent speech, and dysmorphic facial features with a prominent chin, deep set eyes, wide mouth with protruding tongue and microcephaly with a flat occiput and were also hypopigmented with fair hair and blue eyes [38]. The behavioral characteristics of Angelman syndrome are striking and it is these which often prompt clinicians to consider the diagnosis [38,39]. There are bouts of laughter unrelated to context, mouthing objects, problems falling or staying asleep, feeding problems during infancy, motoric hyperactivity and inattention, and stereotypes such as hand-flapping or twirling [45]. Furthermore, hyperactivity and sleep disturbances are common in childhood and can pose major management problems for parents and guardians. Sleep disorders are present in 90% of patients at some stage but are more pronounced between the ages of 2 and 6 [39]. The main problem is represented by a reduced need for sleep, which children sleeping 5 - 6 hours per night on average [38,39].

Figure 4 depicts the pathogenesis of Angelman syndrome. As mentioned earlier, the genetic causes leading to the cause of Angelman syndrome are uniparental disomy, imprinting defects and microdeletion of region q11-13 on maternal chromosome 15. Several researches suggest that the imprinting defects make the small minority of cases that lead to the diagnosis of Angelman syndrome and that UPD and microdeletion of region q11-13 leading to the failure to inherit maternal copy of UBE3A is much more common. As mentioned above, and illustrated by figure 4, Angelman syndrome presents with very peculiar and distinct physical and behavioural characteristics and it is these characteristics that ultimately lead the clinicians to consider Angelman syndrome as a diagnosis. Paroxysms of easily provoked laughter begin within the first few weeks of life and smile frequently [38]. The inappropriate laughter and extremely happy demeanor lead to the syndrome to previously be referred to as the "happy puppet syndrome" [46]. A study conducted by Vanagt., *et al*. (2005), concluded that the uncontrollable outbursts of laughter lead to recurrent episodes of ventricular asystole and syncope due to severe vagal hypertonia [47]. The administration of intravenous atropine, in this case, ensured that the laughing no longer induced asystole or syncope. The laughter in Angelman syndrome is usually provoked, but the stimulus is often minimal, and the laughter can be inappropriate [38]. The uncontrollable bouts of laughter are more prevalent in childhood and as the patient gets older, he/she tends to have fewer bouts of laughter [48]. The exact mechanism of what causes the uncontrollable bouts of laughter is not fully understood but there is some mentioning that the hyperactivity of the motor areas leads to the patient having frequent episodes of laughter. The bouts of laughter are one of the many distinct characteristics associated with Angelman syndrome. These patients also present with hyperactivity that is usually comorbid with sleep disturbances [38]. Individuals with Angelman syndrome may present with sleep/wake rhythm disorders, multiple nocturnal awakenings, or difficulties in falling asleep [49]. There is indication that these patients deal with reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid eye movement (REM) sleep and periodic leg movements [50]. A high proportion of children are reported to experience great difficulties in settling and falling asleep [51]. It has been hypothesized but not confirmed that this might be due to decreased production of melatonin, decreased expression of its receptors or other factors determining sensitivity to this hormone [52].

Another very peculiar and distinctive characteristic of patients with Angelman syndrome is their fascination with water and also have a fascination for reflective surfaces, places and balloons [38]. While this feature is characteristic for patients with Angelman syndrome, the exact mechanism causing these patients to be fascinated with water is unknown and there is also no working theory as to why this preference is prevalent.

Patients with Angelman syndrome also present with truncal hypotonia, that ultimately leads to the prevalence of floppy infant syndrome in these patients. On neurological examination, it is usual to find truncal hypotonia with limb hypertonia and brisk reflexes [53]. Infants with Angelman syndrome will present with global developmental delays, along with delayed head growth. The decreased muscle movements of the trunk are significant as, otherwise, hyperreflexia is prevalent. On examination, infants with Angelman syndrome do not control his/her head well, truncal hypotonia and strikingly uncoordinated and jerky upper limb movements A study conducted by Harting., *et al.* (2009) found that in the MRI of 5 patients examined during infancy revealed myelination delay and deficit of white matter [54]. This finding explains why many of the signs and symptoms, behavioral in nature, that are found in Angelman syndrome tend to diminish into adolescence or become minimal [55].

The type of epileptic seizures that occur vary from individual to individual. A study was conducted in 15 patients with Angelman syndrome by Viani., *et al.* (1995) and 7 patients had complex partial seizures with eye deviation and vomiting, 3 patients had both sporadic atypical absences and myoclonic-astatic seizures and the other types were generalized tonic-clonic seizures, infantile spasms and clonic unilateral seizures [56]. The seizure onset occurs between the ages of 3 months and 20 years, but onset in infant or early childhood is reported in most patients [56,57]. The first convulsive seizure that occurs in these individuals is often precipitated by a fever [56,58]. As presented earlier, Viani., *et al.* (1995), concluded that complex partial seizures with eye deviation and vomiting, possibly indicating occipital lobe region were estimated to occur quite frequently [56]. Most often, however, there is concomitant mild jerking, rhythmic or arrhythmic, typical of myoclonic status [56,59], however, the episodes of myoclonus after the age of 6 are rare [59]. While seizures are generally difficult to treat in infancy and early childhood, the severity of epilepsy shows marked attenuation later in childhood [57]. It is currently not known how many of the patients with Angelman syndrome continue to experience seizures as adults.

In Angelman syndrome, some of the children seem to have enough comprehension to be able to speak, but in even the highest functioning conversational speech does not appear. Clayton-Smith (1993) reported that a few individuals spoke one to three words and in a surgery of 47 individuals [53], Buntinx., *et al.* (1995) reported that 39% spoke up to four word; however, it was not noted if these words were used meaningfully [60]. Babies and young infants cry less often and have a decreased cooing or babbling [61]. The delay in speech development becomes more visible as the child becomes between 2 - 3 years of age. By the age of 3 years, children may start to point to body parts and indicate some of their needs by use of simple gestures, but they are much better at understanding commands [53,61]. The nonverbal language skills of children with Angelman syndrome vary greatly, with the most advanced individuals able to learn some sign language and to use such aids as picture-based communication boards [53].

There is no exact treatment related to Angelman syndrome, to date. The patient may be prescribed anti-epileptic drugs for the seizures that occur, but studies have noted that some in some patients, the seizures may occur refractory to medication. Physical, occupational and speech therapy may be initiated to allow the patients to be able to integrate into mainstream society.

Cri du Chat syndrome

Cri du Chat syndrome (CdCS) is a genetic disease resulting from a deletion of variable size occurring from the short arm of chromosome 5 (5p-) [62]. Cri du Chat syndrome is more commonly seen in women with a sex distribution of 2:1 (female:male). Cri du Chat syndrome is a genetic disease that results from a partial or a total deletion on the short arm of chromosome 5 [63]. The characteristic phenotype that is associated with Cri du Chat syndrome is due to the partial deletion of the short arm of chromosome 5 [64]. Patients with CdCS present with a cat-like cry at birth, which is usually considered diagnostic of this syndrome [65]. Cytogenetic studies have helped identify two regions, 5p15.3, which is responsible for the characteristic cry, and 5p15.2 which is responsible for the other major clinical findings [64]. Other additional features of Cri du Chat syndrome patients include the failure to thrive, hypotonia, microcephaly, hypertelorism, epicanthal folds and severe mental retardation [63,65]. The high-pitched cry that is similar to the meowing of a cat, usually disappears in the first years of life [66]. Most patients with a 5p deletion have de novo mutations [67]. Children with Cri du Chat syndrome present with other behaviorally distinct characteristics such as repetitive movements, obsessive attachment to objects, hypersensitivity to sensory stimuli, stubbornness and clumsiness and sometimes, even self-injurious behavior [68]. The clinical picture, severity and progression of

the disease vary depending on the region of the chromosome that is deleted and whether it is terminal interstitial [69]. The deletion will occur as random events during the formation of reproductive cells in early fetal development [64,68]. Around 80 - 90% of the cases of Cri du Chat syndrome are paternal in origin, which can arise from a chromosomal breakage during game formation [64].

Figure 5 presents a diagrammatic presentation of Cri du Chat syndrome. As mentioned earlier, the most characteristic finding is a high-pitched, monotonous cry, which normally disappears within the first few months of life [64]. The characteristic cry can be attributed to the anatomical alteration of the laryngeal morphology which may be a result of a small, floppy epiglottis, hypoplasia of the larynx, narrow or diamond-shaped larynx or an abnormal airspace in the posterior area during phonation [62,64]. Newborn also exhibit low birthweight and microcephaly as well asphyxia, muscle hypotonia and impaired suction which ultimately leads to impaired growth and development during the first few years of life [64,66]. As the infant gets older, the presentation of some of the features might change. The hypotonia that ultimately leads to floppy infant syndrome in the neonatal age, will be replaced with hypertonia [64]. Furthermore, moon face presentation changes into a narrower vertical face in adulthood [66]. The exact mechanism as to why the presentation for some of these features change is not fully known. The change from floppy infant syndrome with hypotonia causes a delay in development that is prevalent through delayed milestones. Once the infant has reached the milestones and the growth is no longer as impaired, it can be postulated that the hypotonia becomes altered and presents as hypertonia.

