49,XXXXY syndrome: behavioural and developmental profiles

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Abstract

Behavioural, psychological, and cognitive profiles of three cases, including a 5 year old male with a 49,XXXXY karyotype and a (3;15) translocation, a 9 year old male with a 49,XXXXY karyotype, and a 32 year old male with 48,XXXY/49,XXXXY mosaicism, are presented. Significant behavioural problems were seen in the two older patients. The degree of mental retardation and impairment of language abilities were shown to be more severe in the older subjects as well. These findings are discussed with respect to the effects of the X chromosome on brain development.

Cases of sex chromosome aneuploidy are not uncommon and a broad spectrum of developmental outcome has been described. Since the first report of a patient with a 49,XXXXY karyotype by Fraccaro *et al*¹ in 1960, a clinical description has been established for this syndrome. However, relatively little is known regarding the behavioural, psychological, and cognitive profile of these patients. Evidence indicates that despite X chromosome inactivation, an increased number of X chromosomes is associated with an increase in cognitive and language disability.² This report describes three subjects with partial or complete 49,XXXXY sex chromosome aneuploidy. Particular emphasis is placed on the severity and range of disability associated with this condition and the possible mechanisms by which it is produced.

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Methods

The behaviour of our subjects was examined using a modified version of the Aberrant Behavior Checklist (ABC),³ which covers five aspects of behaviour frequently encountered in developmentally disabled persons: irritability and agitation, lethargy and withdrawal, stereotypy, hyperactivity and non-compliance, and inappropriate speech. The checklist was completed by both a parent and a teacher. Individual behaviour items were rated from 0 to 3, according to the severity of the problem.

Language abilities were assessed through an interview with the parent(s) of the subject using the Vineland Adaptive Behavior Scale, Survey Form.⁴ Language impairments were also noted by observation.

Cognitive assessment using the Stanford Binet, 4th edition was performed on one subject at the time of evaluation. General cognitive ability was obtained for the other subjects from reports of previous testing.

Case reports

CASE 1

Case 1 was a 4 year 10 month old male with a karyotype of 49,XXXXY, t (3;15) (q29; q26.1) who was ascertained as a control subject for a research project. The translocation noted in this patient was also present in his mother, maternal uncle, and maternal grandfather. The maternal uncle was described as a slow learner with possible mild cognitive delays, although no formal diagnosis of mental retardation had been made. He weighed 2728 g at birth. His IQ was 78±6 as measured by the Stanford Binet, 4th edition.

Case 1 was reported to have no significant behavioural problems. There were no significant findings from the ABC data. Vineland score in the communication domain was low with a mild deficit. Expressive subdomain score was low, while his receptive subdomain score was adequate. He had a statistically significant weakness in the communication domain when compared to his mean domain score. When compared to a National Standardization Sample,⁴ the difference between his communication domain score and mean domain score was found to fall in the extreme 16th centile, indicating significant weakness

Clinical data for the three patients

	Patient 1	Patient 2	Patient 3
Age	4 y 10 mth	9 y 5 mth	32 y
Karyotype	49,XXXXY t(3;15)(q29;q26.1)	49,XXXXY	48,XXXXY/49,XXXXY
IQ	Low average	Mild MR	Moderate MR
Behavioural problems	None	Irritability/agitation, hyperactivity/non-compliance, inappropriate speech	Irritability/agitation, lethargy/withdrawal, stereotypy, hyperactivity/non-compliance, inappropriate speech
Vineland	Low	Low	Low
Communication domain	Mild deficit, low expressive, normal receptive	Moderate deficit, low expressive, low receptive	Profound deficit, low expressive, normal receptive

in communication skills as compared to other overall developmental abilities.

CASE 2

Case 2 was a 9 year 5 month old white male with a 49,XXXXY karyotype. At birth he weighed 1936 g. His IQ was in the mildly mentally retarded range.

His family history was significant for depression. He had a long history, beginning around the age of 6, of disruptive and oppositional behaviour, irritability, and temper tantrums. Problems with self-control and impulsivity were present and included aggression with peers such as throwing things, hitting, kicking, and pinching. On the ABC, case 2 was rated by his parent and teacher as having significant behaviour problems in the following areas: irritability and agitation, hyperactivity and non-compliance, and inappropriate speech.

Speech contained significant problems with dysarticulation. Vineland Adaptive Behavior score was low with a moderate deficit in the communication domain. A statistically significant weakness in the communication domain was noted when compared to the mean domain score. The difference between his communication domain score and the mean domain score represented a difference seen in only the extreme 5% of the National Standardization Sample,⁴ indicating a significant weakness in communication ability as compared to his general developmental functioning.

CASE 3

Case 3 was a 32 year old male with a 48,XXXXY/49,XXXXY karyotype. He weighed 1496 g at birth. His IQ was in the moderately mentally retarded range.

Case 3 suffered from recurrent episodes of dramatic change in mental status involving psychomotor behaviour, affect, social withdrawal, self-injury, and possible psychotic symptoms. He also showed problems with self-control, including grabbing at people. Parent ABC data, rated during times of

adverse change in mental status, showed extreme behaviour problems in the following areas: irritability and agitation, lethargy and social withdrawal, hyperactivity and non-compliance, and inappropriate speech. Stereotypic behaviour was also a serious problem. Teacher ABC data, rating overall behaviour, showed extreme problems with inappropriate speech.

