Journal of Pediatric Neurology 2003; 1(1): 9-14
www.jpneurology.org

REVIEW ARTICLE

Aggression, rage and dyscontrol in neurological diseases of children

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Abstract

Behavioral neurology has been bridging the gap between neurology and psychiatry in children. There are several neuropsychiatric disorders of children in which aggression is a dominant symptom. Both global disorders like attention deficit hyperactivity disorder as well as localized dysfunction of the brain may lead to aggression. A number of neurometabolic disorders as well as post-epileptic and post-surgical states may present with aggression in children. Drugs are sometimes effective especially in combination with a multimode approach. In this review some of the more common causes for aggression in neurologically impaired children, the associated co-morbidities and treatment are discussed. (J Pediatr Neurol 2003; 1(1): 9-14).

Key words: neuropsychiatric disorder, impaired child.

Introduction

Behavioral neurology has been bridging the gap between neurology and psychiatry in children. A number of behavioral problems are presented to the child neurologist as a primary or secondary symptom in the normal or developmentally delayed child. One of the more common behavioral problems seen in children is aggression and dyscontrol. A pure biological model for aggression and dyscontrol may have ethical and legal implications (1). Neuroscientists and clinicians have demonstrated that aggression has a neuroanatomic and chemical basis, that developmental and acquired brain disorders contribute to recurrent interpersonal violence, that both biologic and sociologic factors are involved, and that to ignore either is to invite error (2).

There are several neuropsychiatric disorders of children in which aggression is a dominant symptom e.g. Lesch-Nyhan syndrome, Prader-Willi syndrome etc (Tables 1 and 2). Self-mutilation has been seen in 15% of institutionalized mentally retarded patients (3). Physical and verbal aggression may also be a symptom of frontal lobe epilepsy in children in association with other psychological deficits (4). Rage outbursts and increased aggression have been noted to occur in higher rates in children with temporal lobe epilepsy (5).

Aggression can be seen both in previously normal children who develop pathology following an acute injury (e.g. head injury) and then become unable to control their behavior and in adolescents in whom aggression is a manifestation of long standing antisocial personality or conduct disorder.

Brain lesions and behavior

The role of the amygdala in the neural basis for aggression has been well known. Animal studies indicate that stimulation of the lateral and medial hypothalamus result in different types of aggression (6). Plotnik (7) divided aggression based on the relationship between stimulus and behavior and argued against attributing aggressive behaviors to direct involvement of specific anatomical sites. In the first type stimulus produced direct aggression and in the second type stimulus produced direct aggression and in the second type stimulus to the relevant brain area produced an initial noxious reaction, which lead to aggressive behavior. The relationship between specific neuroanatomic sites and aggressive behavior is complex. Most human studies of aggression are based on ictal aggression and amelioration with surgery. Trieman (8) points out that cerebral stimulation as part of evaluation for epilepsy surgery rarely led to aggressive behavior.

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Received: February 28, 2003.
Revised: April 8, 2003.
Accepted: April 21, 2003.

Table 1. Disordes which may present with aggression in children

Attention deficit hyperactivity syndrome
Post surgical states
Acute confusional states
Post ictal states
Following an acute injury (e.g. head injury)
Diseases of the hypothalamus
Episodic dyscontrol or rage attacks
Ictal aggression (rare)

Table 2. Neurometabolic diseases which may present as aggression

Huntington disease
Wilson disease
Lafora disease
Acute intermittent porphria
Hartnup disease
Lesch-Nyhan syndrome
Neuroacanthocytosis

behavior. The relationship between specific neuroanatomic sites and aggressive behavior is complex. Most human studies of aggression are based on ictal aggression and amelioration with surgery. Trieman (8) points out that cerebral stimulation as part of evaluation for epilepsy surgery rarely led to aggressive behavior.

