Child Neurology

Acquired Reversible Autistic Syndrome in Acute Encephalopathic Illness in Children

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- In seeking the neurologic substrate of the autistic syndrome of childhood, previous studies have implicated the medial temporal lobe or the ring of mesolimbic cortex located in the mesial frontal and temporal lobes. During an acute encephalopathic illness, a clinical picture developed in three children that was consistent with infantile autism. This development was reversible. It was differentiated from acquired epileptic aphasia, and the language disorder was differentiated from aphasia. One child had rises in serum herpes simplex type 2 antibody, and a computerized tomographic (CT) scan revealed an extensive lesion of the temporal lobes, predominantly on the left. The other two, with similar clinical syndromes, had normal CT scans, and no etiologic agent was identified. These cases are examples of acquired and reversible autistic syndrome of childhood, emphasizing the clinical similarities to bilateral medial temporal lobe disease as described in man, including the Klüver-Bucy syndrome seen in postencephalitic as well as postneurosurgical states. (Arch Neurol 1981;38:191-194)

The autistic syndrome in children is a distinctive behavioral syndrome characterized by failure to develop social relationships, disturbances of speech and nonverbal communication, repetitive and stereotyped behaviors, and disorders of attention including abnormal preoccupation and resistance to change. The neurologic substrates of this symptom complex are unknown. We have previously reported that pneumococcal meningitis in a subset of children with the autistic syndrome showed medial temporal lobe damage, especially evident on the left side. We are led by this finding to explore the analogy between autistic symptomatology and that seen with medial temporal lobe disease in adult man and in experimental studies in animals (the Klüver-Bucy syndrome and the amnesic syndrome). Boucher and Warrington noted the similarities between autistic behavior and the behavioral deficits reported in animals with hippocampal lesion and extended these observations by demonstrating (1) memory deficits in infantile autism similar to those found in the amnesic syndrome; and (2) perseveration in tests of alternation and response to novelty, similar to findings in animals following bilateral hippocampal lesions. Recently, Damasio and Maurer have proposed that "the syndrome results from dysfunction in a system of bilateral neural structures that includes the ring of mesolimbic cortex located in the mesial frontal and temporal lobes, the neocortex, and the anterior and medial nuclear groups of the thalamus." Thus, while they include other areas, they also focus on medial temporal lobe.

We report three cases in which striking autistic features developed in previously normal children in the course of an acute encephalopathic illness in which clinical evidence was compatible with involvement of function ascribed to a temporal lobe localization. In two of these, the etiology was not identified and the children eventually made a complete recovery. In the third, herpes simplex infection was verified, and extensive left temporal lobe necrosis was verified by computerized tomographic (CT) scan. We emphasize the complete reversibility of the profound autistic symptomatology in the first two cases, and the clinical correlates of extensive temporal lobe damage, predominantly in the left temporal lobe, in the third.

REPORT OF CASES

CASE 1.-A 5-year-old, right-handed girl developed normally until the abrupt onset of restlessness and hyperactivity; within four days she had stopped talking, stopped feeding herself, withdrew from interacting with other children, became agitated and uncontrollably frightened with periodic screaming, and began walking on her toes. At examination three weeks after the onset, she was alert and displayed no motor or reflex abnormalities. She sat, stood, walked, climbed onto a chair, reached for objects, and manipulated a reflex hammer and stethoscope. However, she was noncommunicative, with no appropriate social responsiveness. She showed no interest in toys but was fascinated by chrome fixtures on the wash basin. She looked blankly at the examiner and reached out to touch him, but with no evident emotional response, no relating, no smile, and no mimicry. She showed no recognition of or response to her mother. She followed no commands, verbal or gestured. She was mute except to repeat "no" with perseveration. Given a pencil and paper, she drew the letter "H" (the first letter of her name) mechanically and with perseveration all across the page. Left alone, she stood or sat largely immobile, often whimpering and rarely initiating any action, especially no purposeful or goal-directed action. At this time, she showed no fear or affection.

Viral titers including measles, tests for sedimentation rate, cold agglutinin, and heterophile, screening tests for drugs and lead, BUN tests, liver function tests, and tests for antimicrobial antibodies showed no abnormalities. The CSF was normal, with normal protein and γ-globulin, and had no viral antibodies for measles, varicella, herpes, and cytomegalovirus (CMV). An EEG showed periodic bursts of 1.5- to 3-Hz slow waves bilaterally, more in temporal regions. A CT scan was normal. On psychometric testing in the sixth week of illness, the Merrill-Palmer test with verbal items omitted indicated a mental age of 2 years 7 months (at chronic age 5 years 3 months). Verbal testing was not possible.