He exhibited abnormal speech form and content. His score in the Vineland communication domain was low with a profound deficit. Expressive subdomain score was low, while receptive subdomain score was adequate. A statistically significant weakness in the communication domain was noted in comparison to the mean domain score. This difference between the communication domain score and mean domain score represented a difference found in only 1 to 5% of the National Standardization Sample.⁴ This indicates a severe deficit in communication ability as compared to general developmental abilities. A summary of the clinical data for all three patients is shown in the table.

Discussion**COGNITIVE DEVELOPMENT**

Borghgraef *et al*⁵ reported a widespread variation of intellectual performance in 49,XXXXY syndrome with IQ ranging from 20 to 70 with a mean of 35; the majority of adult patients fell in the moderate to severe range of mental retardation. For the patients described in this report, the youngest subject had an IQ of 78 ± 6 as measured by the Stanford Binet, 4th edition, showing that IQ in this population can fall in the low average range. Shapiro *et al*,⁶ Schmidt *et al*,⁷ and Borghgraef *et al*⁵ noted a decline in intellectual development with age in 49,XXXXY males.

In our report, language impairment and degree of mental retardation appeared to be most severe in the older subjects. Although this cross-sectional evaluation cannot definitely address the issue of intellectual decline in 49,XXXXY syndrome, our findings suggest the need for other longitudinal investigations.

BEHAVIOUR

Patients with 47,XXY karyotype have been described by Walzer *et al*⁸ as exhibiting low activity, low intensity of responsiveness, and high withdrawal, especially from new situations. Stewart *et al*² described 47,XXY patients as less social, less assertive, and less active than 46,XY males. These patients have also been described as having problems with impulsivity and self-control.^{9,10} Subjects with 49,XXXXY, which is often considered a variant of the 47,XXY syndrome, have been noted as exhibiting behavioural problems, but no consistent profile has been described. Borghgraef *et al*⁵ described 49,XXXXY patients as very timid and shy, with low frustration tolerance and very anxious reactions to minor charges. Stereotyped language and hyperactivity were also described. Of the patients described in our report, cases 2 and 3 were shown to exhibit serious behavioural problems, especially in the areas of irritability and agitation, hyperactivity and non-compliance, and inappropriate speech. However, in this study, cases 2 and 3 were both ascertained after referral for evaluation of behavioural problems. As previously noted, case 1 was ascertained as a control subject for a research project and was shown to exhibit no behavioural problems on the ABC. Therefore, behavioural problems in the two older subjects may not be representative of the general 49,XXXXY population. However, case 2 did not exhibit major behavioural difficulties until an age at which the demands of a structured setting were encountered. This suggests that our youngest subject, case 1, may have not yet reached an age at which behavioural problems are exhibited.

TRANSLOCATION

Ockey and de la Chapelle¹¹ and de la Chapelle and Schroder¹² described a 49,XXXXY male with a balanced 4;11 translocation. The translocation was inherited and present throughout the family members. The patient showed no clinical abnormality other than that characteristic of 49,XXXXY syndrome. In this study, case 1 was shown to have an inherited 3;15 translocation that appeared to be balanced. There seems to be no evidence of a relationship between the presence of a translocation as shown in these two subjects and the occurrence of the 49,XXXXY karyotype.

LANGUAGE

Poor language development is well documented in cases of excess X chromosome material. It has been shown that anomalous numbers of X chromosomes are associated with specific deficits in intellectual ability. A study of the intellectual abilities of children with excess X chromosomes by Netley and

Rovet¹³ showed a significant deficit in verbal ability, while non-verbal skills were intact. Rovet and Netley¹⁴ found a group of trisomy X girls to be deficient in verbal skills. They found greater impairments with verbal tasks than with spatial tasks. In the case of deficient amounts of X chromosome material (that is, 45,X Turner's syndrome), the opposite pattern of ability, defined by a marked spatial deficit with normal verbal skills, has been reported.¹⁵ Similar results were stated by Money,¹⁵ who reported that when verbal and performance values are compared, it is found that subjects with sex chromosome monosomy (45,X) have a lower performance IQ than verbal IQ. These studies seem to suggest that as the number of excess X chromosomes increases the severity of verbal impairment also increases.

In a study of 47,XXY males, Graham *et al*¹⁶ described greater impairment in language production than in language comprehension. These findings suggest a relation between the amount of X chromosome material and the relative development of verbal and non-verbal abilities. These authors report that specific deficits in expressive language may be indicative of left hemisphere dysfunction that results from the reversal of the usual left-right asymmetry of the brain, leaving the left hemisphere anatomically ill suited to perform language functions.

Severe retardation in language development in 49,XXXXY patients has been described by Borghgraef *et al*⁵ and others. Moric-Petrovic *et al*¹⁷ described a significant discrepancy between expressive ability and comprehension in these patients. In our study, all three patients with the 49,XXXXY karyotype were found to have a significant deficit in language abilities. Cases 1 and 3 were shown to have low expressive language skills while their receptive language skills were adequate according to the Vineland Scale.

Netley and Rovet¹³ have suggested that in cases of a supernumerary X, slow rates of prenatal neuronal growth selectively retard the development of the left hemisphere, thereby disturbing the normal process of hemispheric lateralisation, specifically the specialisation of the left cerebral hemisphere for language functioning. This hypothesis (along with that presented by Graham *et al*¹⁶) may explain the severe language disorder found in the 49,XXXXY subjects in this study. Recent evidence indicates that non-contiguous genes on the X chromosome escape the normal processes leading to inactivation and remain capable of genetic expression.¹⁸ Therefore, gene dosage effects may cause disruption of specific aspects of brain development in subjects with X chromosome aneuploidy.

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