Trisomy 21 and Rett syndrome: A double burden

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Abstract: Rett syndrome is a severe neurodevelopmental disorder generally affecting girls. Affected individuals are apparently normal at birth but later pass through a period of regression with loss of hand and communication skills and the development of hand stereotypes and dyspraxia. Mutations in the methyl-CpG binding protein 2 (MECP2) gene, have now been found to cause Rett syndrome in up to 80% of classical cases. We report a girl with Down syndrome, one of three children with birth defects in a family of five. From the age of 18 months she developed symptomatology considered by her primary physician to be very characteristic of Rett syndrome. However, this remained a clinical diagnosis till the age of 12 years. Laboratory confirmation of the dual diagnosis, which includes a R168X mutation in the MECP2 gene in addition to trisomy 21, has now been possible. The presence of one neurological or developmental disorder does not necessarily preclude a diagnosis of Rett syndrome.

Key words: Down syndrome; methyl-CpG-binding protein 2; Rett syndrome; trisomy 21.

We report here a case of trisomy 21 and clinical features of Rett syndrome, which we presented at the World Congress on Rett Syndrome in Gothenburg, Sweden. Rett syndrome is a neurodevelopmental disorder typically affecting females who, after a period of early normality pass through a period of regression, with loss of hand and communication skills and dysfunction of posture and tone. The development of hand stereotypes, most characteristic of the disorder, occurs contemporaneously with the regression. Slowing of head growth often appears prior to the loss of skills. Associated features include seizures, sleep problems, autonomic dysfunction with agitation and gastrointestinal dysfunction, spinal deformities such as scoliosis and kyphosis, growth retardation and osteopenia. In the absence of a biological marker, sets of necessary, supportive and exclusionary criteria, incorporating many of these and other features, were developed to assist with the diagnosis of this neurodevelopmental syndrome. According to these criteria the diagnosis was to be considered tentative until the age of 5 years. However, in the past decade there has been increasing clinical awareness of the disorder with the diagnosis being made at younger ages.

The underlying genetic basis of Rett syndrome remained obscure until recently when mutations in the gene coding for the methyl-CpG-binding protein 2 (MECP2) located on Xq28 were first reported by Amir et al. Although the mechanism for the pathophysiology is still unknown, Rett syndrome appears to be one of the still small number of human disorders involving chromatin assembly. Subsequent follow-up studies have confirmed the relationship between Rett syndrome and MECP2. In Australia mutations were documented in 72% of those 152 cases used to delineate the phenotype in a population-based study. The Australian Rett Syndrome Database (ARSD), is a population-based registry (first established in 1993) of individuals with Rett syndrome, born since 1 January 1976. Using multiple sources including the Australian Paediatric Surveillance Unit, ongoing ascertainment of juvenile cases continues on a national basis. Since late 1999 in addition to questionnaire data from families and clinicians, samples are also being collected for mutation testing.

CASE REPORT

The child, we report, became known to the registry in 1996 at aged 9 years. Parents are unrelated and mother was aged 35 years at the time of her birth. At 20 weeks gestation the possibility of hydrocephalus was raised when ultrasound monitoring demonstrated some cerebral ventricular enlargement, but this had resolved by 26 weeks. Pregnancy was otherwise uneventful apart from reduced foetal movements at 40 weeks. Delivery was by Caesarean section at 41 weeks and Down syndrome was diagnosed at birth. Birthweight was 3000 g and head circumference 34 cm with Apgar scores of 1 and 6. The infant was tachypnoeic in the first 4 weeks of life, and a ventricular septal defect with pulmonary hypertension was subsequently identified and repaired at age 7 weeks. The index case was one of five siblings. One sister had juvenile rheumatoid arthritis whilst the other sister was healthy apart from experiencing a seizure at the age of 3 years. One male sibling had gastrochisis and jejunal atresia and another had surgically treated congenital heart disease (atrial septal defect, ventricular septal defect, aortic stenosis and coarctation of the aorta). The latter died unexpectedly at 3 months of age with cause of death unconfirmed. This boy would appear to have been affected by an X-linked condition also involving two of the proband’s male cousins. The condition seems to be characterized by severe congenital cardiac disease including aortic coarctation and hypoplastic left heart with affected males dying in the first year of life.