Within two weeks, some change was apparent. She began to put objects in her mouth and then in her mother's mouth, though she showed no other signs of recognizing her mother. She began to display an interest in a baby in the same room. A
week later she appeared to recognize her mother and the next day went to her mother spontaneously. About this time she began repeating irrelevant and apparently unmotivated phrases, such as "You are a devil, eat it out!" "You need my shoulder," "telephone," and a day later, "I'm going to bite you." This last accompanied a phase of hyperactive and aggressive behavior: hitting, biting, kicking, and stripping her clothes off repeatedly. Repetitive picking movements at herself and objects were prominent at the same time. She made fleeting eye contact, but still no appropriate social interactions.

Three days later, she presented a striking picture. She was hyperactive with very short attention span, running from one thing to another, momentarily interested in a variety of objects, manipulating each briefly then discarding it. She showed no interest in other children. She cried and screamed and jumped up and down when held restrained. She was incontinent and masturbated. When she did something wrong, she said "Stop that." She was echolalic, repeating phrases. Spontaneous verbalization was largely limited to counting "one, two, three, four." Speech was sing-song. She failed to respond appropriately to all vocal commands and questions.

Within one week after the stage just described, the picture had changed again; she was briefly cooperative, made eye contact, looked up briefly when her name was called, waved good-bye, and hugged and kissed her mother. She was able to express her feeling in speech: "I don't want to go to bed." At this point, she still smiled, and her speech was perseverative. During the next eight weeks she made a full recovery and is normal at this writing, three years later.

CASE 2—A 7½-year-old, right-handed, previously well boy was admitted to the hospital because of the abrupt onset of bizarre and emotionally hyperreactive behavior, including aggressiveness and unprovoked crying. He complained of being ill, complained that his heart had stopped beating, and expressed fears that he was going to die. His behavior deteriorated over the next week. He began to strike out and bite at people. Though generally mute, on occasion he articulated clear and well-formed, although bizarre, sentences.

Results of initial physical examination were unremarkable. He turned quickly toward a voice but was very slow to respond to verbal questions. He followed simple commands but was frequently perseverative. He produced some jargon-like phrases. He was very hyperactive, striking out, punching, attempting to bite people, and violently hit his lip on a number of occasions. He occasionally seemed frightened and cried out but at other times laughed. Results of neurologic examination were otherwise normal, except for frequent blinking and mouthing movements and occasional right-sided facial twitching.

A CT scan with contrast enhancement and a sodium pertechnetate Tc 99m brain scan were entirely normal. The CSF was normal. Viral cultures had no growth. Other laboratory studies for metabolic, toxic, and infectious diseases were all unrevealing. An EEG showed diffuse, generalized theta and delta slow waves, with some right-sided temporal spikes.

Behavior showed increased self-mutilation, aggressiveness, and mouthing behavior, the patient snapping and biting at people around him in a very animalistic fashion. He responded to no verbal stimuli but remained visually alert to his surroundings. After two weeks, there was prominent dystonic posturing and waxy flexibility in the left hand that decreased over the next week. In the third week, he seemed much less aware of his surroundings. He still had periods of screaming, kicking, rolling, and biting, but these were interspersed with longer periods of quiet behavior. His aggressive behavior was controlled with lithium carbonate.

He was seen again four months later as a passive, uncommunicative youngster with a vacant stare. He did not talk; he was able to do some appropriate manipulation of objects and occasionally throw objects overhand. Eye contact with the examiner was rare, though when spoken to, he would occasionally smile. When candy was offered as reinforcement he initially appeared not to recognize their use; when shown that they were to eat, he accepted them but concurrently began to put all objects presented to his mouth. Behavior was quite rigid and stereotyped, but affected flat. No negative or oppositional behavior was noted throughout the testing. During recovery, he displayed patterns of echolalia, stereotyped utterances, and a wide variety of inappropriate remarks, clearly articulated, but uninterpretable within the context in which they were uttered. When next examined nine months after the onset of the illness, he had made a complete recovery and had returned to his regular classroom, where he was performing successfully.

