CASE REPORT

Unveiling the mystery: Late detection of global developmental delay and hypotonia linked to ring chromosome 22

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SUMMARY

Ring chromosome 22 syndrome (r(22)) is a rare chromosomal disorder first described by Weleber et al. in 1968. Due to lack of clinical recognition and low suspicions, the syndrome is under-diagnosed, and its true incidence remains unknown. We present a case report of a patient diagnosed with r(22) syndrome, exhibiting features of global developmental delay (GDD), hypotonia and autism. The case, a three-year-old girl, presented with developmental delays in motor, cognitive, and language domains, accompanied by generalized hypotonia. Karyotyping revealed the presence of a ring chromosome 22 with deletion q13.3 (r(22q13)). The clinical manifestations, genetic findings, and management strategies of this rare syndrome were discussed in detail. This case report highlights the importance of early basic karyotyping in the investigations of a child with GDD, hypotonia and autism. This also underscores the importance of early recognition of GDD and hypotonia by primary care workers, leading to multidisciplinary intervention to improve developmental gains and quality of life for individuals with r(22) syndrome. The diagnosis of r(22) syndrome should be considered in all individuals with hypotonia of unknown aetiology with speech delay.

INTRODUCTION

Ring chromosome is a rare type of intra-chromosomal structural abnormality with an estimated occurrence of 1 in 50,000 newborns. There are two structural types, which are complete ring chromosome without the loss of genetic materials by telomere-telomere fusion or an incomplete ring.[1] There are various types of ring chromosomes identified but the most frequently seen were ring 13 (14%), X (12%), 22 (10%), 15 (9%), 14 (7%), and 18 (7%).[2] Ring chromosome is diagnosed via karyotype analysis. In clinical practice, most pediatric patients with ring chromosomes are detected through unexplained global developmental delay especially speech domain, growth retardation, hypotonia and intrauterine growth restrictions.[2] The clinical features vary depending on the phenotype and genomic anomalies include terminal deletions of 22q13 (89%), terminal deletions and interstitial duplication (9%), and interstitial deletions (2%).[3] Differential diagnosis for this includes Prader-Willi, Fragile X, velocardiofacial syndrome (deletion 22q13), Williams syndrome, autism spectrum disorders and cerebral palsy.[4] Patients with this syndrome warrant a referral to clinical geneticists for explanation on the variability of the phenotype, including the physical, developmental and behavioral aspects, the relationship between genotype and phenotype and the natural history of the syndrom.[4] In addition, the clinical geneticist can determine the indication for genetic testing of family members and the method of this investigation.[4]

This case report describes the clinical presentations of the child, investigations done prior to detection of abnormal karyotype and the management of the child with r22. This case also highlighted the importance of early detection by primary care during follow-up to improve the quality of life for the individual and optimization of the management.

CASE PRESENTATION

Our case was a three-year-old girl with GDD, hypotonia and autism. She was delivered to a 29-year-old woman via elective Lower Segment Caesarean Section (ELLSCS) at 38 weeks of gestation due to breech presentation. Her parents were not related, and it is not a consanguineous marriage. She was youngest out of three siblings and her two elder brothers were healthy. There was no family history of any syndrome or inherited diseases in the family. She had her routine follow-up at the health clinic as per schedule for immunizations and growth. Her height and weight were within normal range throughout the follow up in the health clinic except for her head circumference noted to be below -2SD in growth chart at the age of three months which over time, after nine months old the head circumference achieved normal size for age.

