Early neurodevelopmental and medical profile in children with sex chromosome trisomies: Background for the prospective eXtraordinarY babies study to identify early risk factors and targets for intervention - Tartaglia et al

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Guide to reading this adaptation:
This is an adaptation of a research paper. It includes information pertaining to children and men with 47,XXY/Klinefelter Syndrome, and other sex chromosome trisomies. This is a shortened version of the original paper, edited for clarity, readability, and relevancy to the XXY community. Page numbers noted in this adaptation correspond to the research paper.

Abstract:
1 in every 500 births will have a sex chromosome trisomy (SCT). Klinefelter Syndrome (KS) is considered one of these SCTs. This review discusses what's currently known about "neurodevelopmental, behavioral, and medical manifestations in young children with SCT" [p.1]. The focus of this review includes:

- Risks of neurodevelopmental disorders
- Medical and endocrine manifestations of SCT

With the rise of prenatal diagnosis of SCT, there's more chance to study children born in recent years to better understand KS. The eXtraordinarY Babies study will:

- Describe historical SCT conditions
- Identify how to predict positive and negative outcomes for SCT children
- Evaluate developmental screenings
- Evaluate autism screening measures
- Build data to help future generations improve health and neurodevelopmental outcomes

Introduction:
SCT is a common diagnosis, with the rate of diagnosis increasing in recent years. SCT is the most common chromosomal abnormality, with XXY/Klinefelter Syndrome occurring in 1 in 600 male births. In the past, less than 10% of SCT was diagnosed before the child reached adolescence. This rate is increasing significantly due to prenatal screenings. Universal screening for newborns is being considered for future practice. In some newborn screening pilot programs, SCTs are being identified where it might previously have been missed. As the rates of SCTs rise due to the increased availability and use of prenatal and postnatal screening, there's a need for further research to help understand the phenotypic variability (the way each child is impacted by

the extra chromosomes), increased morbidities (symptoms of SCT), and how to best treat SCT for positive outcomes.

This review summarizes what's currently known about neurodevelopmental, behavioral, and medical manifestations in children with SCT to help guide care in their early years, and point out areas where further research is needed. Research from the 1970s to the 1990s is included to lay the foundation for what's currently known about SCT, followed by advances in the field. Finally, the eXtraordinarY Babies Study is introduced, which aims to study infants with a prenatal diagnosis of SCT.

Early longitudinal and cross-sectional studies

The majority of knowledge about children with SCT is from infancy and childhood. These studies took place from the 1970s to the 1990s, and followed a group of infants born with SCT into adulthood. The study included infants with SCT identified through prenatal screening, who were followed by seven sites in the United States, Canada, and Europe. When the studies took place, genetic testing was expensive, and reserved for individuals severely impacted by chromosomal abnormalities. The descriptions in these studies lean towards the children who were most significantly affected by their SCT.

Research advances since the newborn screening studies

Since the 1970s, researchers have included children recruited from advocacy groups, and clinical settings. This group (cohort) includes children diagnosed with SCT prenatally, and diagnosed in childhood. Childhood diagnoses were made after the child exhibited developmental delays, pubertal or gonad failure (lack of puberty occurring naturally), or other medical concerns. This created ascertainment bias in these studies, meaning more data was collected from one population than the other. For example, all of the data wasn't gathered from children prenatally diagnosed, but also from those diagnosed later in life. However, this bias has been recognized, and the data from the studies about SCT is still useful. Some of the discoveries made about SCT/KS children show:

- Increased insulin resistance
- Decreased bone health
- Cardio-metabolic disorders
- XXY infants have less testosterone during their mini-puberty at ages 2-4 months
- Androgen (testosterone) treatment in KS children and adolescents can help minimize the impact of some symptoms
- Advances in fertility treatments make it more possible for KS men to have biological children through sperm retrieval

Increases of neurodevelopmental problems such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) have been noted, which weren't found during

the initial studies. Additionally, the environment in which a child with SCT is raised can have an impact on their overall development.

Genetic studies have looked into the heights of children with SCTs, the penile length and pubertal development of XXY males, language abilities for XXY, and autism symptoms. Studies are looking specifically at how genes are altered in children with SCT, indicating more research is needed to better understand how to provide medical and neurodevelopmental support.