CASE 3—An 11-year-old, right-handed girl had developed normally and was doing well in school until the age of 11½ years. At that time, after a one-week illness characterized by upper respiratory infection followed by periodic vomiting and temperature elevations, she was admitted to a local hospital with acute onset of marked lethargy. On admission she was stuporous and responsive only to painful stimuli. Results of laboratory tests were within normal limits except for the CSF, which contained 71 mg/dL glucose, 166 mg/dL protein, and a cell count of 300/cu mm with 90% lymphocytes. Hares simplex titer in serum rose from 1:8 to 1:256 by four days after admission. Antibody levels for mumps, varicella, CMV, rubella, and leptospirosis were negative. Initial EEG showed diffuse left hemispheric depression, and the CT scan on admission was normal.

During her three-week stay in the intensive care unit, her state of alertness gradually increased but she was then nattled

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and aggressive and began self-injurious behavior, including head banging. She had short attention span, both auditorily and visually, and severe dysnesia with inability to identify common objects and shapes. She spoke in repetitive, stereotyped phrases without specificity and was able to follow only simple, gestured, one-step commands.

Approximately 2½ months after the onset of the illness, there were tonic-clonic seizures involving the right upper extremity with periods of staring and lack of responsiveness. The EEG at this time showed evidence of left temporal lobe slowing, and a CT scan revealed a large, low-density lesion involving the entire left temporal lobe and the anterior inferior right temporal lobe (Fig 1). Seizures were controlled with phenobarbital and later with carbamazepine.

Six months after the onset of illness, she exhibited stereotypes, withdrawal, and agitated self-stimulatory behaviors. Severe dysnesia with inability to name common items and shapes and severe expressive, receptive, and syntactic dysphasias with visual cues and dysfunctions were found. Hearing was normal bilaterally. Receptive language abilities fell to below the 18-month level. She was able to execute some simple, single-step, gestured and ungestured commands. She could repeat only three digits given to her auditorily. Stereotyped verbalization was limited to perseverative repetition of rote phrases without specificity. Visual discrimination and visual organizational skills were relatively better preserved, tested at a 4½-year-old level (IQ equivalent, 30 to 40). With blocks she was able to build a bridge and gate and she was able to copy a three-dimensional cube with pencil and paper. She also did well in certain areas of rote skills, eg, she was able to count to ten and to do simple single-column additions and subtractions in paper.

During the course of a six-week inpatient rehabilitation program, she showed improvement in several areas. There was an increase in visual and auditory interest and ability to maintain attention, to imitate, and to learn through demonstration. Repeated attempts at escape presented a single behavior problem. She returned home and attended a class for handicapped children.

Two months after discharge, she showed marked diminution in stereotypic and withdrawn behavior and was able to maintain eye contact with the examiner. Her tendency to escape was also diminished. She was able to follow some simple, two-step verbal commands without gesture and showed a marked reduction in repetition of base phrases. Her responses to questions were more appropriate.

Four months after the illness, she had improved substantially. Her auditory and visual attention span was normal for age. She was able to ask appropriate questions and to respond appropriately. She had only mild dysnesia, being able to name approximately 90% to 95% of common objects and in spontaneous speech she had occasional word-finding difficulty.

**Comment**

These three children each demonstrated a full-blown autistic syndrome in the course of an acute encephalopathic illness. In two cases, encephalitis was presumed but not proved, and in the third, evidence of herpes simplex encephalitis was obtained. The cases are presented as examples of an acquired and reversible autistic syndrome in childhood, affording some insight into the neurologic substrate of that syndrome.

The salient clinical neurologic features were limited to sociobehavioral and language abnormalities. By contrast, motor, sensory, reflex, convulsive, or vegetative abnormalities were absent or inconspicuous. The main abnormalities in behavior were failure of social responsiveness despite preserved cognitive abilities, failure to recognize persons, loss of communicative language and of all interpersonal communication, perseveration, inappropriate emotional expressions during uncontrollable aggressiveness or blank apathy, restless hyperactivity, constriction of interest, and absence of purposeful or motivated actions. At various times, repetitive movements, toe walking, echolalia, obsessive fascination with objects, inappropriate, rote, stereotyped utterances, hyperkinetic behavior with flitting attention span, masturbation, and perseverative speech were observed. This behavior pattern closely parallels that of the autistic syndrome. The distinctive behavioral abnormalities characterizing childhood autism have been recently summarized as ...

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**Language and Language-Related Functions**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Developmental Aphasia</th>
<th>Autistic Pattern</th>
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<tbody>
<tr>
<td>Speech and spoken language</td>
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<td>Pronoun reversal</td>
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<td>Echolalia</td>
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<td>Stereotyped utterances</td>
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<td>Inappropriate remarks</td>
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<td>Language modalities other than speech</td>
<td>Imaginative play</td>
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<td>Use of gesture other than pointing</td>
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*Adapted from Bartel et al.'s indications lack of function; +, presence of function.*

However, there are persistent marked memory deficits. She is unable to remember three objects after a few minutes.