Aggression as a clinical manifestation of neurological disorders

Global disorders

Attention deficit disorder may be taken as a prototype of a global disorder with aggression as a manifestation or co morbidity. Follow up studies of children with this disorder have shown a high incidence of delinquent behavior and explosive personality disorder (9). Approximately 75 % of hyperactive children have some form of discipline problem including aggressive and destructive behavior (10). A profile characterized by behavioral and cognitive impulsivity and emotional labiality may indicate a greater likelihood of the progression to adult antisocial behavior and violent impulse-control disorders (11). Aggression may also be a manifestation of metabolic conditions, post surgical states, acute confusional states and post ictal states.

Localized brain dysfunction

Aggressive behavior in mentally handicapped children may be mediated through the frontal lobe. Children with head injury or cerebral tumors involving the frontal lobe especially may manifest aggression. Orbitofrontal injuries result in a disinhibition syndrome while rage is a more common manifestation of dorsolateral prefrontal damage (12). The involvement of the hypothalamus in a range of pathological conditions may lead to rage reactions. This is most often seen in infiltrative diseases of the hypothalamus. Stereotactic intervention into the posterior hypothalamus gives satisfactory results for controlling both aggressive, violent behavioral disorders and intractable pain (13). Weissenberger et al. (14) in a study of 12 children with hypothalamic hemartoma and gelastic seizures noticed significant rates of aggression, with 58% of the seizure patients meeting criteria for the affective subtype of aggression and 30.5% having the predatory aggression subtype. Unaffected siblings demonstrated low rates of psychiatric pathology on semi structured parental interview and no aggression as measured by the Vitiello Aggression Scale.

Episodic dyscontrol or rage attacks

Children often come to neurological attention when they suddenly develop a temper tantrum, which is out of character for the child's' personality. The attacks may appear suddenly and explosively and consist of uncontrolled behaviors such as hitting, biting, kicking, and throwing objects around the room. Afterwards the child may be completely amnesic to the event or may show remorse. There is usually no prolonged post-ictal like phase (15).

Mark and Ervin (16) argued that the dyscontrol syndrome was a product of limbic dysfunction and that many patients improved on anticonvulsants. Some children with complex partial seizures do exhibit episodic dyscontrol interictally. There is an increased incidence of rage attacks in children with attention deficit disorder and temporal and frontal lobe injury.

Ictal and interictal aggression

Ictal acts of aggression are rare in children. It is unprovoked and usually not directed towards an individual and cannot usually be modified during the event. In a multicenter study involving 5400 patients of varying age it was observed that only 19 patients displayed aggressive behavior during seizures (17). Resistive violence is more common than ictal aggression. This happens when attempts are made the patient reacts with aggression.

It is difficult to always attribute interictal aggression to the epilepsy itself. Both epilepsy and abnormal behavior may be related to brain malfunction. Children with epilepsy may be subjected to ridicule and rejection leading to low self-esteem and potential behavioral abnormalities. Children reared in emotionally and financially impoverished environments are more likely to suffer from neurological disorders and the aggressiveness

may not be related to the epilepsy per se.

Aggression as a manifestation of neurometabolic disease

In general, any organic condition that produces cortical dysfunction could present with psychiatric symptomatology. The full range and incidence of neuropsychiatric manifestations are poorly studied for most of these diseases. In most instances, rarity of these conditions precludes any one clinic from collecting a large enough patient base to assess the full range of manifestation. At present, because it is often not possible to associate a specific cognitive and behavioral profile with a specific metabolic disease, a staged metabolic assessment is indicated in children displaying any of the specific historical features or clinical signs previously noted (18).

In a number of neurometabolic diseases behavioral abnormalities including aggression may precede neurological signs. It is important to be alert to the possibility that behavioral changes may herald the onset of a number of metabolic diseases and that subtle organic signs must be looked for and appropriate investigations done in the right context (19). Sudden onset of aggression in the presence of cognitive decline should make one consider these conditions. These group of diseases include Huntington chorea, Wilson disease, Lafora disease, acute intermittent porphria, Hartnup disease and many others. The aggression in these patients may be a part of a psychotic episode. In Lesch-Nyhan syndrome patients may express aggression towards anyone in the vicinity. Patients may strike out, spit at others and demonstrate verbal aggression. Self-mutilation and aggressive behavior may also be seen in neuroacanthocytosis in association with choreiform orofacial dyskinesia, obsessive-compulsive disorder and acanthocytes in peripheral blood.

