Autism and Genetic Disorders

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Abstract

The syndrome of autism has been documented as occurring in association with a wide variety of genetic conditions. Autistic patients with a coexistent genetic condition, however, are not behaviorally or developmentally distinct from autistic patients for whom there is no known etiology or associated organic condition. This report reviews the literature linking autistic behavior with genetic conditions. Genetic, neurodevelopmental, and neuropathological findings in three genetic conditions which frequently give rise to autism are presented in detail. On the basis of this review, two hypotheses are supported: (1) autism is a behaviorally defined phenotype which arises from diverse causes of central nervous system (CNS) damage, and (2) the autistic phenotype represents only one point along a continuum of psychological dysfunction resulting from CNS damage. Current theories of genetic influences on brain development are reviewed, with emphasis on the relationships among qualitative, quantitative, and temporal abnormalities of CNS maturation and behavioral dysfunction. A hypothesis of abnormal brain development resulting from dysfunctional myelination is proposed as a potential etiologic factor in autism.

It is generally accepted that autism is a chronic debilitating mental illness resulting from central nervous system (CNS) dysfunction. Essential features of the syndrome include disturbances of language, cognition, perception, relatedness, motility, and development (Ornitz and Ritvo 1976). It is unsettled whether autism is a unitary disease with a single etiology or a behavioral phenotype with multiple, heterogeneous causes. The latter hypothesis is supported by the diversity of organic conditions that appear to be causally related to the development of autistic behavior. These include infections such as encephalitis or congenital rubella (Chess 1971; DeLong, Bean, and Brown 1981), seizure disorders, genetic conditions like fragile X syndrome or tuberous sclerosis (Mansheim 1979; Meryash, Szymanski, and Park 1982), metabolic disorders such as phenylketonuria or histidinemia (Friedman 1969; Kotsopoulous and Kutty 1979), and a variety of other conditions which affect brain development and function (Coleman 1976; Ornitz 1983).

Some authors believe that even though autistic patients with organic conditions demonstrate classical autistic behavioral patterns, they should be distinguished from autistic individuals for whom there is no known etiology or associated condition (Rimland 1971; Eisenberg 1972). Autistic patients with a coexisting organic condition or neurological symptoms are not, however, behaviorally or developmentally distinct from autistic patients without such features (Knobloch and Passamanick 1975; Ornitz, Guthrie, and Farley 1977; Garreau, Barthelemy, and Sauvage 1984).

The syndrome of autism may represent only one point on a continuum of cognitive, perceptual, and linguistic dysfunction resulting from specific types of genetically and/or environmentally induced
brain damage. Alternate manifestations of such damage could include specific developmental disorders, uncomplicated mental retardation, hyperactivity, linguistic deficits, a "partial" autistic syndrome, or nonautistic psychosis. These conditions are present in many individuals with organic syndromes which frequently produce autistic behavior such as the fragile X syndrome (Hagerman, McBogg, and Hagerman 1983) or congenital rubella (Chess 1971). They are also present in relatives of patients with idiopathic autism. Siblings of these children manifest cognitive and linguistic disorders with much greater frequency than the general population (Rutter, Bartak, and Newman 1971; August, Stewart, and Tsai 1981; Minton et al. 1982). In their study of twins of autistic children, Folstein and Rutter (1977) reported a 38 percent concordance rate for autism in monozygotic pairs. This figure was increased to 82 percent when the definition of concordance was broadened to include any form of cognitive or language disorder (including autism). The authors concluded that the "genetic factor" in their patient population gave rise to a vulnerability to cognitive/linguistic dysfunction with autism representing only one possible manifestation.

On the basis of the preceding observations, two hypotheses are suggested: (1) autism is a behaviorally defined phenotype which arises from diverse causes of central nervous system (CNS) damage as opposed to a homogeneous, distinct disease entity, and (2) the phenotype represents only one point along a continuum of psychological dysfunction resulting from CNS damage instead of a separate category of psychopathology. If the first hypothesis is valid, any endeavor to uncover a common genetic determinant from a population of autistic patients would be an impossible task. To date, such attempts have yielded inconsistent or negative results (Hanson and Gottesman 1976; Spence 1976).

Further inquiry into the genetic and neurobiological determinants of autism, then, requires an alternate route of investigation. We, therefore, chose to review the literature on known genetic disorders reported to be associated with autism. This approach was chosen in the hope that the biochemical, neurodevelopmental, and pathophysiological data from previous studies of the genetic conditions would yield common neurobiological denominators relevant to autism, and help to elucidate the pathway from gene to behavior.

