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22q11.2 duplication syndrome: A rare chromosomal disorder with variable phenotypical and clinical presentations

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Introduction:

The chromosome 22q11.2 region has been implicated in multiple genomic syndromes, including DiGeorge or Velocardiofacial syndrome, der(22)t(11;22)syndrome, and cat-eye syndrome. These syndromes share a region of overlap containing copies of chromosome 22-specific low copy repeats (LCRs). Eight different LCRs are in proximal 22q. They are presumed to predispose to homologous recombination events and mediate nonallelic homologous recombinations that result in rearrangements of 22q11 due to unequal meiotic crossover.[1] 22q11.2 Duplication Syndrome has a frequency of 1/700 in the intellectually disabled population. Given that approximately 6.5 million people have an intellectual disability in the United States, there are suspected to be roughly 9,285 cases of 22q11.2 Duplication Syndrome.[2] However, just over 60 individuals have been described with 22q11.2 Duplication Syndrome.[3] This discrepancy may be due to the wide phenotypical variety of 22q11.2 duplications, potentially leading to misdiagnosis or no diagnosis.[4]

In this case report with literature review, we describe the clinical course of a 2-year-old female with 22q11.2 Duplication Syndrome inherited from phenotypically healthy parents.

Case Report and Review Results:

The patient is a two-year-old Caucasian female with a medical history of global developmental delay, including an inability to crawl and walk until age one and two, respectively, a two-week stay in the neonatal intensive care unit (NICU), and previous hospitalization for salmonella gastroenteritis. Family history is negative for infant or childhood death, congenital disabilities, or known genetic conditions. She presented to the emergency department (ED) with altered mental status, a shuffling gait, and tongue protrusion. Complete blood count (CBC), complete metabolic panel (CMP), toxicology screen, arterial blood gas, and erythrocyte sedimentation rate were within normal limits. Ammonia, lactic acid, acetaminophen, and salicylate levels were also within normal limits. An electrocardiogram (ECG) showed no acute abnormalities, and COVID-19 and influenza tests were negative.

She was seen by a neurologist who noted left-sided ptosis on the physical exam, with the remaining cranial nerves intact. Her gait was challenging to assess due to poor cooperation, but the neurologic exam was otherwise normal. The patient was admitted to the inpatient service for further monitoring and testing.

Electroencephalogram (EEG) showed no seizure activity or abnormal sleep-wake patterns. Magnetic resonance imaging (MRI) of the brain showed evidence of overall volume loss (greater on the left than on the right), a small left hippocampus, ex vacuo dilation of the lateral ventricles, prominent extra-axial fluid and sulci, and a thin corpus callosum. No mass effects were seen. The brainstem and cerebellum appeared normal, and the basal cisterns were patent. There was no evidence of intracranial enhancement.

After day two of admission, she was discharged in stable condition with diagnoses of

global developmental delay, altered mental status, a probable seizure with associated Todd's paralysis, and possible new-onset epilepsy. The patient's mother was instructed to follow up with a geneticist in one month for further testing. A physical exam by the medical geneticist one month later revealed torticollis, dolichocephaly, down-slanting palpebral fissures, bilateral ptosis (worse on the left compared to the right), broad first digits of the hands and feet, nail hypoplasia of the first, second, and third digits of the feet, a tall and broad forehead, relative macrocephaly in the 95th percentile, left-sided facial droop, generalized hypotonia with an open-mouth posture, and keratosis pilaris. Chromosomal analysis via FISH revealed a 22q11.2 duplication.

Three months later, the patient presented to the ED following a seizure. Her mother described a tonic-clonic seizure lasting less than five minutes with urinary incontinence, transient left-sided paralysis, left-sided facial droop, and slurring of words. The mother added that she had a fever of 101.9 degrees Fahrenheit that improved with acetaminophen and did not recur before the seizure. The mother denied further symptoms. She was admitted for further testing and monitoring. An EEG for two days revealed no abnormalities. Laboratory studies during admission, including CBC and CMP, were also unremarkable. The patient was discharged in stable condition with instructions to follow up with genetics and neurology. The patient was prescribed 300 milligrams of levetiracetam twice per day and 7.5 milligrams of diazepam as needed for seizures lasting longer than five minutes.

On the follow-up appointment, the geneticist performed whole-exome gene sequencing, which was positive for causative variants in diseased genes associated with the patient's phenotype. She had a pathogenic multi-gene copy number variant extending from cytogenetic band 22q11.22 to 22q11.23 involving LCR D to E/F. Both parents tested negative for the variant. The patient and her mother were instructed to follow up with the geneticist in one year for clinical monitoring and genetic counseling, with pediatric neurology and ophthalmology as scheduled, and physical, occupational, and speech therapy. The geneticist also recommended that the patient's pediatrician order neurodevelopmental testing to identify her strengths and weaknesses to inform her educational goals and support.

