Case Report: Further Evidence for a Recognisable Syndrome Caused by Deletion of 1p31

We present our case report on an adolescent female, born to healthy and non-consanguineous parents by normal delivery at term weighing 3500g following a pregnancy complicated by pre-eclampsia. She has an older male sibling with mild dyslexia but who is otherwise well, and there is no family history of learning disability. There were no medical problems in the perinatal or neonatal periods. During the first year of life some mild global developmental delay was noted. The girl walked at 18 months of age. Significant speech and language delay was noted in the second year and later. She was seen by a number of experts over a period of several years, but no clear diagnosis was established. Assessment at the age of 12.8 years revealed mild learning disability, developmental coordination disorder (DCD), and attention-deficit/hyperactivity disorder (ADHD), mainly inattentive subtype (the combination of DCD and ADHD, with or without mild learning disability; is often referred to as “deficits in attention, motor control and perception” (DAMP) (Rasmussen and Gillberg, 2000), and this was the comprehensive diagnosis assigned). The DCD was characterised by overall dyspraxia and apractic gait. A WISC-III test was performed in connection with the neuropsychiatric assessment. The cognitive profile suggested non-verbal learning disability even though the overall IQ-level was depressed. Results of the WISC-III test were as follows: Full Scale IQ 56, Verbal IQ 64, Performance IQ 45, Information (scaled score) 6, Arithmetic 2, Comprehension 7, Vocabulary 8, Similarities 6, Block Design 4, Object Assembly 5, Coding 3, Digit Span 2, and Picture Completion 1. She had a long thin face, a broad prominent nasal bridge, and a prominent nose, hypertelorism, a large mouth, moderate pectus excavatum, thin tapering fingers (with distal broadening), and very thin feet and toes (club-shaped big toe). At the age of 17 years she developed an acute right lower lobe pneumonia requiring hospitalisation.

Standard karyotype and FISH 22q11.2 were normal. Array based comparative genomic hybridisation (array-CGH) analysis using the 0.5Mb “CytoChip” BAC microarray (BlueGnome Ltd, UK) showed del(1)(p31.1:p31.3) with the minimum and maximum sizes of the deletion being 4.86Mb (RP11-175G14-> RP4-547N15 Chr1:67239552-72983939) respectively. The DECIPHER number of this patient is 0001954.

Discussion
Deletions of 1p31.1->1p31.3 appear to be very rare. After a review of the literature of standard cytogenetic banding reports we were able to identify only four published cases (Bene et al., 1979; Lai et al., 1991; Mircher et al., 2003; Petersen and Warburg, 1987), plus one further case with a significantly larger, but overlapping, deletion identified by array CGH analysis (Shaw-Smith et al., 2004). Clinically and cytogenetically the case presented here most
resembles the two cases reported by Lai et al. In particular the prominent nose, long face, arachnodactyly and motor development problems (DCD) are common to all three cases.

There are at least 21 different genes in the deleted region. Only three of these have been linked to human disease; IL23R as a protective factor in inflammatory bowel disease, and biallelic mutations in RPE65 and CTH as causes of Leber congenital amaurosis and cystothionuria, respectively. It has not been possible to attribute obvious genotype-phenotype correlations to the other genes in the region.

References

Sophie Dow
Sophie Dow is a journalist and founder of Mindroom (www.mindroom.org) an organisation that works to create awareness about all kinds of learning difficulties. She has a daughter, Annie aged 19 who is the inspiration behind Mindroom. Sophie was born and raised in Sweden, lived 12 years in London, where she worked as correspondent for Swedish press, radio and TV (arts and culture). Moved to Edinburgh 1994 where she still lives.

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“Well, Mrs Dow,” said the extremely curly-haired, highly recommended child psychologist from Harley Street as he sat in my kitchen, “you’ve got a problem. According to my tests, your daughter is mentally handicapped.”

I smiled politely and complimented him on his briefcase – beautifully worn leather in just the right colour. Exactly what I’d been looking for. Plenty of room, with lots of useful pockets, a zipped pocket for your wallet, a small one for your keys and big enough for newspapers.

“But,” Mr Flowers MA (Hons), Dip Teach, Ed. Psych, MNZ, PSSC Psychology, continued mercilessly, “having seen how sociable and communicative she is, I’m not sure that I agree entirely with the tests.”

He had tested Annie according to the book for more than three hours, using two different tests: one to test the child’s practical abilities and the other the child’s social skills. Apparently the two combined provide a reasonably accurate picture of what the future holds.

Mr Flowers proved to be impeccably professional and immune to my desperate attempts to play down the results of the tests. With an aching heart, I withdrew into a corner of our spacious kitchen. Deep down I knew that something wasn’t right but I was desperate to reassure myself, to seduce myself, into believing that it was only a matter of a couple of courses of penicillin, or at worst, that we’d have to go to an OT for a term or two.

Mentally exhausted, we said goodbye to Mr Flowers on the front step. “Thank you for coming. Have a good day. Lovely weather, isn’t it? Oh, and where did you buy that briefcase?” In a kind voice he explains that he bought it before he moved to the UK. A proper New Zealand school bag, and yes, thank you, he would have a good day.

Self-preservation had already kicked in, bubble-wrapping the shocking news and numbing it with comforting politeness and small talk.

