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Research Letter

A Longitudinal Case Study of a Child With Mosaic Trisomy 22: Language, Cognitive, Behavioral, Physical, and Dental Outcomes

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To the Editor:

Mosaic trisomy 22 is a rare chromosomal disorder compatible with prolonged survival, whereas complete non-mosaic trisomy 22 is incompatible with life [Crowe et al., 1997; Patel and Madon, 2004]. The physical characteristics of mosaic trisomy 22 include growth retardation, severe mental retardation, a webbed neck, limb malformations such as syndactyly and brachydactyly, as well as hypoplasia and an altered pigmentation called hypomelanosis of Ito [Ritter et al., 1990]. Common craniofacial abnormalities associated with trisomy 22 patients include microcephaly, macrocephaly, prominent forehead, flat nasal bridge, cleft palate, preauricular pits, hypertelorism, micrognathia, bilateral epicanthic folds, and malformed low-set ears. These features are not manifest in all patients with the disorder, though most present with an assortment of these characteristics. Additionally, many patients with trisomy 22 have congenital heart defects, hearing loss, and genital disorders such as cryptorchidism [Kukolich et al., 1989; Florez and Lacassie, 2005].

Previous reports on mosaic trisomy 22 have focused on the familial, phenotypic, and cytogenetic characteristics of the disorder. Crowe et al. [1997] described one child's growth to 3 years, the child's physical characteristics, and cytogenetic and molecular analysis. In this article, we provide new information on this child with trisomy 22 on whom Crowe and her colleagues [1997] previously reported. This study documents the cognitive, linguistic, behavioral, physical, and dental development across six time points from birth to 14 years of age.

This study was prospectively reviewed and approved by the institutional review board of University Hospitals of Cleveland. Informed consent was obtained from the child's mother. The child was followed prospectively and longitudinally from birth to his 14th year. Born at 32 weeks gestation, this 1,144 g, small for gestational age, African-American/Caucasian boy was delivered by caesarian for fetal distress. Apgar scores were 5 and 9 at 1 and 5 min, respectively. His length was 38.5 cm and head circumference 27 cm. His mother reported no substance use/abuse during pregnancy.

His Neonatal Intensive Care Unit (NICU) course was complicated by respiratory distress syndrome requiring 15 days of mechanical ventilation, sepsis, a

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patent ductus arteriosus (PDA), and intractable seizures. Seizures began on the 27th day of life and were controlled with dilantin and phenobarbital. The neonatal work-up included a normal EEG, head sonogram, serum NH_3 level, organic acids, urine, and serum amino acids. He was discharged at $2\frac{1}{2}$ months post-natal age. Four days later, he was readmitted after a cardio-respiratory arrest at home. He was ventilated for 5 days for pneumonia and treated with 10 days of antibiotics. While hospitalized, he had a seizure-like episode, again with a negative head ultrasound and EEG. At this time, he responded to additional phenobarbital. An echocardiogram demonstrated a hemodynamically insignificant PDA. He was discharged to home 3 weeks later.

The child remained growth delayed at 40 weeks corrected gestational age, weighing 3,200 g (25th centile), with a head circumference of 36 cm (50th centile), and a length of 44 cm (<5th centile). His vision and hearing tests were normal at that time.

At 3 years of age, Crowe et al. [1997] described him as having a flat nasal bridge, bilateral preauricular pits, hypotonia, whorling of hypopigmentation over the arms, legs, and scapulae (hypomelanosis of Ito), notched upper central incisors, and hemiatrophy, primarily in the upper limbs.

Original cytogenetic analysis [Crowe et al., 1997] showed that two lymphocyte studies were performed, one normal 46,XY, in 30/30 cells and a repeat study (done after the skin fibroblast analysis) showing 4 of 100 cells with trisomy 22. Dermal fibroblasts from two areas showed 4,XY,+22[28]/46,XY[2].

DEVELOPMENTAL ASSESSMENTS

The child was assessed at six time points: 1 month, 8 months, 24 months, 36 months, 8 years, and 14 years of age. Assessments included his physical, dental, and medical status, as well as standardized, normative measures of cognitive, linguistic, behavioral, and social skills.

Physical and Medical Assessments

Physical examinations were performed at 8 and 14 years of age. At age 8 years, the child remained severely growth delayed. He weighed 10.6 kg (<5th centile), with height of 91 cm (<5th centile), and head circumference of 44.6 cm (<5th centile). He was noted to be dolichocephalic, with midface hypoplasia, epicanthal folds, and hypopigmentation. He appeared to have overall decreased muscle strength, with a right elbow contracture and mild impairment in his ability to walk on a straight line. At the time of this assessment, he had undescended testicles and was receiving growth hormones. At the 8-year visit, his mother also reported that the child was being assessed for suspected hearing loss, and she later reported that he was subsequently diagnosed with an 80% loss in the right ear and 20% loss in the left ear.