The studies attempt to address the differences between data gathered from children diagnosed prenatally, as opposed to those diagnosed after birth. Generally, children diagnosed postnatally with SCT are discovered because of a developmental delay, which means they might have more severe phenotypes (symptoms). This can make it seem as though all children with SCT will experience more severe symptoms, which is not the case. Since there are no available long-term studies focusing on just children diagnosed prenatally, this is a limitation when understanding data, and the symptoms children with SCT can expect throughout their lifetimes. This can be a challenge during genetic counseling, as counselors need to explain ascertaining bias in order to help parents understand SCT symptoms are a spectrum, and will vary in severity by each child.

The Extraordinary Babies Study:
This study was designed to follow infants diagnosed prenatally with SCTs, following their neuro and physical development from birth through the first few years of life. It'll also study their quality of life, and parents' experience. The study is being conducted at the University of Colorado/Children's Hospital Colorado, and Nemours-Dupont Hospital for Children. Children aged 2-12 months with a prenatal diagnosis of SCT are enrolled, and the study aims to describe and compare the natural history of a child with SCT. Refer to page one of this guide for goals of the study.

Participants in the study are seen for visits at 2, 6, and 12 months, and then annually. Data is collected at each visit, including historical, developmental, psychological, and physical examination data, as well as biological samples.

The study's goal is to produce predictors of the child's development (phenotypical outcomes) for age 3. They'll also study immediate and long term outcomes, and plan to follow the group through adolescence and into adulthood. 160 infants have been enrolled, with a goal of 200 during the study's current funding period (2017-2022). Following the study, data without identification of the participants will be shared with the "NIH/NICHD Newborn Screening Translational Research Network Longitudinal Pediatric Data Repository (NBSTRN LPDR) per NIH data sharing guidelines" [p.4]. Study results will be shared in presentations, with families, in peer-reviewed publications, electronically, and through social media "as the cohort reaches key timepoints in development" [p.4].

Neurodevelopment in early childhood in SCT:
There are several risks for symptoms associated with SCT that can appear throughout a child's life. Some of these risks include:

- Cognitive, language, and learning disabilities
- Attention and executive function difficulties
- Internalizing and externalizing behavioral and psychological disorders

The focus in this paper will be on unanswered questions, research findings about children ages 3-5, and neurodevelopmental disorders that can present during this time. It will look at language impairment, ASD, and motor skills deficits.

Language impairment and early social cognition:

Over 75% of children with SCTs participate in speech therapy. They're at increased risk for mild delays in language milestones, and may experience challenges with expressive language skills. Common diagnoses include Expressive language disorder and Receptive-Expressive language disorder. These diagnoses help children qualify for speech therapy. A 2018 study indicated that while there's a higher rate of language difficulties amongst children ages 5-16, one third of those children had no language impairment at all.

Other studies reported children with SCT might have delays in phonological processing (how children simplify adult speech to better understand it), oromotor skills (coordination, strength, and movement of the mouth, jaw, and muscles), articulation, and motor planning of speech [p.5]. It's important for speech therapists to identify exactly where the issues are, and how they can assist each child. Speech therapy is an important component of early intervention, as language deficits can lead to scholastic, behavioral, and social problems.

Studies have also found children with SCTs who have extra X chromosomes (such as XXY) seem to struggle with social cognition, meaning they have difficulty understanding how to pick up on cues that help them socially communicate. They can struggle interpreting social situations, reading facial expressions, and understanding tone of voice [p.6].

Autism spectrum disorder:
Results from ASD evaluations at two clinical sites showed "5%-10% of boys with XXY and up to 38% of boys with XYY in these samples met criteria for ASD" [p.6]. These rates are higher than for typical XY boys in the United States. A long term study is needed to further discover why these rates are higher, and help identify ASD predictors.

Motor deficits:

Children with SCT are at increased risk for motor delays and deficits in motor coordination, endurance, and strength. There's a lower deficiency in XYY as opposed to XXY, suggesting androgen (testosterone) deficiency can play a role in motor delays.

Neurodevelopmental disorders beyond early childhood in SCT—Learning disabilities, executive dysfunction/ADHD, and emotional disorders:
While neurodevelopmental disorders can arise in early childhood, they can also appear later in life. These disorders include "increased risk for cognitive problems and learning disabilities, including dyslexia and disorders of written expression," [p.7]. Attention problems and ADHD rates are higher in KS groups, as opposed to the general population. "Children with SCT also have increased risk for difficulties with executive function, including initiation, planning, organization, working memory, and cognitive flexibility," [p.7]. This can make things more difficult for children academically, and personally. They may be at increased risk for depression, anxiety, and mood disorders.