Role of serotonin in aggression

Serotonin is a neurotransmitter, which is widely distributed in the central nervous system. The main nuclei containing serotonin are the raphe nucleus of the brainstem. There is some indication thatseretonin may inhibit aggression. Low levels of 5-hydroxyindoleacetic acid the principle metabolite of seratonin have been demonstrated in the cerebrospinal fluid of patients with aggression (20). There is still controversy as to the specificity of this correlation and it has been suggested that it may be a marker for general loss of control (21).

Aggression in the developmentally delayed child

Contrary to widespread belief aggressive behaviour is not especially common in cognitively impaired children. Environmental factors, over protection by caregivers etc may sometimes lead to low frustration threshold and aggressive outbursts in such children. The behaviour may also be a reflection of the patient's life experience rather than true organicity. Physical pain may arouse the aggressive impulse and may be non-directed aggression in the developmentally delayed child. Grizenko et al. (22) in a study of 176 mentally retarded individuals found that the severity of behaviour disturbance did not vary with age or medical diagnosis. The moderately retarded subjects presented with more severe behaviour problems, such as aggression, than the severely mentally retarded subjects. They found that the variable most predictive of behavioural problems was etiology of the disorder. Individuals with Down syndrome had significantly fewer behaviour disturbances and those with autism and pervasive developmental disorder had significantly more behaviour disturbances than other subjects.

Impulsivity, conduct disorders and aggression

The manifestations of impulsive behaviour in syndromes such as personality disorders, attention deficit hyperactivity disorder (ADHD) and in substance abuse may be different (23). Many different biological systems have been proposed to contribute to the neurobiological basis of impulsivity. The serotonergic neurotransmitter system and the frontal lobes have been proposed to play an important role in regulating impulsivity, although it unclear how specific this is. None of this biological knowledge has yet led to reliable pharmacotherapy for excessive impulsivity and, as yet, there is little understanding of the mechanisms by which those drugs, which have been found empirically to have some efficacy (e.g. the psychomotor stimulants in ADHD), exert their therapeutic effect.

The primary diagnostic features of conduct disorder include aggression, theft, vandalism, violations of rules and/or lying. For a diagnosis, these behaviours must occur for at least a six-month period. Conduct disorder has a multifactorial etiology that includes biologic, psychosocial and familial factors. The differential diagnosis of conduct disorder includes oppositional defiant disorder, ADHD, mood disorder and intermittent explosive disorder (24). Many of these children with these disorders of dyscontrol may present to the pediatrician or child neurologist. High novelty seeking in these children and low harm avoidance were significantly correlated with externalizing symptoms like aggression and delinquency (25).

Other disorders of dyscontrol

There are several other disorders, which may be considered as disorders of dyscontrol. These

Table 3. Some drugs used in the treatment of aggression

Lithium
Valproate
Carbamazepine
Levetriacetam
Clonidine
Risperidone
Propranolol
Sertraline
Clomipramine

include obsessive-compulsive disorder, anorexia nervosa, trichotillomania, pyromania etc (26). These conditions will not be discussed further in this review.

Drug treatment of aggression

Several drugs are apparently effective in treating pathologic anger and aggression (Table 3). One needs to be careful in inferring efficacy of a particular drug in aggressive patients with neuropsychiatric conditions (27). Antipsychotic agents appear to be effective in conduct-disordered children. Psychostimulants seem to be effective in reducing aggressiveness in brain-injured patients as well as in violent adolescents with oppositional or conduct disorders.

Anticonvulsants

The use of anticonvulsants like carbamazepine in aggressive disorders is based on the premise that there is an ambiguous relationship between epilepsy and aggression. However, there are reports of patients with and without electroencephalograpy changes responding to the animal studies. The efficacy of these drugs in patients without a seizure disorder, however, remains to be established, with the exception perhaps of valproate and carbamazepine. In a recent study of ten male autistic children Rugino et al. (28) showed that levetiracetam might reduce hyperactivity, impulsivity, mood instability, and aggression.