At the age of one-year-old, her development was noticed to be significantly delayed as compared to other children and her own siblings but was not addressed by the health clinic personnel during follow-up. Until she was one year and five months, she was finally referred to the Paediatric Clinic for further evaluation. At this presentation, her developmental age was six to nine months old where for gross motor, she was able to sit unsupported and crawl, but not able to pull to stand. For fine motor, she demonstrated inferior pincer grasp and pointing at distant object with index finger, however, not able to bang two cubes or hold pencils to scribble. She responded to her name; however, she was unable to

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Table I: Baseline investigations and results

Investigations	Results	Units	Range
Full blood count			
White cell count	14.7	109 / L	4.0 – 11.0
Haemoglobin	11.9	g/ dL	11.5 – 16.0
Hematocrit	39.7	%	35 – 47
Platelet	285	109/ L	150 – 400
Renal Profile			
Urea	4.0	mmol / L	1.8 – 6.0
Sodium	136	mmol / L	135 – 145
Potassium	4.7	mmol / L	3.5 – 5.0
Chloride	100	mmol / L	98 – 107
Creatinine	40	umol / L	31 - 52
Calcium	2.67	mmol / L	2.25 – 2.75
Magnesium	0.82	mmol / L	0.70 – 0.95
Phosphate	1.69	mmol / L	0.74 – 1.52
Liver Function Test			
Total Protein	74	g / L	56 – 75
Albumin	43	g / L	38 – 54
Globulin	31	g / L	20 – 39
Alkaline Phosphatase	253	U / L	<500
Aspartate Transaminase	42	U / L	5.0 – 34.0
Alanine Transaminase	30	U / L	5.9 – 37.0
Total Bilirubin	3.9	umol / L	5.1 – 20.5
Lactate	3.4	mmol / L	0.5 – 2.2
Ammonia	57	umol / L	18 - 72
Creatinine Kinase	118	U / L	34-204
Thyroid Function Test			
Thyroid stimulating hormone (TSH)	0.96	mIU / L	0.35 – 4.94
Free T4	11	pmol / L	9.00 – 19.00
IEM, blood	Non-significant changes of one or more acylcarnitines / amino acids		

understand “no” or “bye-bye”. Speech domain was the most delayed, where she was able to do polysyllabic sound only with no meaningful word identified. On physical examination, she had a flat nasal bridge with no other features of dysmorphism. There was one naevus depigmentosus over her right posterior calf. She also had haemangioma over her right shoulder, which parents claimed had been reducing in size since birth. Generally, she had normal muscle mass with no fasciculation. Neurological examinations revealed hypotonia and hyperreflexia of all four limbs with no clonus and Babinski were down going.

A list of investigations (Table I) was carried out, and all results were normal. All the organ functions were normal with no clinical features of organ abnormality. Magnetic Resonance Imaging (MRI) was done at the age of one-year-eight-months old to rule out central cause, however, no focal brain lesions identified, but there was incidental finding of presence of fluid in mastoid air cells. This finding correlate with conductive hearing loss detected during hearing test due to bilateral middle ear effusion. Thus, she was also seen by the Ear, Nose and Throat (ENT) team and was planned for bilateral myringotomy and adenoidectomy.

Throughout her follow up at the Paediatric clinic, there was very slow progress in her development with no further improvement in her speech. At two-year-old, she was able to walk independently with a wide based gait, started to have neat pincer grip and mouthing. She was also able to understand simple instructions and “bye-bye”, which corresponds to twelve-months milestones. However, there was no progression in speech and social domains. She was communicating with parents by pointing at objects of interest. As she grew up, she started to show some behavioural features of autism including poor eye contact, decreased socialization, stereotype movements, and inappropriate tantrums. Hence, an early intervention program was recommended and referral to occupational therapist, physiotherapist, and speech therapist were arranged to strengthen her muscle, improve her motor functions as well as communication skills.

In view of her poor progression in developmental milestones, especially in speech despite therapy and normal baseline investigation, basic karyotyping was sent at the age of two-year-eight-months old. Her karyotype result showed a ring at chromosome 22 in which breakage and reunion occurs at 22p13 and 22q13 (46, XX r (22) (p13q13)). The phenotype of this case was terminal deletion of 22p13q13. Given the possibility of inheritance in chromosomal anomalies, parental karyotyping is often considered to determine recurrence risk and genetic counselling needs. With regular therapies, at the age of three-year-old, she was able to walk independently with a wide-based gait, crawling upstairs but unable to run yet. For a fine motor, she was able to hold pencils with palmar grasps and made a tower of three cubes. In addition, she was able to point at toys when requested and obey simple commands. There was also an improvement in self-care, such as dressing and holding and drinking from a cup with little assistance. However, there was no improvement in speech. After a year of early intervention programme (EIP), there was no further developmental gains. Following diagnosis, a referral was made to the clinical geneticist to provide further genetic counselling.