Reports of genetic conditions in which autistic behavior has been described are presented in tabular form. We have included those reports in the literature in which the diagnosis of autism was made with reference to an accepted diagnostic instrument, or where enough details of the case were provided for the DSM-III diagnosis (American Psychiatric Association 1980) to be made post hoc by the authors. The designation of "probable autism" is used to describe cases in which neither of these criteria are satisfied fully, but the diagnosis is strongly suspected from the information available. To concentrate on conditions in which relevant genetic and neurobiological information may be available, we limited this review to autistic patients with chromosomal abnormalities, single gene disorders, and syndromes of unknown etiology that are strongly suspected of having a genetic basis.

Literature Review

Chromosomal Disorders (table 1). The overwhelming majority of autistic children with chromosomal abnormalities reported in the literature have sex chromosome anomalies, particularly the fragile X syndrome. Autistic behavior occurs infrequently in autosomal disorders and is not consistently associated with any single chromosome or chromosome group.

The specific chromosome abnormality in the fragile X syndrome is detected by visualizing a fragile site on the X chromosome when cells are grown in folate-deficient or other specially modified media (Turner and Jacobs 1983). The frequency of the fragile X syndrome in the general population has been reported to be as high as 0.9 per 1,000 live male births (Herbst and Miller 1980), making it at least the second leading cause of mental retardation due to a chromosomal abnormality after Down's syndrome. Studies investigating psychological abnormalities in populations of patients with the fragile X syndrome have described from 4 to 60 percent of affected males as autistic (Turner, Daniel, and Frost 1980; Brown et al. 1982; Levitas et al. 1983; Nielson 1983; Fryns et al. 1984) Although there may be some common characteristic physical features associated with this syndrome such as large ears or macroorchidism (Hagerman, McBogg, and Hagerman 1983), many patients may not have any distinguishing features except for their behavioral dysfunction. One study has reported on the presence of the fragile X chromosome in a large autistic population (Watson et al. 1984). Out of 76 autistic males, four (5.4 percent) demonstrated the fragile X marker.
### Table 1. Chromosomal disorders

<table>
<thead>
<tr>
<th>Genetic condition</th>
<th>Study</th>
<th>Autistic patients (n)</th>
<th>Specific features of patients identified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XYY</strong></td>
<td>Abrams &amp; Pergament (1971)</td>
<td>1, case report</td>
<td>Hypertelorism, high arched palate</td>
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<tr>
<td></td>
<td>Nelson, Christensen &amp; Friedrich (1973)</td>
<td>1, identified from 22 patients with XYY</td>
<td></td>
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<td></td>
<td>Mallin &amp; Walker (1972)</td>
<td>1, case report</td>
<td></td>
</tr>
<tr>
<td><strong>XXYY</strong></td>
<td>Ornitz, Guthrie &amp; Farley (1977)</td>
<td>1, identified from 74 autistic patients</td>
<td>Neonatal distress, hypotonia at birth</td>
</tr>
<tr>
<td><strong>XXY</strong></td>
<td>Campbell, Wolman &amp; Brewer (1972)</td>
<td>1, case report</td>
<td>Self-injurious behavior</td>
</tr>
<tr>
<td><strong>XXX</strong></td>
<td>Wolraich et al. (1970)</td>
<td>1, identified from 25 autistic patients</td>
<td>Probable autism</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Levitas et al. (1983)</td>
<td>6, identified from 10 fragile X patients</td>
<td></td>
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<td></td>
<td>Brown et al. (1982)</td>
<td>5, identified from 22 fragile X patients</td>
<td></td>
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<tr>
<td></td>
<td>Turner, Daniel &amp; Frost (1980)</td>
<td>1, identified from 25 fragile X patients</td>
<td>Probable autism</td>
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<tr>
<td></td>
<td>Nielson (1983)</td>
<td>1, identified from 27 fragile X patients</td>
<td>Probable autism</td>
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<td></td>
<td>Fryns et al. (1984)</td>
<td>3, identified from 21 fragile X patients</td>
<td>Probable autism</td>
</tr>
<tr>
<td></td>
<td>Watson et al. (1984)</td>
<td>4, identified from 76 autistic males</td>
<td></td>
</tr>
<tr>
<td></td>
<td>August (1983)</td>
<td>2, case reports</td>
<td></td>
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<tr>
<td></td>
<td>Gillberg (1983)</td>
<td>3, case reports</td>
<td>Patients are identical triplets</td>
</tr>
<tr>
<td></td>
<td>Meryash, Szymanski &amp; Park (1982)</td>
<td>3, case reports</td>
<td></td>
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<tr>
<td></td>
<td>Reiss (1984, unpublished data)</td>
<td>2, case reports</td>
<td></td>
</tr>
<tr>
<td>&quot;Large&quot; Y chromosome</td>
<td>Hoshino et al. (1979)</td>
<td>9, identified from 32 autistic patients</td>
<td>Patients with large Y had less severe autistic behavior and language disturbance compared to patients with normal Y</td>
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<tr>
<td></td>
<td>Judd &amp; Mandell (1968)</td>
<td>3, identified from 8 autistic patients</td>
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</tbody>
</table>
Table 1. Chromosomal disorders—Continued