Neuroleptics

Risperidone is an atypical antipsychotic drug that blocks dopamine as well as serotonin receptorsystems. There are reports of its efficacy in treating aggression in general and it may be effective for severe aggression in adolescents with disruptive behavior disorders and sub average intelligence (29). McCracken et al. (30) conducted a multisite, randomized, double-blind trial ofrisperidone as compared with placebo for the treatment of autistic disorder accompanied by severe, aggression in children 5 to 17 years old found a significant reduction in aggression, rating of much improved or very much improved on the CGI-I (Clinical Global Impressions Scale) was 69 percent in the risperidone group and 12 percent in the placebo group.

Luiselli et al. (31) in an open label trial in a patient with autism and aggression evaluated an anticonvulsant (clonazepam), beta-blocking (propranolol), and antidepressant (sertraline and clomipramine). They obtained clinically significant reductions in aggressive behavior with the administration of clomipramine and the reductive effects from the medication persisted for 1.7 years.

Lithium

Although some knowledge has been gained concerning indications, therapeutic dose range, and safety of lithium in aggressive children and adolescents with conduct disorder, only a few double blind and placebo-controlled studies have been conducted (32). Malone et al. (33) conducted such a study in children and adolescents with severe aggression and found lithium is a safe and effective short-term treatment for aggression in patients with conduct disorder, although its use is associated with adverse effects. Lithium appears to be an effective treatment of aggression among nonepileptic, mentally retarded and handicapped patients, and among conduct-disordered children with explosive behavior.

Beta blockers

Connor et al. (34) in study of twelve patients showed that overt categorical aggression presenting in developmentally delayed children, adolescents, and young adults may respond to nadolol treatment. Studies have shown beneficial effect with other beta-blockers like proponolol in aggressive episodes etc (35).

The usefulness of clonidine in the treatment of pathologic aggression has not been assessed adequately, and only marginal benefits were observed with this drug in irritable autistic and conduct disorder children. These are just a few of the many drugs used in the treatment of childhood aggression and the reader may find more information in psychopharmacology literature. Studies on various agents are only beginning to accumulate. Given the role of both biological and social factors in the development of aggression, multimodal treatment may ultimately provide maximal benefits (36).

Non-pharmacological intervention in aggression

It is important that whenever possible

behavioural modification and non-drug treatment be considered. These may include such simple measures as reassurance, looking for sources of pain in the developmentally delayed population etc. The need for reactive behavioural management strategies for aggressive behaviours in adults with intellectual disability has been clearly established, but equivalent information concerning children with challenging behaviour is lacking by comparison (37).

Conclusion

The Aspen Neurobehavioral Conference 2001, an annual consensus conference devoted to the understanding of issues related to mind and brain stated the following consensus statement. "Violence can result from brain dysfunction, although social and evolutionary factors also contribute. Study of the neurobehavioral aspects of violence, particularly frontal lobe dysfunction, altered serotonin metabolism, and the influence of heredity, promises to lead to a deeper understanding of the causes and solution of this urgent problem (38). With advances in neurochemistry and neurobiology there has been a renewed interest in the neurological basis of behavior including aggression. It is known that a number of medical conditions can present with aggression in the pediatric neurology patient. There have been instances in which children with metabolic disorders first presented to the psychiatrist. Aggressive behaviors are frequently observed in patients with ADHD, conduct disorder, and pervasive developmental disorders and several theories have been postulated to explain the etiology of aggression in these disorders (39).

A multidisciplinary approach involving psychiatry, neurology, pediatrics and other ancillary support groups may be required to deal with the problem in children. Non-psychiatric physicians should have familiarity with commonly used drugs and should be able to assess environmental, caretaker and other issues involved as well as the medico-neurobiological causes for this symptom. Studies also indicate that for some children noncompliance predicts aggression and externalizing problems (40).

A complete explanation of aggression in the pediatric population would also have to involve issues of poverty, alienation, substance abuse and the role of choice and responsibility in the older child. Nevertheless the aggressive child presents a difficult clinical and management problem to the clinician. More studies on the effect of psychopharmacology are required as are better understanding of behavioural management strategies in the aggressive child.

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