By 14 years of age, this child was still extremely small with a weight of 17.9 kg (<5th centile), head circumference 45.6 cm (<5th centile), and height of 109.5 cm (<5th centile). He continued to have dolichocephaly with the hypomelanosis. He had scarred, retracted tympanic membranes, and tubular breath sounds. His right elbow contracture had advanced to include a thin, small, atrophic, right arm. Testicles were descended but small. His plantar reflexes were equivocal. The subject was also clinically examined at 14 years for tooth enamel defects, dental caries, oral hygiene, and developmental delays in tooth eruption. Assessment of the teeth for enamel defects (opacity & hypoplasia) using the developmental defects of enamel (DDE) index [Commission on oral health research and epidemiology, 1982] revealed no such defects. Dental caries evaluation using the visual–tactile criteria of Radike [Radike, 1972] also showed that he had no visible caries. No data on interproximal caries were available. The subject had very poor oral hygiene as measured by the simplified Oral Hygiene Index [Green and Vermillion, 1964]. Inconsistent eruption patterns of the teeth were observed, as some permanent teeth had not yet erupted by age 14. The subject had severe crowding with some retained primary teeth. Good oral hygiene habits had not been established, with dental sealants and orthodontic treatment recommended to prevent future oral health problems.

Cognitive Assessments

The Bayley Scales of Infant Development (BSID) [Bayley, 1969] were administered at 8 and 24 months and the BSID-II [Bayley, 1993] at 36 months of age corrected for prematurity. The BSID yields two scores: a Mental Development Index (MDI) and Psychomotor Development Index (PDI). At 8 years of age, the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) [Wechsler, 1991] was administered, with the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)[Wechsler, 2003] administered at 14 years of age. The WISC-III yielded a Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FIQ). The WISC-IV yielded four composite scores: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. Subscales of the WISC-IV included Block Design, Letter-number Sequencing, Coding, Digit Span, Vocabulary, Symbol Search, Comprehension, Similarities, Picture Concepts, and Matrix Reasoning.

Examination of the child's cognitive strengths and weaknesses showed an interesting profile. On the MDI, scores less than 55 were obtained at the 8, 24, and 36 month visits. These scores are more than 2 SD below the mean of 100, placing him in the

moderately retarded range of cognitive functioning. Results from the WISC-III and the WISC-IV at the 8- and 14-year visits also revealed significant impairments in his cognitive abilities, with his attainment of a 55 or less FIQ at both 8 and 14 years of age. Thus, a stable profile of IQ was obtained for the child, with all scores significantly below average. At 8 years of age, VIQ = 56 and PIQ = 57 scores were comparable. In contrast, at 14 years of age, subscales on the WISC-IV suggest an unusual pattern of strengths and weaknesses. Perhaps his most interesting strength is his processing speed composite score, where his score of 70 was 1 SD above his global IQ scores. Although this score places him in the borderline range, his score of 70 for processing speed represents a strength for him. Additionally, he demonstrated relative strengths in verbal skills, with his verbal comprehension score of 67. Weaknesses were demonstrated in working memory (54) and perceptual reasoning (61) which appeared consistent with his overall level of cognitive functioning at both 8 and 14 years of age. Also, he had great difficulty manipulating letter-number sequences as reflected by his scaled score of 1 on the letter-number sequencing subscale. Further support for his difficulties manipulating ideas was obtained on the picture concepts subtest on which he earned a scaled score of 3. Means of 10 on these subtests reflect average processing and as such suggest that he has great difficulty using his working memory to recall and manipulate sequences of abstract information.

Motor Skills

PDI from the BSID [Bayley, 1969; Bayley, 1993] at 8–36 months of age and the Bruininks–Oseretsky Test of Motor Proficiency, short form [Bruininks, 1978] administered at 8 years of age revealed significant and consistent delays in motor skills. PDI standard scores (SS) were <50 at 8, 24, and 36 months. He achieved a T-score of 24 (mean = 50) on the Bruininks–Oseretsky test at 8 years. By 14 years of age, however, his fine motor skills on the Purdue Pegboard Dexterity Test [Tiffin and Lafayette Instruments, 1999] suggested that fine motor skills may be a relative strength for his preferred hand. Z-scores on this test ranged from −0.8 on peg placement with the preferred hand to −1.8 for assembly.

Language Skills

Three-year outcomes from the communication domain of the Batelle Developmental Inventory [Newborg et al., 1988] indicated language skills SS = 65 consistent with his cognitive abilities. At 8 years, the Clinical Evaluation of Language Fundamentals, 3rd edition (CELF-3) [Semel et al., 1995] revealed a relative strength in receptive language (SS = 84) compared to his expressive language skills (SS = 61). At 14 years, his early strength in receptive language was less apparent, with performance in receptive (SS = 61) and expressive (SS = 53) language more comprable. See Table I for a summary of his language skills.