<table>
<thead>
<tr>
<th>Genetic condition</th>
<th>Study</th>
<th>Autistic patients (n)</th>
<th>Specific features of patients identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Wakabayashi (1979)</td>
<td>1, case report</td>
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<td></td>
<td>Maltz (1979)</td>
<td>1, case report</td>
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<td></td>
<td>Knobloch &amp; Passamanick (1975)</td>
<td>1, case report</td>
<td></td>
</tr>
<tr>
<td>Trisomy 22</td>
<td>Turner &amp; Jennings (1961)</td>
<td>1, case report</td>
<td>Probable autism</td>
</tr>
<tr>
<td>t(22,13)</td>
<td>Hansen et al. (1977)</td>
<td>1, case report</td>
<td>Severe mental retardation, seizures, abnormal electro-</td>
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<td></td>
<td></td>
<td>encephalogram, ataxia, hypotonic</td>
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<tr>
<td>Gp + (t(13))</td>
<td>Crandall, Carrel &amp; Sparkes (1972)</td>
<td>1, identified from 700</td>
<td>IQ = 45, chromosome abnormality is probable normal variant</td>
</tr>
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<td></td>
<td></td>
<td>outpatients referred to</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>child psychiatry</td>
<td></td>
</tr>
<tr>
<td>3p− (deletion of material from chromosome 9)</td>
<td>Hagerman (1984, unpublished data)</td>
<td>1, case report</td>
<td>Prominent ears, pectus excarotum, probable autism</td>
</tr>
<tr>
<td>5p +</td>
<td>Hagerman (1984, unpublished data)</td>
<td>1, case report</td>
<td>Hyperreflexia, tremor, probable autism</td>
</tr>
<tr>
<td>8p−</td>
<td>Hagerman (1984, unpublished data)</td>
<td>1, case report</td>
<td>Multiple dysmorphic features, probable autism</td>
</tr>
<tr>
<td>17p−</td>
<td>Hagerman (1984, unpublished data)</td>
<td>1, case report</td>
<td>Hypertelorism, low-set ears, supernumerary digit</td>
</tr>
<tr>
<td>Increased chromosome breakage</td>
<td>Siva San Kar (1970)</td>
<td>Population of 31 autistic patients</td>
<td></td>
</tr>
</tbody>
</table>

Two studies (Judd and Mandell 1968; Hoshino et al. 1979) have found an association between large size of the Y chromosome and autism. Large chromosome size is correlated with the presence of increased repetitive DNA sequences (McKay, Bobrow, and Cooke 1978). Increased size of the Y chromosome is particularly of interest because of the high male-to-female ratio seen in autism and the association of autism with the XYY karyotype (Abrams and Pergament 1971; Mallin and Walker 1972; Nelson, Christensen, and Friedrich 1973). Considerable variation in the size of the Y chromosome within populations is a normal finding, however (Emery and Rimoin 1983).

Increased chromosome breakage in autistic children compared with other psychiatric populations (Siva San Kar 1970) is also of unknown significance. Increased chromosome breakage is seen in several genetic syndromes (Emery and Rimoin 1983), viral infections, and secondary to ionizing radiation and certain drugs (Jackson and Schimke 1979). In the single study reporting this finding (Siva San Kar 1970), detailed information pertaining to medical history,
number of chromosome breakages per patient, or location of the breakage sites was not provided.

Single Gene Disorders (table 2). The list of single gene disorders associated with autism includes a diverse group of autosomal dominant and recessive conditions, each of which gives rise to a broad range of cognitive, language, and behavioral abnormalities in affected individuals. Most of the reported cases, though, come from the well-known association of autism with phenylketonuria (PKU). PKU is an autosomal recessive disorder caused by the inability to metabolize normal amounts of phenylalanine in the diet, leading to an accumulation of this substance throughout the body. A number of factors resulting from the inability to metabolize phenylalanine are presumed to cause the psychiatric and neurological symptoms seen in untreated patients (Menkes 1980).

In his review of PKU and chromosome anomalies, Friedman (1969) reported that most studies analyzing behavior of untreated patients described a large percentage of affected individuals as manifesting part or all of the autistic syndrome. In a separate report (Knobloch and Passamanick 1973), the incidence of PKU in an autistic population identified in a "pediatric developmental service" was 21.9 percent (14 out of 64). Lowe et al. (1980) screened 65 children with "pervasive developmental delays" for PKU, including 50 children with autism. Three cases were discovered, including one 2-year-old child who had reportedly had a negative test for PKU shortly after birth. Hackney et al. (1968) studied 46 children with documented PKU and reported that nine were autistic. These reports imply a much greater association between PKU and autism than would be expected if these two disorders were not causally related.

