Should children with ADHD and normal intelligence be routinely screened for underlying cytogenetic abnormalities?

Report by

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You are assessing a 7 year old boy with attention and behaviour difficulties, and poor school performance. He has an average IQ and meets the diagnostic criteria for attention deficit hyperactivity disorder (ADHD). There is no evidence of developmental delay, dysmorphism, or other physical abnormalities and no relevant family history. Parents are keen on investigation for a "cause" for his problems. You are aware that some chromosomal and cytogenetic abnormalities may be associated with ADHD. You wonder if you should check karyotype and look for cytogenetic abnormalities with genetic implications for the family.

Structured clinical question

Should children with ADHD and normal intelligence [subject] be routinely screened* [intervention] for underlying cytogenetic abnormalities [outcome with genetic implications]?

Search strategy and outcome

OVID Medline and EMBASE search: "ADHD" AND ("cytogenetics" OR "human chromosomes"). A total of 61 articles were obtained combining these searches. After searching abstracts, 10 relevant articles were retrieved. (The remainder were mainly studies attempting to map ADHD to one/several gene loci using various genetic techniques, including linkage analyses. In the absence of routine and widespread availability of these tests, and their unproven clinical use, they were not considered.)

Secondary sources: Cochrane Library, Best Bets: no papers found.

Search date: September 2005.

* Karyotype, fragile X mutation analysis, FISH for 22q11.2 deletion, and high resolution chromosome banding for other cytogenetic abnormalities.

Commentary

Behaviour and cognitive problems including ADHD in children have been associated with several chromosomal and cytogenetic abnormalities. The most notable of these include velocardiofacial syndrome (VCFS),¹ fragile X syndrome,² sex chromosome aneuploidies (SCA),^{3 4} the X-linked condition Simpson-Golabi-Behmel syndrome, partial trisomy of chromosome 16, as well as certain balanced translocations. Some investigators have suggested that cytogenetic analyses should be considered in children with ADHD.⁵ However, most evidence to date suggests that these abnormalities are found with increased frequency in children with a learning disability (IQ <80) in addition to ADHD.

Using the search strategy above, there was only a single exploratory study⁶ identified that assessed the prevalence of genetic abnormalities in an unselected population of 100 children with ADHD and IQ >80 (see table 1). Giemsa banded karyotype testing for sex and other chromosomal abnormalities, and specific abnormalities for fragile X and VCFS, were performed on this group, with the hypothesis that there would be an increased rate of these abnormalities collectively than in the general population. There were no subjects found with either the fragile X mutation or chromosome 22q11.2 deletion for VCFS. Only one subject had a clear cytogenetic abnormality (a girl with trisomy 47, XXX), and this did not differ significantly from that expected in the general population (1/426). This child was clinically indistinguishable from the other subjects with regard to ADHD symptoms but had slightly lower reading and written language achievement scores.

Although limited by a small sample size, this study showed that children with ADHD and average IQ do not display higher rates of cytogenetic abnormalities. However, definite evidence can only be obtained from larger well controlled studies as many of the conditions mentioned, especially SCA, can remain clinically unrecognised in subjects with normal intelligence. Testing for these abnormalities is expensive and at present, is not indicated in the absence of clinical indications such as developmental delay, relevant physical signs, positive family history, or learning disability.

There were numerous case reports and uncontrolled cohort studies looking at ADHD and specific populations of children with cytogenetic abnormalities⁷⁻¹⁵ (see table 2).

Currently there is considerable research interest in genetic polymorphisms and particular behavioural phenotypes including ADHD. This is a rapidly expanding field and is likely to link particular genotypes with the ADHD phenotype. However, at present none of these research tools has been shown to be of particular use to the clinician.