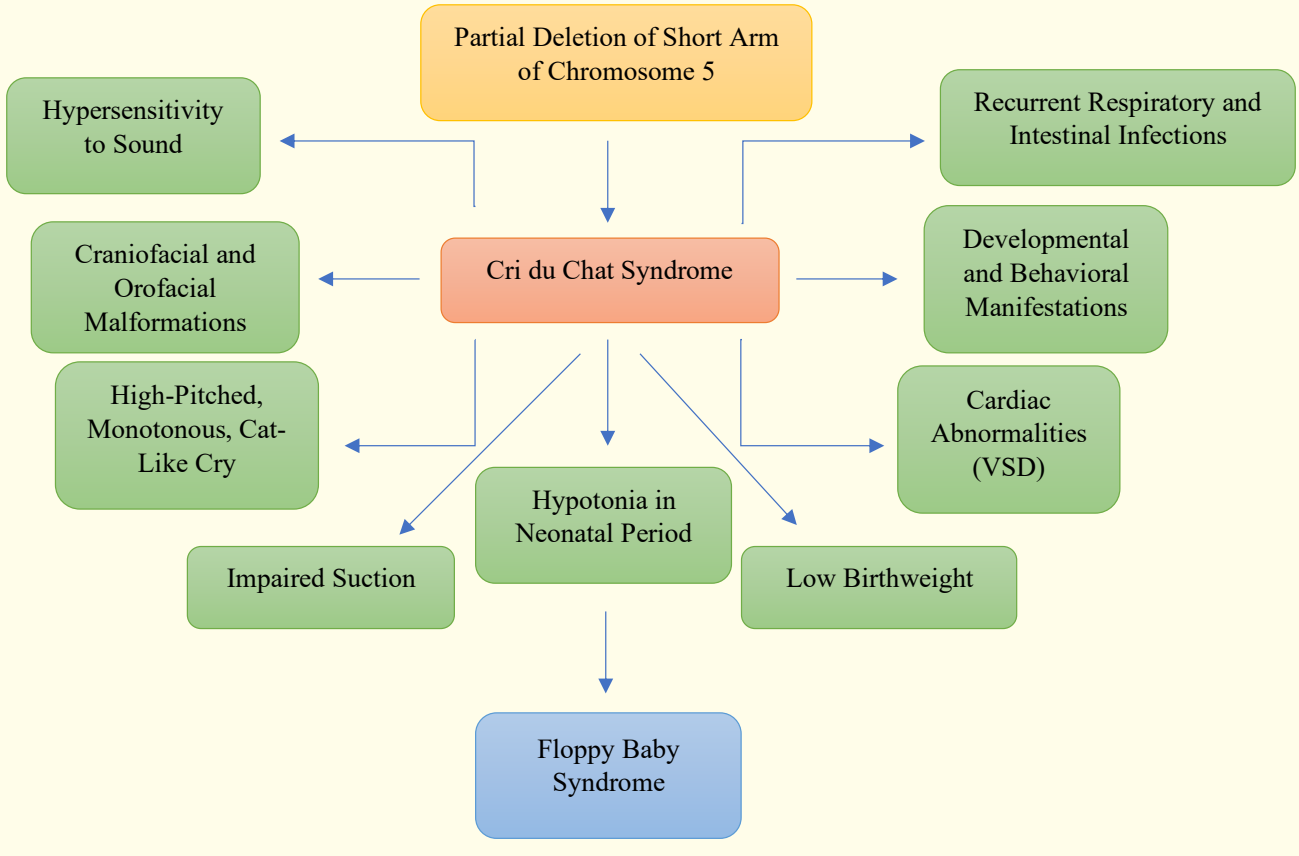

Figure 5: *Pathogenesis and clinical findings of Cri du Chat syndrome.*

As presented in table 1, Ajitkumar (2019) postulated a list of general characteristics that can be seen in an infant with Cri du Chat Syndrome [64]. Presentation of these general characteristics is variable and depends largely on the size of the deletion of the 5p; the larger the deletion, the more of these findings will be present as opposed to a smaller deletion being associated with only a handful of these characteristics.

Craniofacial and Orofacial Malformations	Developmental and Behavioral Modifications	Other Anomalies
• Microcephaly • Moon face • Hypertelorism • Large nasal bridge • Short philtrum • Premature gray hair • Downturned corners of the mouth • High palate • Hypoplasia of the enamel • Chronic periodontitis • Mandibular micro-retrognathia	• Hyperactivity • Self-injurious behavior • Repetitive movements • Obsessive attachment to objects • Comprehension of speech is better than their ability to express or communicate	• Hypersensitivity to sound • Cardiac disorders including congenital heart defects • Cutaneous hemangioma • Renal pathology

Table 1: *General characteristics of Cri du Chat syndrome in the neonatal period.*

There is no specific treatment for patients due to the early onset of damage during the embryonal development [69]. During the neonatal period, physical therapy should be started in the first week of life to help with any difficulty in swallowing and suction and to ensure that breastfeeding is still possible [69]. Physical therapy, psychomotricity, and speech therapy are suggested for psychomotor and speech retardation [64]. Genetic counselling should also be offered for subsequent pregnancies [62]. The management of Cri du Chat syndrome through therapy is important and the family should also be actively involved and in order for them to do so, the parents of these patients should be provided with appropriate information in regard to the disease.

Down syndrome

Down syndrome (DS) is the set of physical, mental, and functional abnormalities that result from trisomy 21, the presence in the genome of three rather than the normal two chromosomes 21 [70]. Down syndrome is the most commonly identified genetic form of mental retardation and the leading cause of specific birth defects and medical conditions [71]. With the discovery that down syndrome was caused by trisomy 21, there was the subsequent proposal that chromosome 21 band q22 was 'pathogenic' for DS [72]. A rare form of DS is due to de novo Robertsonian translocation t(14q;21q) demonstrated maternal origin of the extra chromosome 21q in all cases [73]. In the translocation, only part of chromosome 21 is present in triplicate [72,74]. Down syndrome can also be caused due to nondisjunction, the more common cause of trisomy 21. Chromosomal nondisjunction reflects a malfunction in cell division through which the paired chromosomes that normally separate into different daughter cells during meiosis fail to divide properly, so that each daughter cell receives either two chromosomes or none [74]. In this case, the cells that receive no chromosome at all, will usually die. The cells that receive both be chromosomes, present with a trisomy. Trisomy 21, Down syndrome, is known to be the most common human trisomy seen in live births and this could be attributed to the notion that chromosome 21 is the smallest human chromosome [73,74].

Figure 6 provides a visual representation of the pathogenesis and clinical findings that are associated with Down syndrome. The overexpression of the genes on chromosome 21 and lead to very multi-focal defects and malformations. In a study conducted by Laursen (1976) concluded that the most common cardiac anomaly, ventricular septal defect, was found in 49% of the 80 cases studied while the

second most frequently encountered anomaly, common atrioventricular canal was found in 15% of the cases [75]. 5% of individuals with Down syndrome manifest various gastrointestinal defects, such as those illustrated in figure 7 [76]. Duodenal atresia/stenosis, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300- times more frequently, respectively, in patients with DS than in the general population [77]. Furthermore, greater joint range of motion, presumably attributable to ligamentous laxity [78], delayed development of postural reactions and myelination [79], low muscle tone [80] and congenital defects [81] have been hypothesized as major contributors to delayed motor skill development that is seen in individuals with Down syndrome. Infants with DS have presented with delayed development of walking that could be attributed to pelvic and hip instability, particularly excessive degrees of thigh abduction having also been documented [82]. The increased laxity in the muscle tone and the decreased muscle resistance to passive movement is suggestive of floppy baby syndrome in these patients. The hypotonia in these individuals is also prevalent in the delay in the milestones being met. Patients with DS often have a short stature, obesity, infertility, epicanthus, oblique palpebral fissures, hypotonic tongue, shortening of the extremities (hands, feet, fingers, ears and nose) and a single palmar crease [83,84].