That day of reckoning was the 20th May, 1994 and Annie was three years and four months old. Today, 16 years later, we know that Annie has a unique chromosome deletion of 1p31, chromosome 1.

But first things first, and just like the DNA chain of logical events, the parental adjustment to such an unexpected, life changing scenario needs to proceed at its own pace.

The impossible and rhetorical questions that came tumbling into our unsuspecting parental world that very day all those years ago, do unfortunately to some extent still apply:

- What does mentally handicapped actually mean?
• Will Annie be able to lead an independent life?
• What about school?
• Can she train herself to overcome her difficulties?
• Surely to God, there must be an oracle somewhere that can help her?
• Perhaps somewhere farflung like China?
• Can we protect her and help her?
• What will happen to her when we die?

Falling outside the norm, as Annie and so many others do, places you in a multi-faceted and complex world. The facets involved include the mind, the soul, the environment, the ongoing medical research, the educational system, social services and your own inner feelings, self esteem – and of course, your tears. The complexities are the interplay between them all.

In some ways the term ‘learning difficulties’ applies just as much to society as to the children and adults involved. Our society seems to have a blind spot – its own form of learning difficulty – towards people with different needs, and its inability to meet their needs is both part of, and adds to, the problem.

A few years later I set up Mindroom, a charity dedicated to creating awareness of learning difficulties. We now collaborate across the field with leading experts within the field of neurodevelopmental disorders, with politicians, health and education professionals as well as provide direct help and support to families who are living with learning difficulties.

The second day of reclaiming for us, was the 18th July 2007, when we received the news about the chromosome deletion, from Dr David FitzPatrick, Professor of Clinical Genetics at MRC Genetics Unit in Edinburgh.

After a third assessment in 2003, which failed to pinpoint the cause of Annie’s disabilities, and at the suggestion of Christopher Gillberg, Professor of Child and Adolescent Psychiatry, University of Gothenburg, Institute of Child Health, London and University of Glasgow, Annie was tested for FISH 22q11.2.

Annie has amongst other features; a high/prominent nasal bridge, thin/long face, arachnodactyly, dyspraxia/apraxia including gait apraxia, short attention span, extraordinarily big club shaped big toes and mental retardation/developmental delay. Although results came back as normal, we felt we were now on the right track.

The answer would most probably be found within the rapid unraveling of the human genome. However, our team; Gillberg, FitzPatrick, Sharkey, myself and my husband Robin, were ahead of the technology needed to solve the genetic mystery. It was agreed that Professor FitzPatrick would keep Annie’s blood sample until such technological break through would present itself.

Four years later, the brown window envelope arrived, by 2nd class post, carrying the fundamental information of ‘a small but significant missing fragment on the short arm of chromosome 1’. The technique used was new, called array CGH, and no other case with a deletion of this precise region of chromosome 1 had been detected worldwide to date.

The code for Annie’s array CGH analysis is: 46,XX.arr cgh 1p31.1->1p31.3 (RP4-759M20->RP11-261J10) x 1

As a journalist and as the founder of Mindroom, I was very excited by the news. I felt we were right at the heart of a genetic detective novel. But as a mother, I and our family will always be up against a void in Annie’s genome of about 6 million base pairs of DNA, which is less than 3% of the total length of chromosome 1.

That particular void is irreparable, and perhaps the upside of such an absolute is a blessing, as we are spared the hunt for a cure. But it is the other void, the further scientific understanding of what role those missing 21 genes would have played, had Annie arrived in tact, with a complete count of genes, that needs to be filled. Professor FitzPatrick and his colleagues, are at present unable to answer those questions, which to a layperson seems almost incredible when we have such sophisticated answers to so much in today’s world.

Here we are once again, waiting for technology to catch up with our hypothesis – is there a connection between Annie’s aunts ulcerative colitis and the fact that three of the missing genes are linked to human disease; IL23R as a protective factor in inflammatory bowel disease?

Or could one of the missing genes have been a contributing factor to Annie’s two episodes of acute lobar pneumonia which required hospitalisation at the ages 12 and 17 years, with the latter episode associated with a severe unclassified mucocutaneous disorder?

What we do know though, is that deletions of 1p31.1-1p31.3 are very rare. A review of standard genetic banding by Professor FitzPatrick and his team, revealed only five cases with a further case identified with a significantly larger, but overlapping deletion.

Having done our own genetic detective work, we have checked with the excellent UNIQUE, the rare chromosome disorder support group based in Surrey, who have as complete a database on all known chromosome differences as is possible, and so far Annie is the first person to be identified with this particular chromosome profile. Her specifics are now registered with UNIQUE and available to the world, www.rarechromo.org

It is in the hope that by writing up Annie’s case so far, we will be able to identify other Annie’s out there, thus creating a syndrome from which affected families can draw information and create a frame of reference.

On the wall in my study, within my line of vision and as a thought provoking reminder of who I am, sits a badge from a Parliamentary Reception at the Scottish Parliament that simply says ‘Sophie Dow – Rare chromosome disorders and Mindroom’. Who could have predicted such a deviation in life?

Sophie Dow, June 2010

For more information on Mindroom, please visit www.mindroom.org

Mindroom’s fifth international conference No Mind Left Behind, 29-30 March 2011 at Glasgow Royal Concert Hall, features over 50 of the worlds leading experts within the field of social communication and learning difficulties.

For more information www.mindroom.org/nomindleftbehind