In a review of neuropathological findings in patients with PKU, Malamud (1966) emphasized abnormalities in myelination as the most consistent abnormality found in the brain. The pattern of CNS tissue damage described was one of white matter vacuolation, also called "status spongiosis," and frank areas of demyelination. Spongy white matter lesions, seen in all patients, consistently occurred in the central, subependymal, and periventricular areas of the cerebrum, the cerebellum, the optic tracts, and the fornix. Scattered lesions were also seen in the basal ganglia, brainstem, and spinal cord. Well-demarcated areas of demyelination were localized in lateral-central and adjacent gyral cerebral white matter and in the cerebellum, but were only seen in older patients in which the disease process had been ongoing for many years. The extent of demyelination was proportional to the age of the patient, indicating an ongoing pathological process.

Other reports have also described quantitative and qualitative abnormalities in myelin, or decreased amounts of lipid components of myelin in the brains of patients with PKU (Prensky, Carr, and Moser 1968; Shah, Peterson, and McKean 1972; Agrawal and Davison 1973). Recent studies examining animal models have suggested that actual formation of the myelin membrane may not be abnormal in PKU. Instead, damage to the developing brain may occur during the latter stages of neuronal differentiation. In one report (Huether, Kaus, and Neuhoff 1982), alterations in axonal outgrowth from specific neuronal populations, especially in the forebrain, were hypothesized to cause desynchronization in the temporal coordination of the myelination process. Another study (Cordero et al. 1983) found abnormalities in dendritic arborization and cell orientation of pyramidal cells in the rat cortex. In a post-mortem examination of an autistic patient with PKU (Williams et al. 1980), changes in pyramidal cell dendritic spine density were seen, a finding that was also discovered in the examination of an autistic patient without an identifiable organic condition (Williams et al. 1980).

An area of controversy in PKU research relates to the specific developmental stage or stages during which CNS tissue damage occurs. Examination of untreated patients with PKU and animal models indicate that qualitative or quantitative abnormalities in myelination of CNS white matter tracts, disturbed neuronal differentiation, or both arise shortly after birth. These lesions appear to correlate clinically with the development of the most severe psychiatric and neurological deficits in PKU, including autism (Lemire et al. 1975; Menkes 1980). There is also evidence of aberrations in brain myelin and other neurocellular abnormalities arising during prenatal CNS development. These abnormalities may be causally related to milder deficits, such as specific developmental disorders, seen in patients treated with dietary intervention from birth (Melnick, Michals, and Matalon 1981).

Because of similarities in observed pathophysiology, two of the three autosomal dominant disorders, neurofibromatosis and tuberous sclerosis, are considered related. Mental retardation is found in 10–20 percent of children with neurofibromatosis and at least 70 percent of patients with tuberous sclerosis.

Mental retardation is found in 10–20 percent of children with neurofibromatosis and at least 70 percent of patients with tuberous sclerosis.
Table 2. Single gene disorders