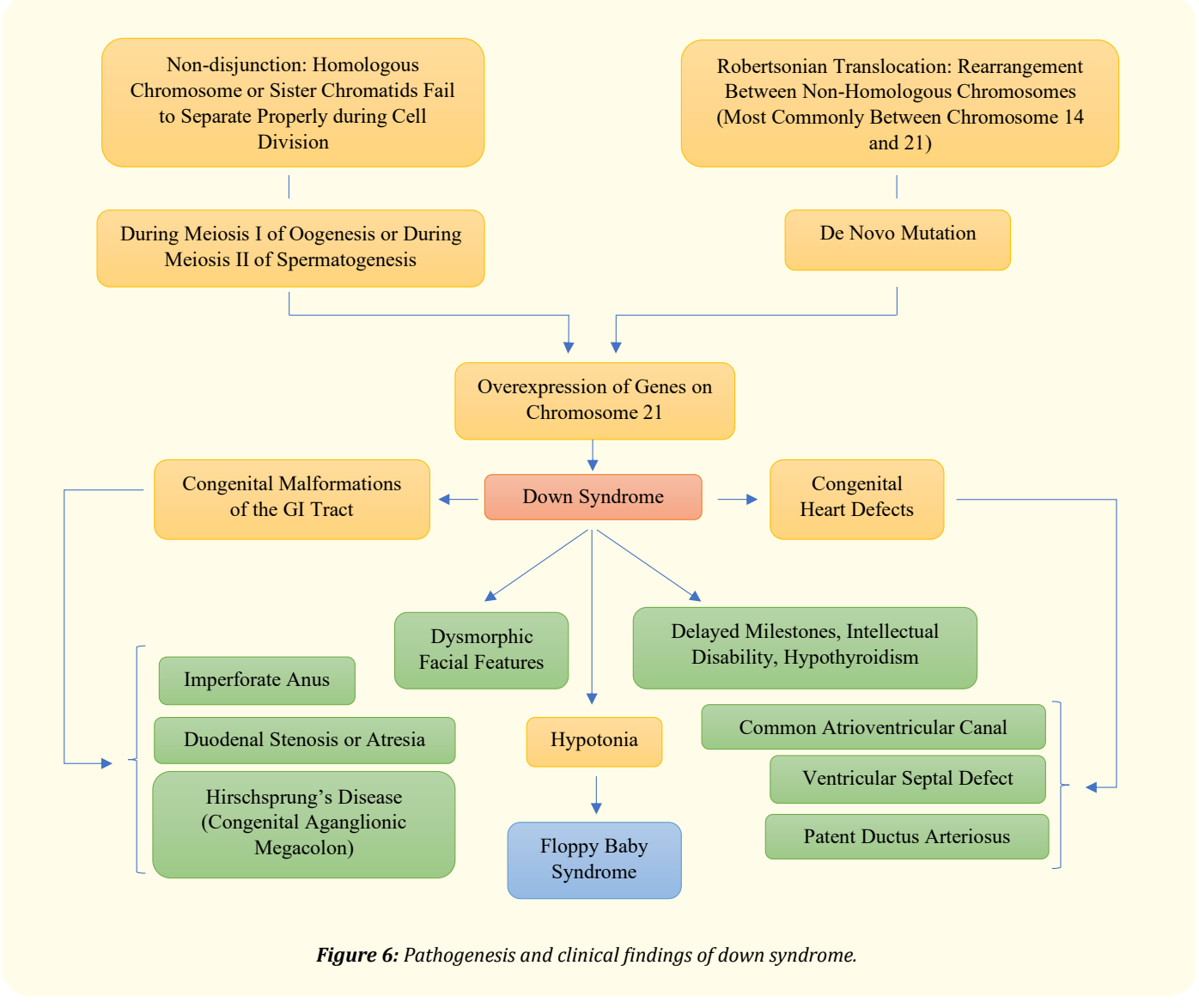

Figure 6: *Pathogenesis and clinical findings of down syndrome.*

Table 2 lists the facial features and the general characteristics that are often associated with Down syndrome. Alongside these characteristic phenotypical findings in patients with Down syndrome, it should be noted that there will be variability amongst the patients that present with these features. Some individuals may present with features that are much more prominent and visible and others may present with features that are more subtle. As mentioned in table 2 and mentioned earlier the presence of the generalized hypotonia ultimately presents as floppy baby syndrome in infants. The hypotonia persists as both milestone and developmental delays are present. Due to the hypotonia, the mean age of starting to walk is delayed by 6 months [85]. Due to DS being a chromosomal malfunction, there is no actual treatment for it, however, various types of therapy and management options are available to provide aid to these infants and allow for the maximum amount of appropriate integration into society. Individuals with DS tend to show relatively high levels of social and adaptive skills but very low levels of grammar and expressive language, as well as age- and task-related slowings as they older [86].

Dysmorphic facial features and general characteristics
• Single palmar crease (simian crease)
• Small, low set eats with overfolded upper helices
• Up-slanted palpebral fissures with epicanthal folds
• Brushfield spots
• Generalized hypotonia
• Short stature
• Brachycephaly
• Flattened nasal bridge
• Large protruding tongue
• Flattened occiput
• Abundant neck skin
• Mouth corners turned downwards
• Lack of Moro reflex
• Small teeth
• Cataracts
• Hearing loss

Table 2: *The facial and general characteristics associated with Down Syndrome*

DS requires constant ongoing assessment throughout childhood. Management and therapy of Down syndrome is a type that focuses on providing the necessary support to the individuals, along with the family as well. Children with Down syndrome have a higher risk of developing obesity and thus, the primary care provider can assist the family in preventing or managing obesity by recognizing the physiological and behavioral factors that place children and adolescents with Down syndrome at an increased risk to become obese [87]. Children with Down syndrome when intervened early by speech therapy, physiotherapy and occupational therapy and given proper medical attention for different health issues, can have a better long-term outcome as compared to other genetic causes of intellectual disability [88].

Fragile X syndrome

Fragile X syndrome (FXS), an X-linked dominant disorder with reduced penetrance, is associated with intellectual and emotional disabilities ranging from learning problems to mental retardation and mood instability to autism [89]. Although both males and females could be affected, Fragile X syndrome is more commonly more severe in males [90]. Majority of the cases of Fragile X syndrome are caused by the expansion to over 200 copies of a CGG repeat in the 5'-untranslated (UTR) region of FMR1 that shuts off transcription of the gene [89]. Everyone carries the FMR1 gene, which produces a protein that is important for brain development [91].

As systematically presented in figure 7, individuals who have the premutation, small expansion between 55-200 repeats, are carriers and are usually unaffected cognitively. When the premutation is carried by a female and passed to the next generation, it will usually expand to a full mutation (more than 200 CGG repeats) [91]. The full mutation is usually methylated within the promotor region, including the CGG repeat, and is typically associated with a lack of activity of the gene, such that little or no FMR1 protein (FMRP) is produced [89,91]. FMRP binds to specific mRNAs and has an important role in the regulation of protein synthesis at a local level in the dendrites of neurons [89]. A proposed role for FMRP at the synapse is that it is a negative regulator of protein synthesis stimulated by group 1 metabotropic glutamate receptor (mGluR) activation [91]. Fragile X syndrome, then, is at least partially a result of exaggerated responses to mGluR stimulation [89]. The testing procedure encompasses of PCR and a Southern blot. The PCR with primers flanking the repeat is used to determine the number of CGG repeats in the FMR1 5'-UTR and a Southern blot of genomic DNA is used to determine the methylation status and to gauge the size of full mutations, which are often resistant to PCR amplification [92]. The same testing approach can also be used to identify premutation carriers [89].