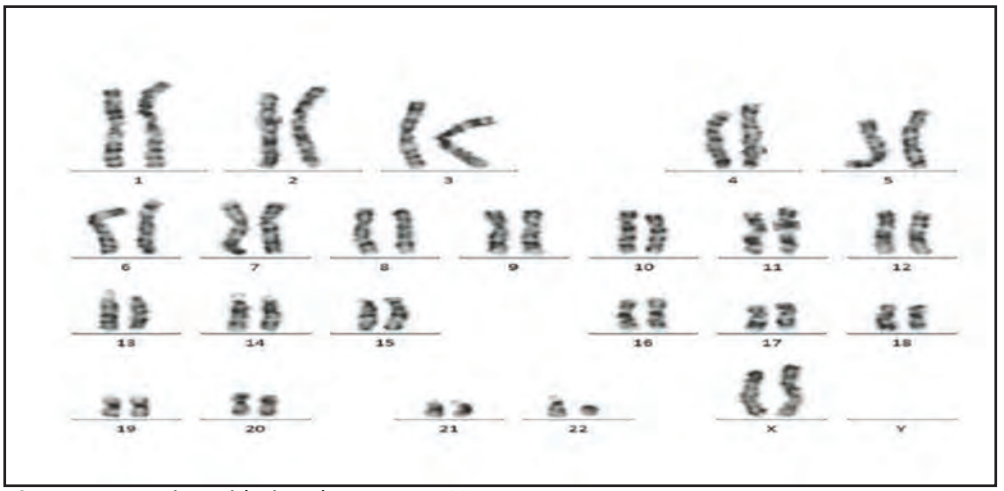

Fig. 1: Karyotyping with ring chromosome 22

DISCUSSION

Our case was a three-year-old girl, who presented with global developmental delay with severe speech impairment and hypotonia. The clinical manifestation or features of an individual with a ring chromosome varies depending on the chromosome involved and its phenotype. According to previous studies, the most seen features in r(22) include mental retardation, delayed motor development and hypotonia. Dysmorphic features such as epicanthic folds, microcephaly, hypertelorism, flat nasal bridge and high arch palate were also reported.[5] In this case, the only feature seen was a flat nasal bridge. Microcephaly was detected at a later age which subsequently became normal for her age.

As she grew up, she started to demonstrate autism features in terms of behaviours. Based on previous case reported, 75% of cases were diagnosed with autism, 9.4% as autism spectrum with wider variability in symptoms, skills and disability.[6] There were also cases reported with central nervous system abnormalities including dilatation of ventricles, cerebral atrophy, large cisterna magna and meningioma.[5] Other than that, mental and physical regression also reported with mood and anxiety disorder, chronic seizures requiring anticonvulsant as well as sensorimotor polyneuropathy.[5]

As for this case, she had routine follow up at a health clinic for development and immunization. Unfortunately, developmental abnormality and hypotonia were not identified earlier. The non-specific presentation, combining global developmental delay (GDD), hypotonia, with or without autism, leads to a broad range of differential diagnoses. Thus, it was important to recognize the problem early and proceeded with further investigations to identify the cause including basic karyotyping. As illustrated by this case, there was a delay in establishing the diagnosis which further delayed the intervention therapy. This was due to lack of recognition that chromosomal abnormality could be the cause for developmental delay and hypotonia with or without autism. To improve this, continuous education among primary care personnel should be provided, especially on how to identify and evaluate developmental delays that need early referral. A periodic clinical audit and communications strategies had been suggested as means to evaluate healthcare performance, reduced diagnostic error and to improve the quality of patient care.[7] A comprehensive developmental assessment by a trained primary care doctor should include a thorough review of development and growth. This process must be conducted closely together with specialist evaluations at the primary care centre and that early referral should be initiated as soon as when there is suspicion of developmental delay.