<table>
<thead>
<tr>
<th>Genetic condition</th>
<th>Study</th>
<th>Autistic patients (n)</th>
<th>Specific features of patients identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive Phenylketonuria</td>
<td>Friedman (1969)</td>
<td>Over 40, described in literature review</td>
<td>Probable autism</td>
</tr>
<tr>
<td></td>
<td>Knobloch &amp; Passamanick (1975)</td>
<td>14, identified from 64 autistic patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lowe et al. (1980)</td>
<td>2, identified from 50 autistic patients</td>
<td>Original PKU screen negative in one patient</td>
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<tr>
<td></td>
<td>Hackney et al. (1968)</td>
<td>9, identified from 46 patients with PKU</td>
<td></td>
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<tr>
<td></td>
<td>Williams et al. (1980)</td>
<td>1, case report</td>
<td></td>
</tr>
<tr>
<td>Neurolipidosis</td>
<td>Creak (1963)</td>
<td>2, identified from 100 patients with &quot;childhood psychosis&quot;</td>
<td>Diagnosis made at autopsy</td>
</tr>
<tr>
<td>Hurler's syndrome</td>
<td>Knobloch &amp; Passamanick (1975)</td>
<td>2, identified from 64 autistic patients</td>
<td>No longer autistic at followup</td>
</tr>
<tr>
<td>Histidinemia</td>
<td>Rutter &amp; Bartak (1971)</td>
<td>1, case report</td>
<td></td>
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<td></td>
<td>Kotsopoulos &amp; Kutty (1979)</td>
<td>1, case report</td>
<td></td>
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<tr>
<td>Oculocutaneous Albinism</td>
<td>Ornitz, Guthrie &amp; Farley (1977)</td>
<td>1, identified from 74 autistic patients</td>
<td></td>
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<tr>
<td>Autosomal dominant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Gillberg &amp; Forssell (1984)</td>
<td>2, identified from 26 autistic patients</td>
<td>Both patients had perinatal complications</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Creak (1963)</td>
<td>1, identified from 100 patients with &quot;childhood psychosis&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lotter (1974)</td>
<td>1, case report</td>
<td>Probable autism, diagnosis at autopsy</td>
</tr>
<tr>
<td></td>
<td>Manshelm (1979)</td>
<td>1, case report</td>
<td>34-week gestation, seizures</td>
</tr>
<tr>
<td></td>
<td>Dick and Ziegler (1967)</td>
<td>1, case report</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taft and Cohen (1971)</td>
<td>2, case reports</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O'Gorman (1970)</td>
<td>1, case report</td>
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</table>
Although patients with tuberous sclerosis have frequently been reported to manifest autistic behavior (Creak 1963; Dick and Ziegler 1967; O'Gorman 1970; Taft and Cohen 1971; Lotter 1974; Mansheim 1979), there have been no systematic behavioral studies of a population of patients with this condition. Autism has also been described in association with infantile spasms (Riikonen and Amnell 1981), a severe form of epilepsy that is often the first presenting sign of tuberous sclerosis.

Neuropathological reports of patients with tuberous sclerosis are dominated by descriptions of the gross anatomy, histology, and ultrastructure of cortical tubers and supependymal nodules (Urich 1976; Bender and Yunis 1980; Trombley and Mirra 1981). The aberrant cell type most often detected in these lesions is considered to be of neuroglial origin (Urich 1976; Trombley and Mirra 1981), although some studies of cellular ultrastructure have found cells with neuronal markers (Bender and Yunis 1980). Neuroglia, specifically oligodendrocytes, are the myelin-forming cells in the CNS. There is also evidence of disordered synaptogenesis within these lesions (Bender and Yunis 1980). These findings have been interpreted as being “most consistent with a defect, possibly metabolic, that affects CNS cells at an early stage and results in varying degrees of abnormal differentiation” (Bender and Yunis 1980). With involvement of neuroglial differentiation in tuberous sclerosis, it is not surprising that areas of deficient or disordered myelin are also seen in this disorder. These areas are often diffuse, involve large areas of white matter independent of tuberous or nodular lesions, and can be visualized by computed tomography (CT scan) (Garrick, Gomez, and Houser 1979). Evidence from studies of fetuses and neonates indicates that pathologic changes in the CNS of patients with tuberous sclerosis, like those in PKU, begin before birth (Thibault and Manueldis 1970).

The two cases of autism and one case of childhood psychosis with autistic features associated with neurofibromatosis (Gillberg and Forsell 1984) were discovered from a total of 51 cases of childhood psychoses of unknown etiology, one half of whom were autistic. The authors found the association of childhood psychoses with neurofibromatosis to be 120 times greater than the expected population incidence if these two disorders were unrelated.

### Table 3. Disorders of unknown etiology

<table>
<thead>
<tr>
<th>Genetic condition</th>
<th>Study</th>
<th>Autistic patients (n)</th>
<th>Specific features of patients identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornelia de Lange syndrome (CDLS)</td>
<td>Johnson et al. (1976)</td>
<td>7, identified from 9 patients with CDLS</td>
<td>Probable autism</td>
</tr>
<tr>
<td></td>
<td>Nyhan (1972)</td>
<td>3, identified from 3 patients with CDLS</td>
<td>Probable autism</td>
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<tr>
<td></td>
<td>Knobloch &amp; Passamani (1975)</td>
<td>1, identified from 64 autistic patients</td>
<td></td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>Reiss et al. (1985)</td>
<td>2, identified from 13 autistic patients</td>
<td>Both patients had elevated serotonin levels</td>
</tr>
<tr>
<td>Moebius syndrome</td>
<td>Ornitz, Guthrie &amp; Farley (1977)</td>
<td>1, identified from 74 autistic patients</td>
<td>Club feet, unilateral absence of pectoralis major</td>
</tr>
<tr>
<td>Marshall-Smith syndrome</td>
<td>Keith et al. (1972)</td>
<td>1, identified from 4 patients with physical features similar to Marshall-Smith Syndrome</td>
<td>Probable autism</td>
</tr>
</tbody>
</table>
and Jervis 1966). Abnormalities in developmental cerebral cortex (Schlesinger et al. 1963). In a postmortem examination of a 5-month-old infant with this disorder demonstrated diffuse deficiency in brain myelination, especially prominent in the brainstem (Ptacek et al. 1963). In a postmortem examination of a 5-month-old infant with CDLS at our facility, deficient and delayed myelination was seen in the basal ganglia (unpublished data). Neuropathological reports have also described more severe developmental damage including abnormalities of gyral and sulcal size (Ptacek et al. 1963), microcephaly (Ptacek et al. 1963; Falek, Schmidt, and Jervis 1966), cyt架构ural abnormalities of the cerebral cortex (Schlesinger et al. 1963; Hart, Jaslow, and Gomez 1965), and pituitary abnormalities (Ptacek et al. 1963; Falek, Schmidt, and Jervis 1966).