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**Autistic Syndrome—DeLong et al.**

193
ing the differences between the present cases and that entity. (1) Our two patients did not have normal nonlanguage comprehension; they did not respond to gestures, to persons, or to ambient situations. (2) Our patients had complete incapacity for social responsiveness. (3) Our patients had an acute or subacute onset, rapid evolution to profound deficits, and full recovery within months.

In contrast, the patients with acquired epileptic aphasia have had an insidious or gradual onset, discrete aphasia with normal nonverbal intelligence, preserved response to gestures, and a prolonged course with slow recovery or various permanent dysphasic deficits. Features shared by our patients and those with acquired epileptic aphasia are global attentional disorders and generalized hyporeactivity. We conclude that the first two cases cannot be subsumed under the diagnosis of acquired epileptic aphasia. They may have the same relation to acquired epileptic aphasia that idiopathic infantile autism bears to developmental receptive aphasia.  

Evidence of Anatomic Localization

In case 3, extensive damage to the left temporal lobe and insula was seen by CT scan, with much more restricted involvement of the right insular region and right temporal lobe. The CT scan gave no evidence of medial or basal frontal lobe disease. In this case herpes simplex titers rose, supporting a presumptive diagnosis of herpes simplex encephalitis. This case allows the suggestion that a major portion of the neurobehavioral syndrome seen in this child may be the consequence of acute extensive temporal lobe lesions, predominantly in the left lobe. More widespread disease cannot, of course, be excluded. Clinically, she had severe impairment of language function. She uttered rote phrases with perseveration, without evident communicative intent, but without defects of articulation. These features contrasted with the better preservation of visuospatial skills (e.g., the ability to copy a three-dimensional cube). These findings indicate that left hemispheric language-related functions were severely impaired, with sparing of right-hemispheric visuospatial functions. This correlates with the CT finding. Other striking features, including lack of social interaction, lack of sustained attention, and agressive and impulsive behavior, may be correlated with temporal lobe disease.

In the other two cases, although the clinical syndromes were quite similar, CT scans were normal and anatomic localization could not be defined. Electroencephalograms showed bilateral diffuse slowing in both, but patient 1 had slow wave bursts of greater amplitude in the temporal regions, and patient 2 at that point had paroxysmal spiking localized to the right midtemporal region. These findings suggest that the temporal lobes may have been major foci of disease but provide no further information about localization.

The behavior shown by these patients is commonly described as "postencephalitic." We wish to emphasize its similarity to behavior characteristic of the infantile autism syndrome. In our cases, the behavioral syndrome was acquired at a clearly definable time, in the context of an acute encephalopathic illness, and was reversible. Case 3 alone provides data regarding the possible anatomic substrate for this behavioral syndrome complex, supporting in general the ideas advanced by Hauser et al. and by DeLong that extensive medial temporal lobe disease in children, perhaps particularly on the left side, produces a syndrome having many of the characteristic features of the autistic syndrome. Damasio and Maurer have advanced a similar interpretation, implicating mesiolimbic structures including mesial frontal and temporal lobes. The behavioral syndrome in our patients is likewise similar to the Kleinner-Bury syndrome of bilateral medial temporal lobe disease described in adult humans after bilateral surgical ablations of medial temporal lobes and as a consequence of herpes simplex encephalitis. The syndrome in man includes "... an incapacity for adaptive social behavior, and a loss of recognition of the significance of persons and events. Such patients show an empty blandness, an absence of emotion or concern for family or other persons and pursues no sustained purposeful activity." In addition, they have a profound amnestic syndrome.

Finally, the three children in these case reports showed a distinctive language and communicative deficit, which we have not seen described except in relation to autism (by Barak et al.) and which is clearly differentiated from receptive or global aphasia.

These arguments must be qualified by the recognition that infantile autism, or the autistic syndrome, has multiple etiologies, some encephalitic and some presumably not. Behavioral studies will not as yet predict which patients have demonstrated anatomic lesions. Certainly not all cases of infantile autism, nor even majority, show neuroradiologic or neuropathologic evidence of brain-tissue damage or loss. Nevertheless, those cases showing overt tissue destruction are valuable in permitting us to draw clinicanoatomic correlations. In other cases, deficits in particular neurotransmitter or neuropeptaminergic system may result in impairment of the same functions without gross anatomic lesions.

Nonproprietary Name and Trademarks of Drug


References