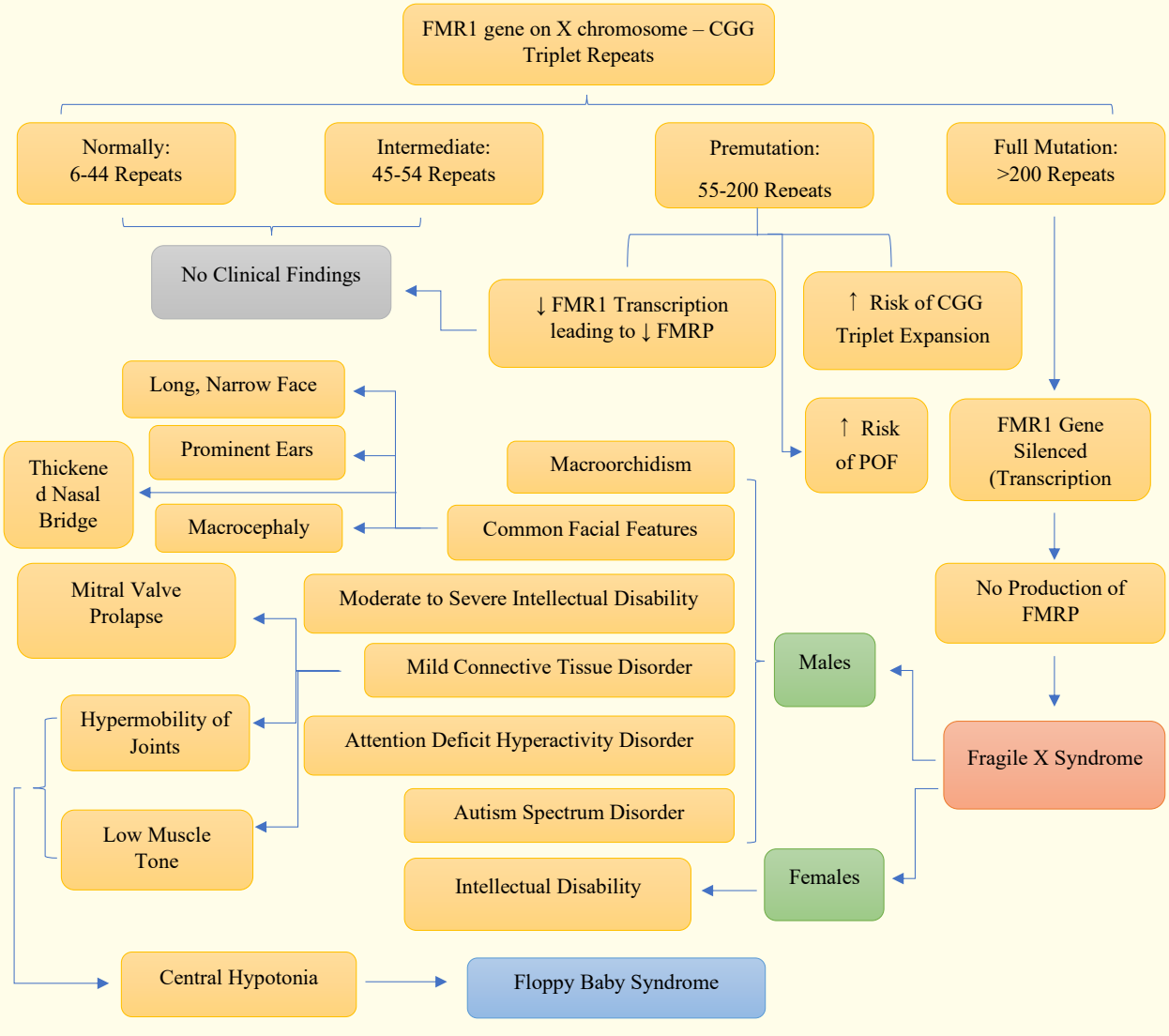

Figure 7: *Pathogenesis and clinical findings of Fragile X syndrome.*

Figure 7 presents with the pathogenesis of FXS. FXS will only cause alleles, or full mutations, when the FMR1 gene is silenced, causing the prevention of transcription. More than 200 copies of the repeat ultimately lead to the presence of clinical manifestations. As presented in figure 6, normal and intermediate repeats of CCG lead to zero clinical relevance. The risk of FXS occurring increases when there is a presence of unstable alleles. These unstable alleles that give rise to full mutations are referred to as permutations and as associated with phenotypes distinct from FXS [89]. In Fragile X syndrome, hypotonia in infants is mild and children who have FXS are usually not diagnosed early in life until a delay in developmental milestones is detected [3]. The hypotonia may also present with hypermobility of the finger joints and flat feet but both usually improve with age [91]. Because the disorder is X-linked, females are generally much more mildly affected than males, particularly in terms of cognitive functioning, but they tend to have a higher risk of emotional problems compared to the general population [93]. Females with full mutation the full mutation are prone to social anxiety, shyness, social avoidance, withdrawal, language deficits, mood lability and depression [91]. Furthermore, females with premutation have also been described to have social anxiety [94]. Approximately 20% of women who carry an FMR1 premutation have premature ovarian failure (POF), which is the premature cessation of menses before the age of 40 [95].

Fragile X syndrome can also lead to increase the risk of autism spectrum disorder or attention deficit hyperactivity disorder, especially in males. The autistic-like features that are commonly seen including hand flapping, hand biting, gaze avoidance, tactile defensiveness, and hyperarousal to sensory stimuli [96,97]. These autistic-like features - along with impaired social skills, such as soci-emotional reciprocity - are expressed with varying degrees in children with FXS and may be indicative of a concurrent diagnosis of autism spectrum disorder or autistic-like behavior [98]. Anxiety and mood disorders, hyperactivity, impulsivity, and aggressive behavior can also be present [92]. Macroorchidism, or enlarged testicles is apparently not only in adults but also in infants and fetuses with fragile X syndrome and this leads to a dysfunction of spermatogenesis at the chromosomal level [99]. Although the testicles are enlarged, fertility appears to be normal, for the most part [91]. The facial characteristics associated with FXS can be subtle and may become more apparent with increasing age [89]. The somewhat prominent ears may have cupping, and the ears may appear to be more prominent at the tips [91]. As individuals age, the face may become long and narrow and the jaw may become prominent after puberty [100]. Treatment for FXS tends to be symptomatic and focuses on providing aid relating to behavioral problems or treating the attention deficit hyperactivity disorder. Furthermore, support groups to be a form of treatment that provides information and aid to the families with FXS members [101].

Sotos syndrome

Sotos syndrome is an autosomal dominant condition characterised by a distinctive facial appearance, learning disability and overgrowth resulting in a tall stature and macrocephaly [102]. Sotos syndrome is a well-defined and relatively common overgrowth syndrome characterized by pre- and postnatal overgrowth, developmental delay and advanced bone age, and a typical facial gestalt including macrodolichocephaly with frontal bossing, frontoparietal sparseness of hair, apparent hypertelorism, downslanting palpebral fissures and facial flushing [103]. Mutations and deletions of the NSD1 gene (located on chromosome 5q35 and cording for a histone methyltransferase implicated in transcriptional regulation) are responsible for more than 75% of cases [104]. Miyake., *et al.* (2003), found that microdeletions in Sotos syndrome mostly occurred in the paternally derived chromosome 5 [105]. In the neonatal period, ~70% of babies with Sotos syndrome develop jaundice and/or have difficulty with feeding and the latter is in part because neonatal hypotonia is also very common, however, these neonatal problems are generally self-limiting and do not result in long-term problems [106]. Most individuals with Sotos syndrome are the result of de novo mutations [102]. Recently, deletions encompassing the nuclear receptor binding SET-Domain 1 (NSD1) gene have been described as the major cause of Japanese patients with Sotos syndrome, whereas point mutations have been identified in the majority of European Sotos syndrome patients [103]. There may also be the present of delay of early developmental milestones because of a child's large size, hypotonia and poor coordination [106], for example, walking until after age 15 months and speech until after 2.5 years [107]. Behavioral problems are also frequently reported [108].

Figure 8 illustrates the clinical manifestations associated with Sotos syndrome, following the mutations in the NSD1 gene in 5q35. Throughout childhood, the advance growth is particularly pronounced in the first year of life, after which it stabilizes with a height consistently above the 97th centile between age 2 and 6 years [104]. Most of the patients with Sotos syndrome have a non-progressive

neurological dysfunction manifested by clumsiness and poor coordination and there is also a delay in expressive language and motor development during the infancy is particularly common [104,109]. In neonatal period, many infants experience early feeding difficulties, variable degree of congenital hypotonia, jaundice by hyperbilirubinemia or hypoglycemia [109]. Although improving with age, the hypotonia resented in a delay of developmental milestones, such as starting to walk around 2 years of age [104]. The congenital hypotonia will ultimately present as FIS in the neonatal period, however, there will be a variable degree of hypotonia present from patient to patient. As mentioned in several studies, the hypotonia does improve with age and thus, FIS does not require any sort of intervention. Psychiatric manifestations, including social inhibition or psychosis have been noted, along with dilatation of the cerebral ventricles also common [110]. Other non-specific neurological abnormalities include absent corpus callosum, prominent cortical sulci, cavum septum pellucidum and cavum velum interposition [111]. There is also a variable degree of scoliosis present in about 30% of the NSD1-positive cases. The most common cardiac anomalies are septal defects and patent arterial duct [110]. Genitourinary anomalies including renal anatomical anomalies (bifid duplex or absent kidneys, vesico-ureteric reflux, pelvo-ureteric junction obstruction), cystic kidneys and genital anomalies such as hypospadias and cryptorchidism are present in 15% of children with NSD1 abnormalities [112]. Management of Sotos syndrome begins very early in the infant's life. In early childhood, programs including infant stimulation, occupational therapy, speech therapy, and adaptive physical education play a significant role in the nurturing of a child with Sotos [109,112].