Whole-exome sequencing of the patient's genome detected an 1834 kb duplication of 22q11.22 to 22q11.23 involving LCR-D to LCR-E/F while both of her parents tested negative for this mutation. The phenotype of patients with 22q11.2 Duplication Syndrome may range from severe mental retardation, dysmorphic facial features, and heart malformations to an asymptomatic presentation. Patients with Chromosome 22q11.2 Duplication Syndrome often have a phenotype reminiscent of DiGeorge and Velocardiofacial Syndrome with features such as cleft palate, cardiac abnormalities, and abnormal facies but frequently with significant clinical variability. The etiology of this clinical variability is unknown, but non-penetrance, epigenetic factors, modifier genes, and environmental factors are proposed explanations. Common phenotypical features of distal duplications of 22q11.22q11.23 include speech and developmental delay, seizures, and hypotonia.[5]

The patient's phenotypical features include torticollis, dolichocephaly, down-slanting palpebral fissures, broad first digits of the hands and feet, nail hypoplasia of the first, second, and third digits of the feet, a tall and broad forehead, macrocephaly, and generalized hypotonia with an open-mouth posture. Of the three other reported cases of our patient's specific duplication, one patient was a newborn, and the other was a toddler. The infant had unilateral hydronephrosis, patent foramen ovale, finger anomalies, toenail hypoplasia, and mild scoliosis. The toddler reportedly had mild joint contractures, sacral dimples, a developmental defect of one eye, and slight tapering of the fingers and toes.[5]

Our patient also had a variety of clinical presentations, including global developmental delay and transient stroke-like symptoms with left eyelid and lip drooping. However, no stroke or acute abnormality was detected on radiologic imaging. She was diagnosed with a probable seizure associated with Todd's paralysis. She presented to the ED with transient left-sided paralysis and urinary incontinence after a reported tonic-clonic seizure.

She had an extensive workup, including multiple laboratory studies, EEG, ECG, and brain MRI. The MRI showed overall volume loss (more significant on the left than on the right), a small left hippocampus, ex vacuo dilation of the lateral

ventricles, prominent extra-axial fluid and sulci, and a thin corpus callosum, and the workup was otherwise normal. She was discharged in stable condition with a diagnosis of new-onset epilepsy.

Discussion:

Chromosome 22q11.2 duplication has been observed to be inherited most often in an autosomal dominant pattern but can also occur de novo, as is likely in our case. Individuals who harbor the duplication can present with a complex phenotype but may also be phenotypically normal or near normal.[3] In addition, pathogenicity cannot be predicted based on megabase (Mb) size as many carriers with significant Mb sizes display normal phenotypes, making diagnosis challenging.[5] As a result, the current medical literature has documented only three cases with the same specific copy number variant duplication in the LCR-D and LCR-E/F regions.[6]

Our patient did not learn to crawl until one year and could not walk until she was two. Her family history did not provide insight into why she was not achieving developmental milestones appropriately. There is no family history of multiple miscarriages, infant or childhood death, congenital disabilities, or known genetic conditions. Her mother has been diagnosed with anxiety, depression, and migraines, while her father has hypertension and a history of sleepwalking. Other notable family history includes a maternal uncle with "heart issues," a paternal grandmother diagnosed with fibromyalgia, an unspecified neuropathy, and an autoimmune disorder. Her paternal grandfather has a history of hypertension and stroke. No other family members have been diagnosed with disease.

Common causes of epilepsy include an imbalance of neurotransmitters, brain tumors, stroke, and brain damage from illness or injury. Most cases, however, have no known cause.[7] Epilepsy can also arise from specific gene mutations, a combination of genetics and environmental factors, mutations in mitochondrial DNA, and missing or mutated chromosomes.[8] Our patient had structural abnormalities on MRI and known chromosomal abnormality propose a source of her new-onset epilepsy, though a febrile seizure cannot be ruled out. Her seizure activity has been well-controlled on 200 mg of levetiracetam twice daily and diazepam 7.5 mg as needed. She has also received physical, occupational, and speech therapy for neurologic deficits, including bilateral ptosis, left-sided facial droop, and generalized hypotonia; she has reportedly been progressing well with therapy and will continue to be monitored for symptomatic management.

Conclusion:

22q11.2 Duplication Syndrome is a rare chromosomal disorder with a complex phenotype. Our case report highlights an individual who has 22q11.2 duplication syndrome and a complex phenotype including global developmental delay, macrocephaly, and generalized hypotonia. She also has presented to the ED on multiple occasions for seizure-like activity, possibly due to intracranial abnormalities detected on brain MRI. Her seizures have been controlled on a regimen of levetiracetam and diazepam, and she has progressed well with physical, occupational, and speech therapy.

Following her clinical course and others will be crucial to gain further information regarding the clinical presentation, diagnostics, and more effective treatments and management for 22q11.2 duplication syndrome.

Author Contributions:

Christopher Mikulas: drafted the article and revisions. Vanessa Knapp: data acquisition and manuscript review. Gabriele D'Orsi: data acquisition and analysis. Massimiliano Ferrari: conception and design, acquisition of data, and analysis. Marc Berger: editing of manuscript and principal investigator

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