Williams syndrome is diagnosed by abnormalities in developmental history, physical appearance, and associated congenital anomalies (Smith 1982). Clinical reports indicate that most patients have abnormalities in social relating, language dysfunction, and cognitive deficits (Jones and Smith 1975).

**Discussion**

**Autism as a Behavioral Phenotype.** The heterogeneity of genetic conditions associated with autism supports the hypothesis that the syndrome represents a behavioral phenotype as opposed to a homogeneous disease entity. Many genetic conditions lead to widespread neurological damage and result in significant psychological and behavioral dysfunction (Smith 1982). Autism only occurs in a few of these conditions with a frequency much greater than would be predicted by chance. This suggests that particular genetic disorders are especially likely to cause a pattern of CNS damage that results in the manifestations of the autistic phenotype.

The premise that autism is a behavioral phenotype resulting from different etiologies is supported by studies of patients with idiopathic autism which indicate heterogeneity in this population, as well. Evidence of brain pathology is apparent in these patients. Many demonstrate "hard" signs of neurological dysfunction (Gubbay, Lobascher, and Kingerlee 1970; Maurer and Damasio 1982; Garreau, Barthelemy, and Sauvage 1984). CT scans have revealed increased ventricular size and other abnormalities in gross brain structure in a large percentage of patients (Damasio et al. 1980; Campbell et al. 1982; Gillberg and Svendson 1983; Rosenbloom et al. 1984). The CT abnormalities are quite diverse, however, and inconsistent from one patient to the next, suggesting that different pathological processes are operating in different patients.

These observations indicate that the autistic phenotype is the result of damage to one or more specific functional systems of the brain. This damage can result from a variety of organic or genetic etiologies, some of which remain unidentified. The presence of a recognizable organic condition or signs of CNS dysfunction such as mental retardation, seizures, neurological signs, or ventricular dilation may provide clues as to the etiology, timing, extent, and location of the damage that has occurred.

**Autism as a Spectrum Disorder.** The hypothesis that the autistic phenotype represents only one point on a continuum of psychological dysfunction is also supported by our review. With almost no exception, each of the genetic conditions we have presented gives rise to a spectrum of cognitive, linguistic, perceptual, and behavioral abnormalities in affected individuals. This is similar to Folstein and Rutter's (1977) twin data from patients with idiopathic autism. The spectrum of deficits can range from minimal or virtually no manifestations to severe, multiple handicapping conditions such as profound mental retardation and/or autism. Conditions such as the fragile X syndrome (Hagerman, McBogg, and Hagerman 1983) and CDLS syndrome (Johnson et al. 1976) have more individuals represented on the "severe" or autistic end of the spectrum, whereas sex chromosome aneuploidy tends to cause milder deficits in most affected individuals (Stewart et al. 1982; Stewart, Netley, and Park 1982).
Genetics, Brain Development, and Autistic Phenotype. The association of a single behavioral phenotype with varying genetic disorders suggests that a specific, functional brain system is vulnerable to damage through a variety of pathological mechanisms. Pathology in genetic disorders is ultimately derived from aberrant genes giving rise to qualitative or quantitative abnormalities in one or more proteins. The genetic disorders associated with autism are vastly different with respect to location and extent of abnormality in gene structure, protein deficiencies, and/or physical manifestations. This suggests that there is not a single protein abnormality that is responsible for producing the pattern of brain dysfunction underlying autistic behavior.

The concept of a single phenotype being associated with different genotypic conditions is well recognized in genetics and can best be illustrated by common physical malformations such as cleft lip or palate. Orofacial clefting is found in at least 154 different genetic conditions (Cohn 1978). It is thought to be caused by pathological disruption of facial morphogenesis before 36 days of gestation (Smith 1982).