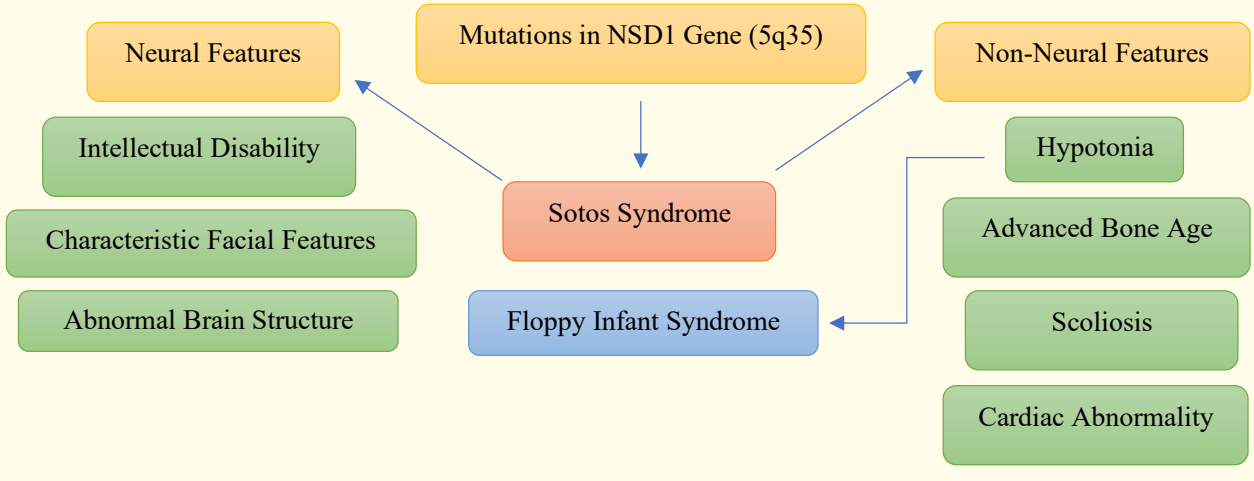

Figure 8: *Pathogenesis and clinical findings of Sotos syndrome.*

Smith-Magenis syndrome

Smith-Magenis syndrome (SMS) is a distinct and clinically recognizable multiple congenital anomaly (MCA) and mental retardation syndrome caused by an interstitial deletion of chromosome 17p11.2 [113]. SMS is generally a sporadic disorder caused by either a 17p11.2 deletion encompassing the retinoic acid-induced 1 (RAI1) gene or a mutation of RAI [114]. SMS is caused by haploinsufficiency of the retinoic acid-induced 1 (RAI1) gene on chromosome 17p11.2 [115]. The functional role of RAI1 is not completely understood, but it is likely involved in transcription, based on homology and preliminary studies [113,115]. The mutation of RAI1 causes the disorder to be characterized by variable mental retardation, sleep disturbance, craniofacial and skeletal anomalies, self-injurious and attention-seeking behaviors, and speech and motor delay [116].

Figure 9 provides a visual representation of the cause of SMS, along with the characteristic features present. Characteristic features of SMS are variable from individual to individual that is largely dependent on the size of the deletion or how extensive the mutation of the RAI1 gene. Abnormalities in 17p11.2 or RAI1 gene create a wide range of various symptoms and features that are very specific to SMS.

The neurological and behavioural symptoms range from sleep disturbances, speech delay, to more distinctive features such as onychotillomania or polyembolokoilamania. Hypotonia is also listed as one of the neurological/behavioral symptoms present in Smith-Magenis syndrome. Early infancy in SMS is complicated by feeding difficulties leading to failure to thrive, marked oral sensory motor dysfunction with poor suckling reflex, gastroesophageal reflux and hypotonia [117]. The infantile hypotonia present in SMS patients is accompanied by generalized lethargy and mimics Down syndrome and Prader-Willi syndrome phenotypes [113]. Patients with SMS also present with other neurological symptoms such as balance problems and a decreased sensitivity for pain, which is often observed in associated with the self-injurious behavior that is present in this disorder [118].

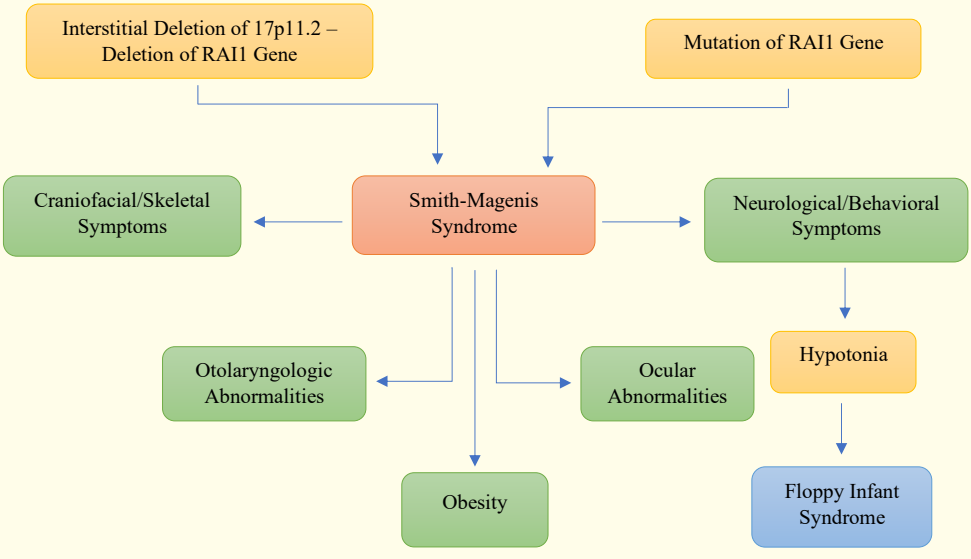

Figure 9: *Pathogenesis and clinical findings of Smith-Magenis syndrome.*

Table 3 depicts the various characteristic features that are present in SMS individuals. Table 3 is an expansion of the features illustrated in figure 10. Most SMS individuals tend to present with mild-to-moderate mental retardation with IQ ranging between 20 - 78, however, the IQ decreases as the child ages, ultimately placing the individual in the mild retardation range by adulthood [115]. Furthermore, sleep disturbances have been listed as one of the earliest diagnostic indicators of SMS with infants typically experiencing hypersomnolence during the first year of life [115,117]. As presented in table 3, the behavioral issues associated with SMS are one of the unique characteristic features of the syndrome [115]. Maladaptive behaviors are a cause of major concern and include frequent outbursts/temper tantrums, attention seeking, aggression, disobedience, distraction, and self-injurious behaviors [113]. Self-injurious behaviors, including head banging, skin picking, and wrist biting often begin at 15 - 18 months of age, while two features unique to SMS, onychotillomania (pulling out fingernails and toenails) and polyembolokoilamania (insertion of objects into bodily orifices) are more often seen in older children [113,119]. Stereotypical behaviors unique to SMS include the spasmodic upper body squeeze or 'self-hugging' and page-flipping, or 'lick and flip' behavior often seen in association with excitement [119]. Malformations observed by brain imaging include ventriculomegaly, enlarged cisterna magna, partial agenesis of cerebellar vermis, frontal lobe calcification and Joubert syndrome [120]. Similarly, MRI and PET studies on SMS patients have shown decreased gray matter in the insula and lenticular nucleus [121].

While there is no treatment of SMS, it is essential that there is an appropriate assessment of the degree of cognitive, developmental and behavioral deficits and severity of systemic/organ abnormality is essential for appropriate and specific management of SMS [115]. Early use of sign language as an adjunct to speech therapy is effective in overall speech development and also helps to decrease the child's frustrations associated with problems in expressive language, and thus, has a positive implication on behavior [118]. Behavioral therapies

include special education techniques; for example, children with SMS tend to do better in a calmer, smaller and more focused classroom setting [115]. Empirical evidence exists for the use of psychotropic medications (ex. thioridazine, carbamazepine, and serotonin-reuptake inhibitors) to increase attention, decrease hyperactivity and stabilize behavior, although no single regimen has shown consistent efficacy [118].

Craniofacial/Skeletal Abnormalities	Otolaryngologic Abnormalities	Neurological/Behavioral Abnormalities	Ocular Abnormalities
• Brachycephaly • Midface hypoplasia • Tented upper lip • Prognathism • Cleft lip/palate • Broad, square face • Brachydactyly • Short stature • Scoliosis	• Chronic ear infections • Hearing loss • Hoarse, deep voice	• Variable mental retardation • Speech delay • Motor delay • Hypotonia • Sleep disturbances • Self-hugging/hand wringing • Self-injurious behaviors • Onychotillomania • Polyembolokoilamania • Head banging/face slapping • Hand-biting/self-biting	• Myopia • Strabismus

Table 3: *Characteristic features prevalent in Smith-Magenis syndrome.*

Inborn metabolic errors

Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz (SLO) syndrome is a frequently occurring autosomal recessive developmental disorder characterized by facial dysmorphisms, mental retardation and multiple congenital anomalies [122]. Biochemically, Smith-Lemli-Opitz syndrome is caused by reduced/deficient activity of 7-dehydrocholesterol reductase (7-DHCR), the enzyme that catalyzes the reduction of C_7-C_8 (Δ7) double bond of 7-dehydrocholesterol to produced cholesterol - that is, the ultimate step of the cholesterol-biosynthetic pathway [123]. As a result, patients with SLO syndrome have low plasma cholesterol and elevated 7-dehydrocholesterol concentrations, a characteristic used for the diagnosis of the syndrome [122]. The link between this cholesterol-biosynthetic defect and the multiple developmental anomalies typical of SLO syndrome became clear after the recent discovery that cholesterol plays an essential role in animal embryonic development, in that it determines the spatial distribution of hedgehog proteins in the developing embryo by tethering their N-terminal signaling domain to the surface [122,124]. The mutations of the 7-dehydrocholesterol reductase (DHCR7) result in decreased cholesterol and increased dehydrocholesterol levels [125]. Some malformations associated with SLO syndrome are consistent with impaired sonic hedgehog (SHH) functioning as SHH plays an important role in pattern formation of central nervous system, facial structures and limbs [124,126]. Poor feeding and postnatal growth failure are frequent early manifestations of SLO syndrome, and many infants require placement of a gastrostomy tube for adequate nutritional support [125].