Table 1 Prevalence of cytogenetic abnormalities in an unselected population of children with ADHD

Citation	Study group	Study type	Outcome	Key results	Comments
Bastain <i>et al</i> (2002) ⁶	Blood samples from 100 children (64 boys, 36 girls, mean age 10.2 ± 3.1 years) with combined type ADHD and normal intelligence were analysed for the presence of fragile X mutation expansions, the 22q11.2 micro deletion associated with velocardiofacial syndrome, and cytogenetic abnormalities that would be detected with high resolution chromosomal banding	Uncontrolled cohort (level 4)	No. of patients with cytogenetic abnormalities	One girl with ADHD had a sex chromosome aneuploidy (47, XXX). One boy had a premutation-sized allele for fragile X; no subjects showed the full mutation. Testing for 22q11.2 micro deletion was negative for all subjects with ADHD screened. None of these differences exceeded those expected by chance	In the absence of clinical signs or positive family history, these relatively expensive laboratory assessments are not clinically indicated for children with ADHD and normal intelligence, and are not recommended as a component of other genetic investigations of this disorder

Table 2 Case reports and uncontrolled cohort studies linking ADHD with cytogenetic abnormalities in selected groups of children

Citation	Study group	Study type	Outcome	Key results	Comments
Gothelf <i>et al</i> (2004) ⁷	This study investigated the association of familial, developmental, and physical factors with the occurrence of ADHD in 51 patients with non-familial VCFS	Retrospective review (level 4)	Percentage of patients with a diagnosis of ADHD	Twenty one patients (41.2%) were diagnosed with ADHD. There was a significantly greater prevalence of ADHD in the first-degree relatives of the patients with ADHD than in those without	Findings indicate that ADHD in VCFS has a genetic contribution and the patients' VCFS related developmental factors and physical illnesses play a lesser role
Boycott <i>et al</i> (2003) ⁸	A mother and two sons	Case report (level 4)	Chromosomal deletion	Terminal deletion of the short arm of the X chromosome (Xp22.3). Both sons had ADHD and learning disability	One or more genes involved in learning and attention may reside in Xp22.3
Niklasson <i>et al</i> (2002) ⁹	Twenty children and young adults (age range 5–33 years, 12 females and eight males) with genetically confirmed 22q11 deletion syndrome	Uncontrolled cohort (level 4)	No of patients with ADHD	In 13 individuals, attention-deficit-hyperactivity disorder (ADHD), mainly inattentive or combined type in most cases, were diagnosed	A significant number of patients with 22q11 deletion have ADHD along with the VCFS phenotype
Hagerman <i>et al</i> (1985) ¹⁰	Four boys had physical and cytogenetic features of the fragile X syndrome	Uncontrolled cohort (level 4)	No of patients with ADHD	All four patients demonstrated similar learning difficulties that included hyperactivity	The IQ scores of these patients extended into the normal range
Le Caignec <i>et al</i> (2004) ¹¹	Single patient with inherited Ring chromosome 8 and ADHD	Case report (level 4)	Chromosomal abnormality	Child had short stature and mental retardation while family members had normal intelligence	First case report with this particular abnormality
Prabhakara <i>et al</i> (2004) ¹²	Single patient	Case report (level 4)	Chromosomal translocation and sex reversal	46XX and familial (9;11) (p22;p15.5) translocation	Associated with delayed development and cryptorchidism
Doherty <i>et al</i> (2003) ¹³	Two brothers	Case report (level 4)	Chromosomal abnormality	Unusual Xp; Yq translocation chromosome	Associated with attention deficit, generalised epilepsy and ichthyosis
Baker <i>et al</i> (2001) ¹⁴	Single patient	Case report (level 4)	Chromosomal abnormality	Chromosome 2 interstitial deletion (del(2)(q14.1q21))	ADHD associated with connective tissue laxity
Ruud <i>et al</i> (2005) ¹⁵	Two boys	Case report (level 4)	Chromosomal abnormality	47, XXY karyotype	ADHD was diagnosed and stimulant medication used but full criteria were not met on psychological testing

CLINICAL BOTTOM LINE

- There is limited evidence from an uncontrolled study that children with ADHD and normal intelligence do not display higher rates of underlying cytogenetic abnormalities (Grade D). Testing for these is therefore not indicated at present. Large well controlled studies would be required to provide more definite evidence
- Cytogenetic abnormalities are more commonly found in the presence of learning disability, developmental delay, relevant physical signs or positive family history, and testing should be limited to these situations (Grade D)

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