MEDICAL AND ENDOCRINE MANIFESTATIONS OF SCT:
Overview of testicular and ovarian function and cardiometabolic health in SCT:
The atypical sex chromosomes impact the development of a boy with KS' gonads (testes). Boys with XXY/KS don't produce normal amounts of testosterone, and require testosterone replacement therapy. As sperm production is impaired, there can be issues with fertility. Gonadal function is important to observe in infants for physical, and neurodevelopmental function. This is important to follow into adulthood, as men with XXY are at significantly higher risk for metabolic syndrome. Reports are also finding cardiometabolic disorders (insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, etc). Boys with XXY/KS are noted to have "low inhibin B, a hormone reflecting testicular function in prepubertal boys" [p.7].

Testicular function in infants with XXY:
One of the major symptoms of XXY is a lack of testicular function, which can lead to hypogonadism. However, there's limited research into the testicular function of infants and adolescents. All infants go through what's referred to as a mini-puberty in the first months of life. In studies of mice, there's been some evidence that including testosterone during this early mini-puberty can help physical and cognitive development. In humans, there's been less than 100 XXY infants studied who've gone through a mini-puberty. The largest of these studies indicated testosterone levels "fell below the median in 83% of XXY infants," [p.8]. There's been increased interest in treating infants with XXY with testosterone during the mini-puberty phase.

A study following infants given testosterone during the mini-puberty phase showed decreased body fat, as opposed to other XXY boys who didn't receive the testosterone. They also had longer penile length, and no serious adverse effects from the treatment were noted. The

eXtraordinarY Baby study will continue to explore whether motor function contributes to body fat accumulation, looking at if XXY children may have more body fat due to delayed motor function. It'll also explore if poor testicular function can contribute to body composition later in life.

Improved cognitive outcomes were indicated in children who received testosterone during the mini-puberty, as opposed to those who didn't. However, the study that indicated this did not have a blind group, or a group who did not receive the shot, nor did it test androgen (testosterone) levels prior to administering the treatment. More studies are needed to determine if the early treatment is effective.

Hormonal and genetic research considerations
It's thought "that hormonal treatments are unlikely to normalize neurodevelopmental and brain function in XXY," [p.9]. This is because there are hundreds of other genes that can impact how the brain develops and functions, not just the ones associated with the child's SCT. As the number of sex chromosomes impacted increases, so do the errors caused by the extra chromosomes.

Congenital malformations and other health problems:
SCT conditions including KS have "increased risk for other congenital malformations and medical diagnoses," [p.10]. Some of these risks include:

- Congenital cardiac and renal malformations
- Allergies
- Autoimmunity
- Eosinophilic esophagitis
- Dental problems
- Velopharyngeal insufficiency
- Elbow abnormalities
- Hypotonia (low muscle tone)
- Pes planus (flat feet)
- Tremors and seizure activity
- White matter MRI abnormalities

XXY has been associated with increased rates "of hernias, venous thrombosis, and certain malignancies such as germ cell tumors" [p.10].

CONSIDERATIONS OF NEWBORN SCREENING FOR SCT:
Newborn screening for SCTs may provide "opportunity for interventions to improve long-term outcomes" [p.10]. Recent research shows possible benefits of early hormone therapy in infants and children with XXY/KS, as it might allow for disease modifying early intervention. Some

argue SCTs shouldn't qualify for early screening due to the wide array of how children are impacted. They recommend delays should be observed before making a diagnosis.

There are also concerns that by knowing about their child's SCT before or from birth, the relationships parents have with their child may be impacted. Parents may have less expectations of their child, and the child's self-identity may be negatively impacted by being aware of the possible symptoms of their SCT. On the other hand, one could argue that by being aware of the diagnosis from birth, parents can be more prepared to raise their child, and better offer interventions and support.

CONCLUSIONS AND FUTURE DIRECTIONS:

The goal of the eXtraordinarY Babies Study is to help improve upon care for children with SCTs by utilizing past research, and answering new questions about the health, development, and care of a child with SCT. The results of the study will be utilized along with previous research to help "inform genetic counseling, guide considerations for newborn screening, improve care recommendations, and to identify targets for intervention trials" [p.11]. With ongoing research, there's hope for "improved quality of life for individuals with all types of sex chromosome disorders" [p.11].