The clinical diagnosis of SLO syndrome is confirmed by finding elevated 7DHC in blood or tissues [123,125]. In addition to the physical manifestations that are peculiar to SLO syndrome, patients have a very distinct behavioral phenotype [127]. As infants, they can be irritable, lack interest in feeding and prefer not to be held [125]. Other children demonstrate various degrees of hyperactivity, self-injurious behavior, temperament deregulation and sleep. Most SLO children demonstrate autistic characteristics and many meet the diagnostic criteria for autism [128]. A fundamental issue regarding the treatment of SLO syndrome patients is to determine the extent to which the behavioral and learning problems in SLO are caused by developmental abnormalities versus the extent they are caused by the

biochemical defect present in the central nervous system [125]. Developmental problems are likely to be fixed deficits, however, deficits due to the biochemical disturbance may be amenable to therapy and for this reason, methods of treating the central nervous system sterol abnormality and the efficacy of such therapies need to be investigated [123,125].

Figure 10 illustrates the pathogenesis and clinical manifestations of Smith-Lemli-Opitz syndrome. The signs and symptoms that are associated with SLO syndrome are associated with the decrease of cholesterol and the increased concentration of 7DHC. The decreased synthesis of cholesterol causes multi-organ abnormalities and problems. Syndactyly of the second and third toes is the most common physical finding in SLO syndrome patients and its presents in a child with other malformations, growth failure, intellectual disability, behavioral problems or autistic characteristics should prompt testing for SLO syndrome [125]. Other abnormalities of the extremities that would be present in SLO syndrome are rhizomelia, postaxial polydactyly, single palmar crease, short, proximally placed thumbs, and retention of fetal pads. Figure 10 further illustrates the general characteristics such as developmental delay, growth retardation, failure to thrive and intellectual disability. The presence of hypotonia in SLO infants causes the rise of floppy infant syndrome in these infants and the lack of proper muscular tone, we see developmental delays along with growth retardation. The other craniofacial abnormalities that are present in SLO patients are broad and vary from individual to individual, depending on the severity of the syndrome.

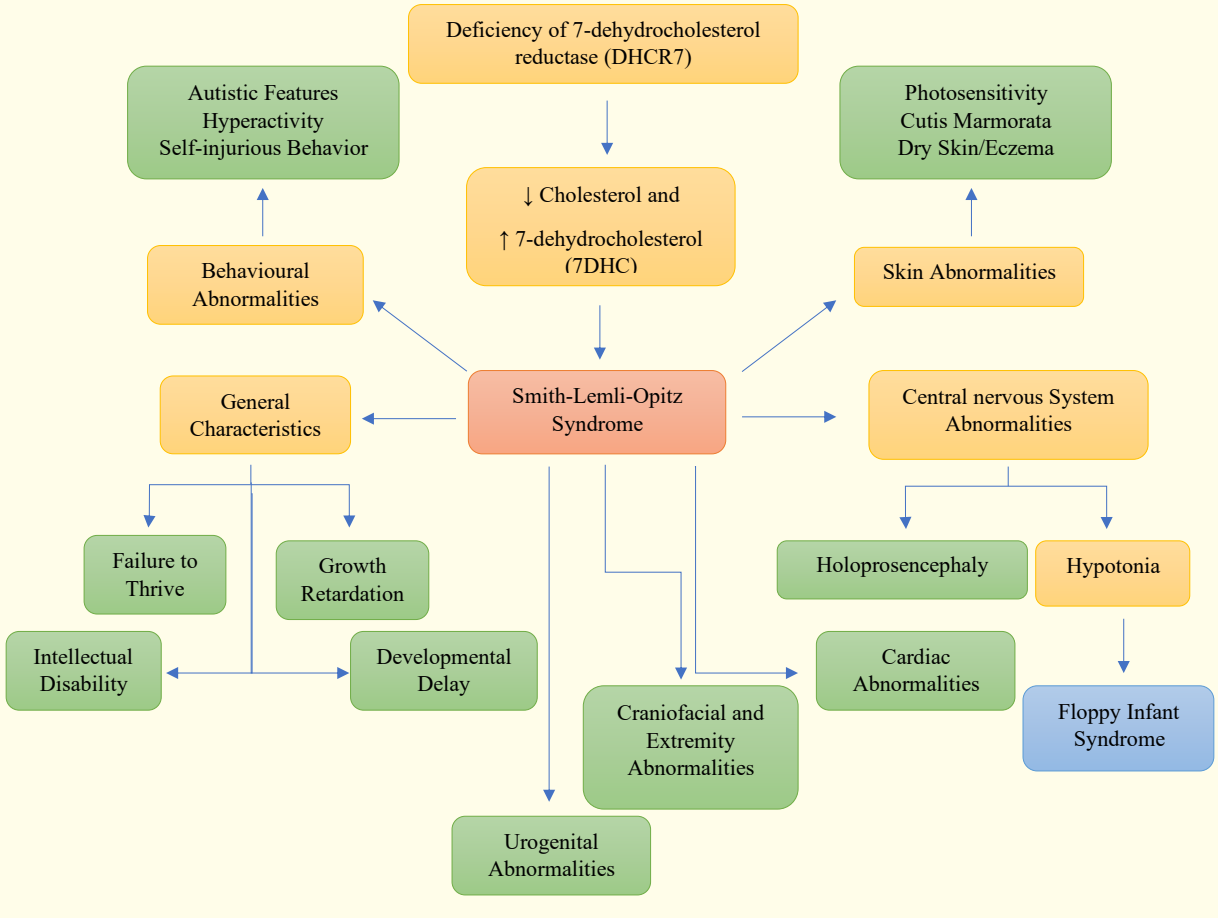

Figure 10: *Pathogenesis and clinical findings of Smith-Lemli-Opitz syndrome.*

Table 4 presents with a list of the various characteristic anomalies visible in Smith-Lemli-Opitz syndrome. In male SLO syndrome patients, genital abnormalities are quite frequent, and these range from small penis through various degrees of hypospadias in mild and classical cases to ambiguous genitalia (referred to as pseudo-hermaphroditism) or gender reversal in more severely affected infants [125,129]. More severely affected patients often have malformations of the brain (holoprosencephaly, agenesis/dysgenesis of the corpus callosum), heart (atrial and ventricular septal defects, patent ductus arteriosus and atrioventricular canal defect), along with some less common abnormalities, such as lungs (abnormal segmentation) or gastrointestinal anomalies (pyloric stenosis and colonic aganglionosis) [125]. A clinical suspicion of SLO syndrome is confirmed by demonstrating elevated 7DHC in plasma or tissue [130]. Currently, most SLO syndrome patients are treated with dietary cholesterol supplementation that can be achieved by including high cholesterol foods, such as egg yolks in a patient's diet, or using suspensions of pharmaceutical grade cholesterol [125]. Observational studies report improved growth, increased socialization, decreased irritability and aggression, increased alertness, decreased tactile defensiveness, decreased photosensitivity, decreased infections, improved hearing, and improved muscle tone and strength in SLO syndrome patients treated with cholesterol [131,132]. Administration of cholesterol supplementation has been indicated to improve muscle tone and improved muscle tone would eliminate the presence of floppy infant syndrome in infants with SLO. The major limitation of dietary cholesterol supplementation is that the cholesterol does not cross the blood-brain barrier and thus, cholesterol supplementation does not treat the biochemical defect in the brain [125]. Sterol analysis can be performed on either amniotic fluid or a chorionic villus sample [133].