The proband sat at 6 months and crawled at 10 months. By 12 months she was pulling to kneel and able to take toys out of...
a box. She was monitored in an early intervention programme using the Macquarie University Down Syndrome Inventory, which showed excellent early developmental progress. Fine motor skills attained by 17 months included a pincer grasp to pick up a raisin, being able to place large rings on a stick, pulling a string to obtain a toy and holding a crayon. Language skills at this time included responding to commands (such as ‘put’ and ‘no’) and imitating sounds. She vocalized to gain attention and participated in games such as ‘peek a boo’. By this age she was able to pull herself into a standing position but never cruised or walked.

At 18 months her parents became concerned because she was having difficulty with chewing and swallowing, was becoming withdrawn with loss of eye contact and failure to cooperate and had become obsessed with her hands. From 19 months there was a definite regression with development of repetitive hand movements such as hand mouthing and wringing. It then became apparent that she had lost both hand skills and vocalization over the previous 2 months. Her behaviour was considered autistic. Between 18 and 36 months a decline in head growth was observed.

Between 2 and 3 years there was further concern because developmental progress had ceased. She was also having episodes of abdominal pain and vomiting and was not gaining weight. Gallstones were detected on an abdominal radiograph and at 3 years she underwent a cholecystectomy. Investigations for a possible neurodegenerative disorder included CT scan, CSF examination, urine chromatography and organic acids, lysosomal enzymes and basic haematology and biochemistry. She also had an electroencephalogram, nerve conduction studies and ophthalmological assessment. All investigations apart from CSF lactate and pyruvate were normal with CSF lactate particularly raised at 0.173 mM/c (normal range .05 to .09). At that time an Alzheimer type degenerative disorder was thought most likely to account for the regression although the possibility of Rett syndrome had already been considered by her managing paediatrician (PE).

At the age of 3 years pathological asymmetry of limb development first became evident with relative enlargement of the right side of her body. She subsequently developed a marked left foot deformity with curling under of the great toe. Obstructive sleep apnoea was diagnosed at 6 years. Seizures, mainly nocturnal, became apparent at the age of 10 years, and are currently fairly well controlled with valproate.

The clinical diagnosis of Down syndrome had been confirmed with an abnormal karyotype demonstrating trisomy 21 with no evidence of mosaicism in lymphocytes. A C>T transition was found within the transcription repression domain of the MECP2 gene at position 502 using methods previously described. This mutation changes an arginine to a stop codon (R168X). Neither parent was found to have the mutation in DNA extracted from peripheral blood.

**DISCUSSION**

We have described a child with both Down syndrome and Rett syndrome. The diagnosis of Down syndrome was made at birth. By the age of 8 years managing clinicians were confident of the additional diagnosis of Rett syndrome. Convincing features were her normal early progress (within the context of trisomy 21) followed by regression with loss of hand skills and vocalization, development of hand stereotypies, slowing of head growth and typical jerkiness of the trunk, when she was pushed off balance. She also demonstrated many supportive characteristics including breathing abnormalities, constipation, sleep disturbance, teeth grinding, abdominal bloating and decreased sensitivity to pain. However in comparison with Down syndrome the diagnosis of Rett syndrome remained a clinical one in the absence of a confirmatory biological marker. This changed with the discovery of the causative relationship between mutations in the MECP2 gene and Rett syndrome. The presence in this child of a R168X mutation, one of the commonest nonsense mutations described in Rett syndrome, confirmed our clinical suspicion.