Academic Achievement

Academic achievement was measured at 8 years with the Woodcock–Johnson Test of Achievement, revised edition (WJTA-R) [Woodcock and Mather, 1987] and at 14 years with the Woodcock–Johnson, 3rd edition (WJTA-III) [Woodcock et al., 2001]. The WJTA evaluates an individual's cognitive processing abilities in the context of academic material. SS range from 0 to 200 with a normative mean of 100 ± 15 SD. At the 8-year visit, the child exhibited moderate delays (>2 SD from the mean) on the WJTA-R. Letter–word identification, passage comprehension subtests, and applied problems were relative strengths (70, 67, and 66 respectively), with mathematics calculations seen as a relative weakness (SS = 50). At 14 years, he earned an achievement age equivalent of approximately 8 years on the WJTA-III, i.e., 6 years behind his chronological age. His math performance (math fluency & applied problems) was slightly better than his reading performance (reading fluency and passage comprehension), with his eligibility for special education services due to his cognitive disability (See Table II).

Behavioral and Social Skills

The child's social skills and mental health at 8 and 14 years were measured through the Youth Self-Report (YSR) [Achenbach, 2001b], as well as the parent report version of the Child Behavior Checklist (CBCL) [Achenbach, 1991; Achenbach, 2001a]. In addition, the Behavior Rating Scale from the BSID was completed by the examiner at 8, 24, and 36 months.

Social strengths were remarkable considering physical limitations and moderate level of mental retardation. The behavioral component of the Bayley revealed an extremely affable child. At all three time points, the child was found to be friendly and cooperative. Social skills were noted as a strength as early as 24 months, when it was noted that he babbled, cooed, and smiled frequently. On the

TABLE I. Standardized Receptive, Expressive, and Total Language Scores for Child With Mosaic Trisomy 22 at Three Time Points

	36 months Batelle	8 years CELF-3	14 years CELF-3
Expressive	65	61	53
Receptive	65	84	61
Total language	65	73	54

TABLE II. Achievement Testing at 8 and 14 Years of Age for Child With Mosaic Trisomy 22

Measure	Subtest	Standard score (age equivalency)
Woodcock–Johnson-R (8 years)	Letter–word identification	70 (6 years 10 months)
	Passage comprehension	67 (6 years 7 months)
	Calculation	50 (6 years 4 months)
	Applied problem set	66 (5 years 11 months)
Woodcock–Johnson-III (14 years)	Reading fluency	22 (7 years 10 months)
	Passage comprehension	19 (7 years 4 months)
	Math fluency	42 (8 years 7 months)
	Applied problems	29 (8 years 8 months)

CBCL, all aspects of his emotional and social behavior were within normal limits, including internalizing and externalizing scores. According to maternal report, social skills have improved with age, with T-scores decreasing with increasing age. Despite maternal report of normal social behavior, the child reported higher levels of problematic social issues (i.e., being teased by peers) at 14 years, as well as higher levels of delinquent behavior and more difficulties with attention.

This is the first study to report prospectively on longitudinal developmental outcomes for a child with mosaic trisomy 22 from birth to 14 years of age. Although this child was physically and genetically described by Crowe et al. [1997] at 3 years of age, no cognitive, language, social, and achievement assessments were available at the time of the report. Consistent with trisomy 22, the child presented with growth retardation, short stature, and mental retardation. Our longitudinal follow-up confirmed persistent and severe growth retardation with psychomotor delay, with fine motor skills improved by 14 years of age. Although children with mosaic trisomy 22 are known to present with hearing loss, hemiatrophy, and hypomelanosis of Ito [Crowe et al., 1997], our subject at 3 years of age did not present with hearing loss, despite hemiatrophy and hypopigmentation. At 8 years, bilateral hearing loss was diagnosed.

Cognitive profiles associated with mosaic trisomy 22 are variable, with most children demonstrating some degree of cognitive delay. A review of 13 cases of mosaic trisomy 22 found that all but one case had mental retardation; however there was no correlation between the percentage of trisomic cells and intelligence [Florez and Lacassie, 2005]. Seven cases reported mild, two cases reported moderate, and three cases reported severe mental retardation. Only one case reported normal developmental milestones and intelligence [Florez and Lacassie, 2005]. The child followed in the current study demonstrated moderate mental retardation, despite significant discrepancies in cognitive strengths and weaknesses. Receptive language and processing speed appeared to be strengths. Deficits in reading and math skills were observed at the 8 years and persisted through 14 years of age.

The social–emotional characteristics associated with trisomy 22 have not been described. Despite poor cognitive and physical abilities, strengths were noted in social skills which may be due in part to language skills. In fact, doctors blinded to his medical condition rated him as "normal" when asked to give their impressions of his cognitive abilities. At 14 years, he self-reported difficulties (teasing by peers, delinquent behavior, and attention problems), mental health issues not noted by his mother. In the teenage years, new social pressures may emerge and support systems should be in place to buffer psychological difficulties.

As low-incidence genetic syndromes are diagnosed, it is critical to evaluate patterns of strengths and weaknesses across domains. Multi-level, longitudinal evaluations are essential to observe developmental trajectories.

Caution should be taken in generalizing a single case study to the population of mosaic trisomy 22 as other phenotypic characteristics and environments may differentially affect the outcomes. Future research should focus on following children into adulthood to determine functional outcomes, and across many children with mosaic trisomy 22 to confirm common traits of the syndrome.

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