Craniofacial and Extremity Abnormalities	Cardiac Anomalies	Urogenital Abnormalities
• Microcephaly • Metopic prominence and bitemporal narrowing ptosis • Broad nasal bridge • Anteverted nares • Micrognathia • Broad aveolar ridges • Cleft palate/Bifid uvula • Rhizomeila • Postaxial polydactyly • Single palmar creases • Short, proximally placed thumbs • Retention of fetal pads • Syndactyly of the second and third toes	• Atrial and ventricular septal defects • Patent ductus arteriosus • Atrioventricular canal • Hypertension	• Renal malformations • Hypospadias • Cryptorchidism • Ambiguous genitalia

Table 4: *Characteristic anomalies in Smith-Lemli-Opitz syndrome.*

Zellweger syndrome

Zellweger syndrome (ZS), also known as cerebrohepatorenal syndrome, is a fatal autosomal recessive disorder manifested in the neonatal period by profound hypotonia, psychomotor retardation, dysmorphic features and an enlarged liver [134]. Zellweger syndrome is a genetic disease characterized by the absence of peroxisomes and deficiency of glycerol - ether lipids in several tissues [135]. Biochemically, in patients with Zellweger syndrome, a mutation in one of the PEX genes coding for a peroxin (a peroxisome assembly protein) creates functionally incompetent organelles causing an accumulation of very long-chain fatty acids, among other complications [136]. Zellweger syndrome patients are characterized by the absence of functional peroxisomes and an almost complete disruption of peroxisomal beta-oxidation, leading to the accumulation of branched and very long-chain fatty acids, abnormal bile acids and leukotrienes [137]. The accumulation of branched and very long-chain fatty acids could lead to structural disruption of cell membranes, particularly in the central nervous system [138]. Increased level of leukotrienes due to beta-oxidation deficiency could precipitate an inflammatory

process that might be involved in the pathogenesis of brain defects [139,140]. Zellweger syndrome is caused by mutations in any one of about a dozen components of the peroxisome assembly machinery [143]. Neonatal epileptic seizures and floppy infant syndrome are two important symptoms that point to an involvement of defective GABAergic signaling in Zellweger syndrome pathogenesis [137]. Zellweger syndrome is a prototype for peroxisome biogenesis disorders in which the organelle is not correctly assembled, leading to multiple defects in peroxisome function [134]. These infants are readily recognized in early postnatal period by their characteristic dysmorphic facial features, profound generalized hypotonia, psychomotor delay and seizures, along with progressive dysfunction of the liver and central nervous system, culminating in death within the first year of life [141].

As illustrated in Figure 11, Zellweger syndrome is associated ocular abnormalities such as cloudy cornea, Brushfield's spots, cataracts, retinal degeneration and optic-nerve atrophy [142]. Zellweger syndrome is characterized by severe CNS involvement and classically, infants with Zellweger syndrome have profound muscular hypotonia; affected infants may have hyporeflexia or areflexia [134]. The severity of muscular hypotonia will lead to severe developmental and milestone delays. There may also be an absence of neonatal reflexes due to the severe hypotonia that results in floppy infant syndrome in these individuals [143]. The characteristic facial features of an infant with Zellweger syndrome consist of a high forehead, epicanthic folds and large fontanels, amongst the many other features [144]. Classical Zellweger syndrome is usually fatal in early life as no effective treatment is currently available [145]. As mentioned in figure 11, Zellweger syndrome is usually fatal; about 85% of the patients die in the first year of [144,145].

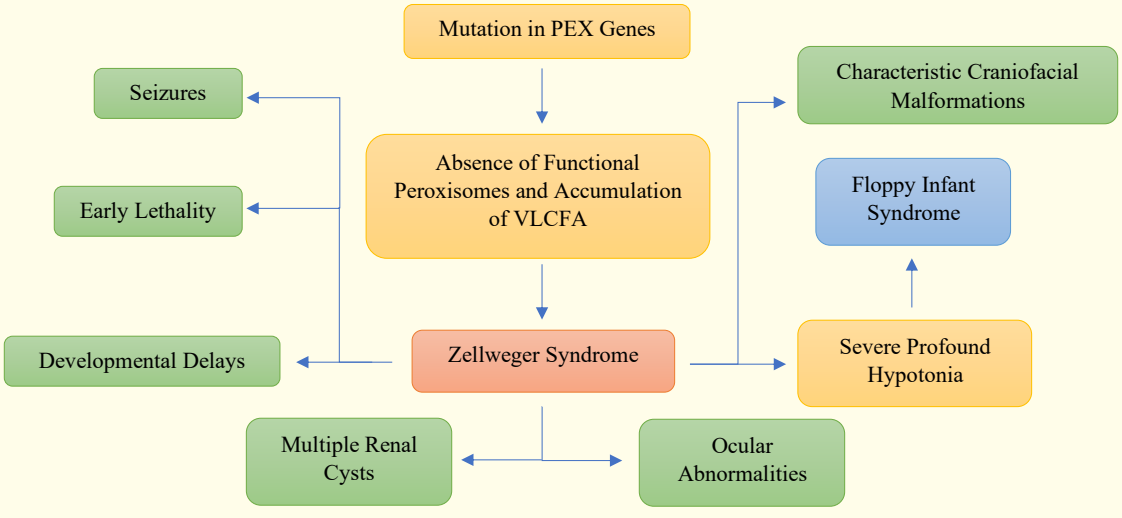

Figure 11: *Pathogenesis and clinical findings in Zellweger syndrome.*

Pompe disease

Pompe disease is an autosomal recessive lysosomal disease due to defect of acid alfa-glucosidase (GAA) deficiency [146]. Classic Pompe disease is infantile form with presents with prominent cardiomegaly, hepatomegaly, weakness and leads to death due to cardiorespiratory failure in the first year of life [147]. Pompe disease results from a lack of functional acid α-glucosidase (GAA), which is responsible for the breakdown of lysosomal glycogen to monosaccharides [148]. The lysosomal glycogen accumulates in striated muscle, resulting in the disruption of normal contractile capabilities [149]. There is a continuum of the disease that is associated with the levels of GAA activity - in the most severe form of the disease, there is little to no residual GAA activity [148,149]. Current treatment of Pompe disease relies on enzyme replacement therapy, where the deficient protein is infused every two weeks; this method has resulted in improved survival in subjects with early onset of disease [150]. For the purposes of this paper, the focus will be on classic Pompe disease, which is also referred to as the infantile form.

Figure 12 is a visual representation of the pathogenesis and the characteristic findings of the infantile form of Pompe disease. It should be noted that despite the variability of Pompe disease, all patients share the same general course, namely the steady accumulation of glycogen substrate in target tissues leading to progressive debilitation, organ failure and/or death; resulting in spectrum of disease severity [151]. The infantile form of Pompe disease exhibit a rapidly progressive disease characterized by death due to cardiorespiratory failure in the first year of life [152]. Because the presence of weakness and hypotonia, these infants will be slower to attain developmental milestones and have decreased weight gain [159]. The clinical picture of infantile onset of Pompe disease is dominated by cardiomyopathy, which is the consequence of glycogen storage in the heart [152]. Cardiac hypertrophy begins in utero and becomes significant in the first few months of life [151]. Conduction abnormalities, due to the interference of the glycogen storage with conducting tissues, produces tachyarrhythmia which can cause sudden death during infections, dehydration, anesthesia [146]. Early diagnosis of Pompe disease allows for prompt initiation of enzyme replacement therapy, which has been shown to decrease complications and prolong survival by decreasing glycogen accumulation in tissues, thereby preserving cardiac and skeletal muscle function [3].