It is likely that developing brain structures or CNS systems are also vulnerable to intrinsic or extrinsic disruption during specific, critical time periods. For example, the presence of steroid receptors during postnatal life is thought to affect neuronal cell survival in specific pathways or structures, cellular differentiation, and development of neurotransmitter systems (Gorski 1978; Kolata 1979). Minor changes in receptor structure, function, timing, or anatomical location could potentially cause specific deficits in functional neuronal connectivity with corresponding behavioral abnormalities (Barlow 1973). By a similar mechanism, disruption of CNS development during one or more critical stages involved in the establishment of perceptual, motoric, language, and related systems could produce the autistic phenotype.

There is indirect evidence which suggests that developmental disruption of the CNS has occurred in at least some autistic children. For example, compared to normal children, autistic patients have a significantly increased incidence of minor physical anomalies (Firestone and Peters 1983). Minor physical anomalies are thought to arise from biological stresses disrupting morphogenesis at specific stages of development. If such anomalies are present, it can be assumed that the developing brain has also been subject to potential developmental interference.

It is likely that many factors influence the severity of psychological deficits that arise in conjunction with particular genetic abnormalities (Gilbert and Opitz 1982). Varying severity of psychological impairment (i.e., a continuum of dysfunction) may be related to variable expressivity of the genetic disorder itself. An example of variable expressivity of physical anomalies is the range of dermatological abnormalities seen in neurofibromatosis. Manifestations range from minor skin lesions to widespread, disfiguring soft tissue tumors. Variable expressivity in females with X-linked conditions such as the fragile X syndrome may be influenced by differential lyonization (X chromosome inactivation) of cells in the CNS. Expressivity can also be affected by the degree of interaction between genetic influences and extrinsic factors.

Disruption of Brain Development in Autism: A Hypothesis. Ciaranello, Vandenberg, and Anders (1982) have reported that the majority of autistic children do not have demonstrable gross neuroanatomical structural abnormalities indicative of early CNS developmental stresses. They argue that the behavioral syndrome must, therefore, result from brain insult occurring in the later stages of neurodevelopment. These are the stages that are responsible for producing functional connections between neurons through the processes of dendritic and axonal elongation, synapse formation, and myelination. Abnormalities in gene function could alter the process of forming functional neuronal connections by affecting the delicate physical, temporal, or metabolic factors involved in one or more of these processes. The data we have presented from studies investigating the neuropathology of genetic conditions strongly associated with autism lend support to this hypothesis.

In his review of the two primary neuroanatomic theories of autism, Ornitz (1983) argues that most clinical and experimental data support a model of brainstem dysfunction as the basis for the constellation of autistic symptoms. This model implicates brainstem vestibular nuclei, and related nonspecific thalamic centers, in particular. Dysfunction in these areas is proposed to lead to abnormalities in processing and modulation of basic sensory input and motor output. This makes crucial information unavailable to processing by higher centers (particularly cortical) because of distortion of signals at lower levels. The other neuroanatomical model of autism supported by experimental and clinical data implicates dysfunction of higher cortical centers, particularly mesial...
Ornitz attempts to integrate these two hypotheses by noting that brainstem and cortical systems are mutually interdependent on transfer of sensory and motor information and regulatory modulation from one area to another. Autistic behavior is explained as a dysfunction in some aspect of this complex operational system responsible for multiple stages of sensory and motor processing.

Dysfunction of specific tracts resulting from abnormal or deficient myelination is an appropriate candidate to consider as one neuropathological mechanism that could lead to the autistic behavioral syndrome. In addition to PKU, CDLS, and tuberous sclerosis, abnormalities in brain myelination have been detected in patients with other genetic conditions associated with autism such as neurofibromatosis (Crome 1962), X-linked mental retardation (Dunn et al. 1962), and, commonly, in the CNS of patients with congenital rubella (Lemire et al. 1975), a disorder in which up to 12 percent of affected children manifest the autistic syndrome (Chess 1971; Desmond et al. 1970). Deficits or abnormalities in myelination in particular brain pathways during development could produce the disconnection within or between functional neuroanatomical processing levels that Ornitz describes.

Although of profound functional significance, subtle, qualitative abnormalities in myelin composition may be difficult to detect with conventional investigative techniques. The process of forming myelin is a complex, biochemical, and neurocellular task involving multiple interdependent stages that are completed in a precise, stepwise fashion (Lemire et al. 1975). The fact that temporal, spatial, and biochemical factors are all crucial variables throughout this entire process implies that there are multiple points and dimensions of vulnerability to disruption. For example, we have described how axonal outgrowth may be altered in specific areas of the brain of patients with PKU. If this occurred, it would cause a disturbance in the temporal relationship between axonal elongation and wrapping of the formed myelin sheath. The result would be inadequate myelination and corresponding functional deficits in neuronal conduction in those specific brain tracts.

