

POINTS OF VIEW

RING CHROMOSOME 22, MOOD DISORDER AND SODIUM VALPROATE (A CASE REPORT)

Introduction

Ring chromosome, also known as ring 22, or r (22), was first reported by Weleber and confirmed by Magenis (Weleber et al., 1968). So far, only a few cases have been described. Its incidence is considered to be one per million in the UK. It arises from terminal breaks on both arms of chromosome 22 followed by fusion. Although familial cases have been described, it is mainly considered to be caused by spontaneous or de novo errors very early in the development of the embryo (Battini et al., 2004).

The physical phenotype is not very distinct with mild and variable dysmorphic features. Cognitive aspects are of moderate to severe learning disability. Behavioural aspects are absence of speech and autistic behaviour. Bipolar affective disorder has been described in ring chromosome 22 (Sovner et al., 1996; MacLean et al., 2000).

Case history

Mr A is a 35 years old immobile (wheelchair bound) service user with severe learning disability who is in a residential setting. He was first diagnosed with ring chromosome 22 at 5 years of age. He has been in long term residential care since he was ten years of age. He is able to understand simple commands, recognises faces, is

aware of his environment, but cannot talk. His basic presentation that required psychiatric input was cyclic changes in his behaviour over a three year period.

Detailed history revealed that he displays mood swings regularly when he can change between manic stages and depression. He presents with the following:

Elated phase

- Makes noises, shouts at staff and has bouts of inappropriate laughter
- Becomes overactive, quite fidgety in bed, moving his hands, while moving rapidly from place to place whilst in his wheelchair
- Pulls staff at every possible opportunity
- Sleep disturbance and on some nights has one hour maximum sleep while shouting at night
- Shows very poor concentration especially while eating and becomes unable to put a spoon in his mouth during that time

Depressed phase

- Is tired and finds it difficult to stay awake
- Shows no interest in any of the routine tasks that he usually enjoys
- Does not eat properly
- Looks tired
- Avoids social situations
- Noticeable motor retardation

All these symptoms go in cycles of

variable duration. Sometimes symptoms can occur in mixed state also or can change on a daily basis. Symptoms were first noticed when he was twenty-three but may predate that as initially the symptoms were considered as attention seeking. The symptoms have become more intense during the last two years and the cycles have become more frequent.

Background information: There is no history of obstetric complications or asphyxia at birth. During the first week his unusual appearance was noted by his mother. He was noted to be hypotonic and slow in reflexes. Global developmental delay with delayed speech resulted in him attending the paediatrician regularly. He was considered as a probable learning disability case at three years of age and this was confirmed when he was five years old. There is no family history of any learning disability or psychiatric illness. His physical disability has deteriorated in the last few years. He has a past history of undescended testis and recurrent urinary tract infection.

Treatment: He was initially started on Haloperidol by his GP for presumed challenging behaviour. This resulted in no benefit except some improvement in sleep. Later on, after review by the psychiatrist, he was started on Carbamazepine that resulted in some improvement for a short while in that the cycles changed to become much longer in duration. This improvement was subsequently strengthened by Quetiapine but the effects were short lived. Olanzapine was then used as an alternative to achieve further improvement but this made no major difference either.

After this, he was started on sodium valproate and showed a marked improvement. He did not exhibit mood swings for the next six months (note that lithium has been avoided because of disturbed renal function).

Discussion

Clinical findings in ring chromosome 22

The following associations have been described in various studies:

Mental retardation, general hypotonia, hydronephrosis, urinary tract infection, downward slanting palpebral fissure, epicanthus, undescended testes, dysphagia, lack of development of speech, unsteady gait, large low set ears, puffy feet, cardiac defects, gum hyperplasia and seizures (MacLean et al., 2000; Ishmael et al., 2003; Hunter et al., 1977). It should be noted, however, that it is not necessary for symptoms to be present in every person - they are not diagnostic and many symptoms are noted only in case reports.

Chromosome 22 related disorders include:

- Chromosome 22 Central
- 22q11 Deletion Syndrome (DiGeorge Syndrome, Velocardiofacial Syndrome)
- The 11/22 Translocation (Emanuel Syndrome, partial trisomy 11/22)
- 22q13 Deletion Syndrome (Phelan-McDermid Syndrome)
- Cat Eye Syndrome
- Complete or Full Trisomy 22
- Mosaic Trisomy 22
- Chromosome 22 Ring
- Microduplication 22q11 Syndrome

(taken from Chromosome 22 central Inc., USA (<http://www.nt.net/a815/learn.htm>)).

The symptoms represented in this service user fulfil the DC-LD (Diagnostic criteria for psychiatric disorders for use with adults with learning disabilities/mental retardation) criteria of bipolar affective disorder in learning disability. The diagnosis is strengthened by the good response to sodium valproate. Bipolar disorder is often considered a condition that reflects ge-

netic influence. If one identical twin develops bipolar disorder, the likelihood of the other twin developing the condition is 85 to 89%. Only 15% of instances of bipolar disorder can be attributed to factors specific to individuals or to their unique life experiences outside the family of origin (Tsuang and Faraone, 1990; Bertelsen et al., 1977; Mendlewicz and Rainer, 1977). Occasional families may exist in which a single gene plays a major role in determining susceptibility, but the majority of bipolar disorder involves more complex genetic mechanisms such as the interaction of multiple genes and environmental factors. Molecular genetic positional and candidate gene approaches are being used for the genetic dissection of bipolar disorder. No gene has yet been identified but promising findings are emerging. Regions of interest include chromosomes 4p16, 12q23—q24, 16p13, 21q22, and Xq24—q26 (Kelsoe, 2001). A genome survey of bipolar disorder using 443 micro-satellite markers in a set of 20 families from the general North American population to identify possible susceptibility loci was conducted. A maximum logarithm of odds score of 3.8 was obtained at D22S278 on 22q (Craddock and Jones, 2001). Chromosome 22 is involved in catechol-o-methyltransferase (COMT). This is the enzyme, which is responsible for postsynaptic dopamine and norepinephrine degradation. Alteration in the gene responsible for "COMT" formation can be implicated in mood alteration. Contrary findings, however, have been reported in an investigation by Rice et al., (1984), who showed that there was no difference in control in those with mood disorder in these monoamines levels (Rice et al., 1984).

Chromosome 22 has been implicated in schizophrenia and bipolar disorder in a number of linkage, association and cytogenetic studies (Kelsoe, 2001; Coon et al. 1994; Vallada et al., 1995). Recent evidence has also implicated CAG repeat tract expansion in these diseases (Saleem et al., 2001). The 8-repeat allele at this locus was significantly over represented in both schizophrenia and bipolar patient groups when

compared to ethnically matched controls, while alleles at the other three loci did not show any such difference.

Conclusion

- Bipolar affective disorder appears to be associated with ring chromosome 22.
- Bipolar affective disorder in ring chromosome 22 can present with more atypical symptoms and in rapid cycling fashion.
- This patient's bipolar disorder showed a better response to sodium valproate than it did to other mood stabilisers.

Summary

The case of a 35 year old man with severe learning disability, ring chromosome 22, rapid cycling bipolar illness and the effectiveness of sodium valproate is reported. We were led to write this case report because of the limited research on both ring chromosome 22 and its unusual manifestation with rapid cycling bipolar illness in severe learning disability. Although velocardiofacial syndrome and its association with psychotic illness is well documented, there has not been much work on bipolar disorder in association with this genetic abnormality.

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