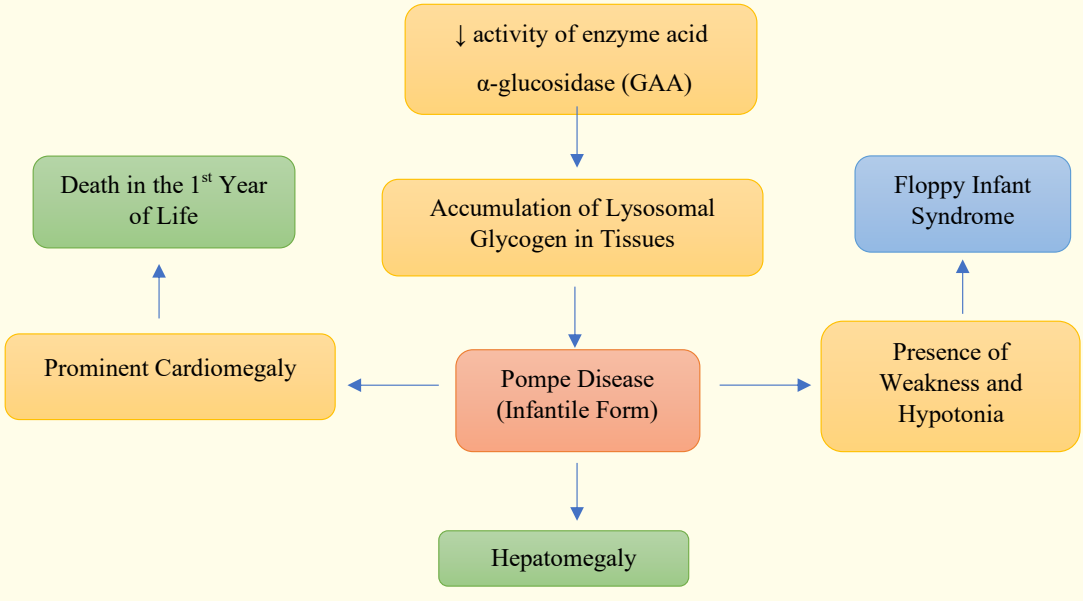

Figure 12: *Pathogenesis and clinical findings in Pompe disease.*

Menkes syndrome

Menkes disease, also known as 'kinky hair disease,' is an X-linked recessive genetic disorder of copper transport leading to a maldistribution of copper in the body [153]. As seen with other X-linked recessive disorders, Menkes syndrome is more commonly seen in males [154]. Menkes syndrome is a rare neurodegenerative disorder caused by mutations in the ATP7A gene such that direct sequencing of ATP7A gene revealed a de novo point mutation which resulted in an early stop codon with truncated protein [155]. ATP7A is an energy-dependent transmembrane protein, which is involved in the delivery of copper to the secreted copper enzymes and in the export of surplus copper from cells [154]. ATP7A gene is located on the long arm of the X chromosome between positions q13.2 and q13.3 and about one-third of the cases arise from de novo mutations [4]. Menkes syndrome belongs to a group of diseases that mainly affect the gray matter of the brain [156]. Menkes syndrome is characterized by a general copper deficiency with death occurring in early childhood, often by three years of age despite treatment of copper histidine supplementation [157]. Mutation in ATP7A gene results in a defective copper transport across the gastrointestinal tract, placenta and blood brain barrier and also causing a reduced activity of several copper dependent enzymes [157,158]. Characteristics of Menkes syndrome include hypothermia, neuronal degeneration, mental retardation

and abnormalities in hair, skin and connective tissue [159]. Abnormalities in connective tissue can present as weak muscular tone and thus presenting with varying degrees of hypotonia - leading to floppy infant syndrome. At around 3 months of age, infants with Menkes syndrome present with truncal hypotonia and progressive spasticity of the limbs with often marked failure to thrive [160]. In severe cases, there is progressive deterioration and death occurs usually by 3 years of age, however, in milder phenotypes, the infant may present with marked cerebellar ataxia and mild developmental delay around the age of 2 [161,162]. By ages 2 to 2.5 months, loss of motor skills and muscle tone, seizures and feeding difficulties manifest [160].

Figure 13 illustrates the clinical manifestations of Menkes syndrome. The most serious symptoms associated with Menkes syndrome are neuronal deterioration and arterial abnormalities [163]. Premature delivery is also very frequently seen amongst infants with Menkes syndrome and this is presumably because of a weakness of the membranes [162]. Patients with Menke syndrome are seldom diagnosed in the neonatal period because usually, these patients seem to be normal after then neonatal period until 2 - 3 months of age [163]. After 2 - 3 months, however, developmental delays may be witnessed, along with a loss of early developmental skills, hair abnormalities and hypotonia. As time progresses, neurological deterioration becomes increasingly more severe. Most patients are unable to smile, control their head or sit by themselves due to the hypotonic muscles, specifically truncal hypotonia. The pathological characteristic of Menkes syndrome is the hair abnormalities. There may be no visible hair but there is always a palpable stubble on the scalp [154,163]. The characteristic hair abnormalities are the first sign of Menkes syndrome as unusual sparse and lusterless scalp hair that becomes tangled on the top of the head at the age of 1 - 2 months [154]. Also around 1 - 2 months of age, the appearance of the infant is typically described as being unusual such as the infant may present with pale skin, frontal or occipital bossing, micrognathia, pudgy cheeks and a rather expressionless appearance, however, these changes tend to be very subtle and therefore, are not usually noticed as they first present [163]. The initial psychomotor skills in infants with Menkes syndrome are normal up to about 2 - 4 months of age, however, the infant ceases to develop further and gradually loses some of the previously developed skills but these regression of skills does not become obvious until the infant is about 5 - 6 months of age [154]. Muscular tone is also evidently decreased early in life but is later replaced by spasticity and weakness of the extremities and furthermore, as the motor dysfunction progresses and gets worse, spontaneous movements become limited and drowsiness and lethargy will emerge [154,163]. Patients may also present with skeletal changes such as, spontaneous fractures due to generalized osteoporosis and hyper extensive joints [154]. For the time being, Menkes syndrome does not have a corrective treatment however, very early copper-histidine treatment may correct some of the neurological symptoms [154,163].

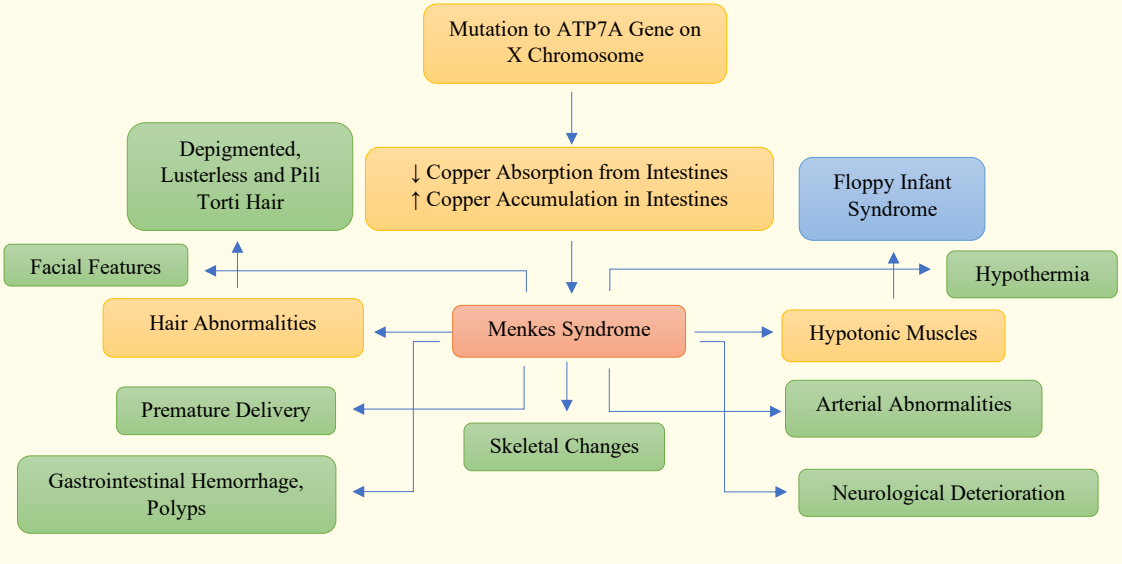

Figure 13: *Pathogenesis and clinical findings in Menke's syndrome.*

Conclusion

Through this paper, we intended to provide an insight on just a handful of the chromosomal disorders and the inborn metabolic errors that lead to the presentation of floppy infant syndrome. As mentioned throughout the paper, calculating the exact incidence of floppy infant syndrome due to the various causative agents proved to be a challenge due to the vast majority of syndromes that ultimately lead to varying degrees of hypotonia amongst infants. Syndromes that create central hypotonia, such as chromosomal and genetic disorders, also present with variable degrees of mental retardation and peculiar behavioral characteristics that are present very early in life as well. The diagnosis of many of these syndromes proves to be as diagnosing floppy infant syndrome encompasses understanding the underlying cause of the level of hypotonia in the individual as well. As many of these syndromes are associated with gene mutations or microdeletions of regions on different chromosomes, providing an exact treatment is rare. Instead of attempting to find a treatment for hypotonia, the focus turns to providing adequate management and therapy to both the affected individual and the family that is specific and focused to the underlying cause of the hypotonia and therefore, management and therapy even between different syndromes varies. Because the symptoms and clinical manifestations between, for example, Cri du Chat syndrome and Fragile X syndrome are considerably different, the management and therapy provided would also be very different. There are other causes of hypotonia amongst infants that could manifest as floppy infant syndrome and some of these other varying causes are anterior horn cell disorders, neuromuscular junction disorders and these types of disorders present with a more peripheral cause of hypotonia and present much different as compared to the central causes of hypotonia as presented in this paper. Despite the underlying cause of central hypotonia, the physical examination conducted by clinicians encompasses checking for signs such as the 'U' posture or checking for a positive 'scarf sign.' Once the hypotonia has been checked for, more specific tests can be conducted to come to exact causation of floppy infant syndrome. Rehabilitation and therapy are crucial in early life of the infant dealing with floppy infant syndrome to attempt to ensure that developmental milestones are occurring at the proper age and to ensure that the infant is provided with the appropriate skills that allow appropriate integration into society. The term floppy infant syndrome, sometimes called rag doll syndrome, is visible to varying degrees in many infants due to the vast nature of disorders leading to such a presentation and for that reason, it is imperative that clinicians and physicians are able to identify early signs of floppy infant syndrome and provide the appropriate intervention.

Conflict of Interest

The authors have no conflict of interest.

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