Brain myelination occurs at a particularly rapid rate from the last trimester of gestation through the first 2–3 years of life. A hypothesis of dysfunctional myelination is therefore consistent with the suggestion that CNS damage in autism occurs in the latter stages of brain development. The period of extensive brain myelination also corresponds with the clinical observation that autistic behavior is usually first noted before 30 months of age. The critical stage of neurodevelopment we have referred to previously, then, may actually be one or more time frames during which myelination of specific pathways involved in sensory and motor modulation is occurring. For example, myelination of vestibular tracts is begun at approximately month 5 of gestation and is 50 percent completed by 2 years of age (Lemire et al. 1975). Myelination of reticular formation pathways proceeds from birth to at least 30 months of age (Lemire et al. 1975).

If disruption in myelination of specific tracts of the brain was responsible for the CNS dysfunction occurring in autistic children, variability in timing, extent, and location of disruption could potentially explain the inconsistent neurological data obtained in studies of autistic patients to date. Disruption could take place within different levels and locations within the same functional system and outwardly still produce the same behavioral phenotype. For example, lesions in tracts within the brainstem would be likely to produce abnormal brainstem evoked responses (BSER). Although it may disrupt the same functional system and produce an identical behavioral phenotype, lesions in pathways above brainstem structures would not be expected to cause abnormalities on BSER.

It may be that myelination is only one of many potentially vulnerable processes during neurodevelopment that are etiologically relevant to autism. The findings of abnormal neuronal architecture and polarity, deficient axonal and dendritic growth, and disordered synaptogenesis in the genetic conditions previously described also reflect damage in the later stages of brain development. The means by which damage is produced in autism may not be nearly as important as the timing and the location within the intricate network of functioning systems that the human brain comprises.

The diversity of CNS abnormalities seen in the genetic conditions we have reviewed makes a thorough discussion of neuroanatomical location impossible at this time. From our review, a location which was commonly affected in the genetic disorders we have discussed at greater length is the periventricular area, particularly regions near the thalamus, subependymal lining, and basal ganglia. This area is of particular interest since limbic system structures are located in this region.
An abnormality in CNS serotonergic systems has been mentioned as a possible factor in the pathophysiology of autism (Young et al. 1982). One third of autistic patients have consistently been found to have elevated serotonin levels (Young et al. 1982). In contrast, decreased levels are more frequently seen in several genetic conditions we have reported to be associated with autism such as PKU, trisomy 21, histidinemia (Young et al. 1982), and CDLS (Greenberg and Coleman 1973).

Clinical Implications. The association of autism with genetic disorders clearly points out the need for comprehensive medical and genetic evaluation of all autistic children, including cytogenetic assessment. There are many potential benefits for detecting a genetic condition in autistic patients. Many children with genetic disorders associated with autism can have serious and potentially life-threatening medical problems as well as congenital anomalies that are secondary to their genetic condition. Examples are congenital heart disease in Williams Syndrome, epilepsy in tuberous sclerosis and CDLS, and metabolic defects in PKU. Once diagnosed, these problems are often responsive to specialized treatment. This can maximize benefits derived from nonmedical, academic, or psychological interventions as well as prevent medical and psychological deterioration from occurring. Like dietary management in PKU, actual treatments for many genetic conditions may soon be developed. The administration of supplemental folic acid to patients with the fragile X syndrome (Hagerman, McBogg, and Hagerman 1983), for example, may aid in the treatment of psychological symptoms associated with this disorder. Genetic counseling issues are also of utmost importance to the extended family with respect to disease prevention. This is especially pertinent with disorders in which prenatal diagnosis is possible such as the fragile X syndrome.

Conclusions

Our review has provided support for the hypothesis that the autistic syndrome is produced by damage to a developing, functional, neuroanatomical system in the brain. Since many different pathological processes can potentially produce this damage, it is not unexpected that within the entire autistic population, one will find a wide range of associated behavioral symptoms, neurological signs, psychophysiological abnormalities, and neuroanatomical lesions. Mental retardation, neurologic signs, and CT scan abnormalities are all frequently (although not always) seen in autistic patients with or without organic conditions. This suggests that CNS damage often occurs in more than one functional system.

Before concluding, we must emphasize that the neuropathological findings we have described in this article are from children with genetic conditions who have not had comprehensive psychiatric evaluations. Studies investigating behavioral, neuropsychological, biochemical, and neurophysiological findings from children with genetic syndromes associated with autism are obviously indicated to obtain more precise information. These data would be particularly beneficial if obtained from patients both with and without autistic behavior to delineate neurobiological differences between these two groups. Magnetic resonance (MR) brain imaging, a more accurate, noninvasive method of identifying subtle white matter lesions, may also help confirm the presence and nature of the CNS dysfunction in patients with the autistic syndrome.

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