This case report provides further evidence that Rett syndrome may coexist with other disorders. A missense mutation (T158M) has already been found in a male with Klinfelter syndrome and a nonsense mutation (R255X) in a female with multiple congenital abnormalities. Wan et al. identified a frameshift mutation (L138X) in a female with incontinencia pigmenti. Associations between autosomal chromosome abnormalities and Rett phenotype had also previously been reported before the availability of molecular diagnosis. However Gordon et al. considered that the belief by clinicians that such a scenario was unlikely might have resulted in the under-reporting of these cases.

In addition to the dual diagnosis finally able to be confirmed by molecular testing this case has some other puzzling features. Hemihypertrophy is not a characteristic feature of Down syndrome. However asymmetrical function can occur in Rett syndrome. We have now shown that the pattern of hand preference in Rett syndrome is anomalous with a left hand preference reported for as much as a third of cases, an equal hand preference for a quarter and only in the remaining 41% a right hand preference. Side asymmetries involving loss of function, dystonia and hypotrophy on the right side more than the left have also recently been described in 24 Swedish cases. However hemihypertrophy of the degree seen in our case is seldom seen. This hemihypertrophy could be a manifestation of mosaicism perhaps in another tissue, but we have no other supporting evidence for this. The other unusual characteristic is the cholelithiasis, normally rare in childhood but gall bladder pathology has been reported to the International Rett Syndrome Association as having occurred in 27 other girls and young women with Rett syndrome (personal communication Cathy Hunter April 2004). Our subject did not appear to have experienced any of the major paediatric risk factors such as haemolytic disease, gall bladder stasis due to starvation or total parenteral alimentation. However early hyptonia is a feature of both Rett syndrome and Down syndrome. One could therefore speculate that in a child with both disorders poor muscle tone, poor feeding ability in infancy and reduced mobility all might have a permissive role in biliary tract dysmotility and subsequent bile stasis. Alternatively could there be stasis secondary to dysfunction of the sphincter of Oddi due to the autonomic abnormality known to occur in Rett syndrome.

Finally we should consider whether this dual diagnosis of Rett syndrome and Down syndrome is a chance occurrence or whether there was an underlying liability for this to occur. In this family there was an unusual clustering of birth defects with three out of five children affected. A syndrome of X-linked congenital heart disease appears to account for one of these. In the families of Australian Rett syndrome cases (although based on small numbers) we have noted a relative increase in prevalence of trisomy 21 in sibs (including one prenatal diagnosis) but could provide no biologically plausible explanation for this. In females Down syndrome is 10 times more common than Rett syndrome with the incidence of the latter being about 1 : 10 000. The likelihood of both conditions occurring together by chance is 1/10^7 female births or once every 80 years in Australia. At the present time we believe that this is the only
such case of trisomy 21 with confirmed MECP2 mutation testing. However the comment of Gordon et al.,25 about the under-reporting of such anomalies may mean that other cases have occurred but have not yet been identified or reported. In addition the presence of Down syndrome may ‘mask’ a second diagnosis such as Rett syndrome, as occurred for some time in the case presented here. The role of MECP2 mutations is now being explored in individuals who do not meet the strict criteria for Rett syndrome including milder variants,26 females25,34 and also males26 with autism or autistic features, females with mild learning disability,15,39,40 males and a female with neonatal encephalopathy,14,41–43 males with non-specific or X-linked mental retardation39,40,44,45 and normal mothers30,41,42 (pers. comm. S Budden 19/10/2000, unpubl. data). Hence the spectrum of effects of this mutation is clearly much broader than the classical Rett syndrome.46 We still do not know whether our case is a chance occurrence in this family. In the meantime however, we would alert physicians to follow their clinical suspicion when presented with such a case and not to dismiss the possibility of Rett syndrome occurring together with another disorder.

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REFERENCES

7 Leonard H. Rett Syndrome in Australia. Perth: Department of Public Health, University of Western Australia, 1996.