Early detection can play an important role in managing individuals with r(22) for a better quality of life. Since the main presentation was developmental delay, early intervention programs, intense occupational and physiotherapy as well as speech therapy will be beneficial to strengthen their muscles and improve their communication skills.[8] Early referral to physiotherapy, occupational therapy may give a major advantage for the child's development. Speech and language therapy were important as speech delay was usually the hallmark feature for r(22) syndrome. Many children may require ongoing and intensive speech-language therapy throughout their formative years.[9] The introduction of augmentative communication methods in the early stages of development can facilitate language utilization and alleviate frustration among a significant number of children undergoing speech-language therapy.[9] It was crucial to periodically reassess speech-language profiles as they can evolve over time, influencing the therapeutic approach needed for each child.[9] Similarly, to this case, she was in an early intervention program and on regular therapy with physiotherapy, occupational and speech therapy, but her speech progress was poor.

There were case reported that child with ring chromosome had concurrent recurring or persistent otitis media with or without effusion.[10] This case also was diagnosed with middle ear effusion (MEE) detected through hearing assessment and proven through her Magnetic Resonance Imaging (MRI) brain. She was planned for grommet insertion in view of persistent effusion despite pharmacological treatment. Speech delay is a hallmark feature of Phelan-McDermid syndrome (PMS), a genetic disorder most often caused by deletions or mutations affecting the SHANK3 gene on chromosome 22q13.3.[11] Marked impairment or even absence

of speech is reported in 50–88% of individuals with PMS, with up to 70% being non- or minimally verbal, and language impairment is consistently observed across diverse populations and genetic backgrounds.[12] Additional factors such as intellectual disability, hearing problems, and neurological issues can further influence communicative abilities.[13] In this case, her hearing improved following treatment of the middle ear effusion (MEE). Therefore, her speech delay is more likely attributable to underlying features of the chromosomal anomaly or possibly related to autism spectrum disorder.

The most important management for those with ring chromosomes was referral to genetics, especially for the parents. Geneticists can provide a thorough information and explanation to the parents to have more understanding about the r(22) syndrome.[4] The size of deletions will provide information on the number of medical comorbidities, gross motor skills, qualitative abnormalities in reciprocal social interactions, and qualitative abnormalities in communication. Larger deletions were associated with a higher likelihood of dysmorphic features and more severe medical comorbidity especially neurological symptoms, whereas smaller deletions were correlated with autism spectrum disorder, seizures, hypotonia, sleep disturbances, abnormal brain MRI, gastroesophageal reflux, and certain dysmorphic features.[10] Similarly, to our case, she was planned for fluorescence in situ hybridisation (FISH) to identify the genomic sequence. The clinical geneticist can determine the indication for genetic testing of family members. In this case, the clinical geneticist has not yet decided on parental karyotyping; however, it may be conducted in the future to determine inheritance.

CONCLUSION

The clinical features of ring chromosomes vary depending on the specific chromosome affected and its genotype. Diagnosing individuals with this condition was challenging due to the combination of non-specific symptoms, mimicking other disease or syndromes. However, the emphasis should be placed on early chromosomal analysis to detect any abnormalities, rather than solely focusing on the early detection of this specific anomaly. Early chromosomal analysis is to be considered in all cases of hypotonia and global developmental delay, even when dysmorphism is minimal and that baseline and IEM screening are unremarkable. To achieve that, the health care staff especially in primary care must have high level of suspicion and curiosity to detect the abnormalities. Proper counselling by a geneticist is recommended to provide further information and investigations needed. A long-term monitoring and follow up would be beneficial to monitor and detect any complication or other medical problems that may occur as the age increases.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable data included in this article.

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COMPETING INTEREST

The authors declare that they have no conflict of interest.

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