NEW APPROACHES IN TREATMENT OF AUTISTIC DISORDER

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In 1867, Henry Maudsley was the first psychiatrist to pay serious attention to very young children with severe mental disorders involving a marked deviation, delay, and distortion in the developmental processes. If autism is most strictly defined, prevalence rates of 2 cases per 10,000 are usually reported; less stringent definitions typically suggest prevalence rates of 4-5 cases per 10,000. It is clear that autistic individuals, as a group, exhibit significant increases in peripheral blood levels of serotonin, a central neurotransmitter involved in various regulatory neuronal systems that is also found in blood platelets and the digestive system. Educational approaches, behavior therapy and either haloperidol or serotonin reuptake inhibitors, in different patient groups, may be beneficial in the treatment of autistic disorder.

***Key words**: Autistic disorder, serotonin, pharmacotherapy,educational approaches, behavior therapy*

Otistik bozukluğun tedavisindeki yenilikler

Henry Maudsley 1867 yılında, gelişimsel geriliği olan küçük çocukların varlığına dikkat çeken ilk psikiyatrist olmuştur. Kullanılan tanımlamalara bağlı olarak, otistik bozukluğun yaygınlığı onbinde 2 ile 5 arasındadır. Aynı zamanda trombositlerde ve sindirim sisteminde de bulunabilen ve çeşitli düzenleyici nöronal dizgelerde işlev gören bir nörotransmitter olan serotoninin, otistiklerde yüksek kan düzeylerinde bulunduğu bilinmektedir. Eğitimsel yaklaşımlar, davranış tedavisi ve değişik hasta gruplarında olmak üzere haloperidol ve serotonin geri-alım inhibitörlerinin otizm tedavisinde yararlı olduğu bildirilmektedir.

***Anahtar kelimeler**: Otistik bozukluk, serotonin, farmakolojik tedavi, eğitimsel yaklaşım, davranış tedavisi*

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Autistic disorder is the best known of the pervasive developmental disorders. It is characterized by sustained impairments in reciprocal social interactions, communication deviance, and restricted, stereotypical behavioral patterns[1].

HISTORY

In 1867 Henry Maudsley was the first psychiatrist to pay serious attention to very young children with severe mental disorders involving a marked deviation, delay, and distortion in the developmental processes[2] . In 1943, this condition was described by Kanner who suggested the name infantile autism[3] .

Afterwards it was also known as childhood psychosis or childhood schizophrenia[4] . In the third edition of DSM (Diagnostic and Statistical Manual), autistic disorder was recognized as a distinct clinical entity, in 1980[5] .

According to Volkmar[6] , in response to the criticism that DSM-III criteria for autism were too 'infantil' in nature (i.e., most appropriate to younger and more impaired individuals), major revisions were made in DSM-III-R.

The DSM-III-R provided a series of 16 individual criteria for autistic disorder. These 16 criteria were grouped into 3 categories (impaired social interaction, impaired communication, and restricted repertoire of activities). To achieve a diagnosis of autism, an individual had to exhibit at least 8 of the 16 criteria, with a specified distribution across categories. Age of onset was no longer an essential diagnostic feature, although onset (before or after 36 months) could be specified[7] .

The term childhood autism is used in the International Classification of Diseases (ICD-10), and autistic disorder in DSM-IV[8,9] . In the DSM-IV the definition of autism was developed on the basis of a very large, international, multi-site field trial[6] .

EPIDEMIOLOGY AND DIAGNOSIS

The final DSM-IV definition retains historical continuity with previous definitions of autism, i.e., in relation to the requirements for disturbance in three broad areas of developmental dysfunction. It differs from DSM-III-R in that age of onset is included as a necessary diagnostic feature. More importantly, this definition is conceptually identical to that employed in the ICD-10[8,9] .

If autism is most strictly defined, prevalence rates of 2 cases per 10,000 are usually reported; less stringent definitions typically suggest prevalence rates of 4-5 cases per 10,000. It is clear that autism is much more common in boys than in girls: Typically, ratios of 4:1 or 5:1 are reported[10] . But, girls are more severely affected[11] .

Although available evidence is somewhat conflicting, it is now clear that the condition is observed in families from all levels of education and that various factors may bias case ascertainment and may account for the initial impression of an unusual social class distribution [12] . Kanner believed that autism was present from, or shortly after, birth; but subsequent work has suggested that the disorder can be observed after some period of months, or even a few years, of normal development[13] .

ETIOLOGY

Parents of autistic children do not exhibit specific deficits in child-rearing practice, nor do they exhibit unusual personality traits[14] .

The role of genetic mechanisms is suggested by the observation that siblings of affected individuals are at greater risk for autism and are at higher risk for the development of various language and cognitive problems; studies of monozygotic and dizygotic twins have shown an increased concordance for autism in monozygotic twin pairs[14] .

Studies of biochemical correlates of the disorder have examined various neurotransmitters, hormones, trace elements, and amino acids. Although no specific biochemical marker has been found, it is clear that autistic individuals, as a group, exhibit significant increases in peripheral blood levels of serotonin, a central neurotransmitter involved in various regulatory neuronal systems that is also found in blood platelets and the digestive system. The observation that approximately one-third of autistic individuals exhibit high peripheral serotonin levels has proved to be remarkably robust, but its significance remains unclear, since elevations in peripheral serotonin levels are observed in other disorders notably mental retardation not associated with autism and since

the relationship of peripheral measures to central activity of the compound remains unclear [15].

Defects have been hypothesized at various levels of the CNS, ranging from the brain stem to the cortex. Taken as a whole, the available evidence clearly suggests some degree of CNS involvement, and most researchers now share the view that some factor, or combination of factors, acts through one or more mechanisms to produce the final behavioral syndrome known as autism. Precise neuropathological mechanisms remain to be established[14].

TREATMENT

Given the severity of these conditions and the relatively poor prognosis, it is not surprising that essentially all possible treatments have been utilized, including various pharmacological treatments, somatic treatments (such as electroshock therapy and 'patterning'), behavior modification, educational intervention, psychotherapy, dietary change, and the like[6].

BEHAVIOR THERAPY: The goals of treatment are to decrease the behavioral symptoms and to aid in the development of delayed, rudimentary, or nonexistent functions, such as language and self-care skills. In addition, the parents, often distraught, need support and counseling. Structured classroom training in combination with behavioral methods is the most effective treatment method for many autistic children and is superior to other types of behavioral approaches[2].

After a behavioral analysis is performed, techniques such as shaping or prompting are used to develop desired responses, which are then reinforced by increasingly mature rewards. In one study, very young autistic children who took part in an intensive behavioral program during which they received 40 or more hours of one-to-one behavioral treatment for two or more years showed significant improvement in I.Q. and higher levels of adaptive functioning than a control group of autistic children that did not receive the intensive treatment. By the end of the treatment period the experimental group included a subgroup of eight (42 percent) normal functioning children who were able to be enrolled in regular classes. By contrast, no child in the control group achieved a favorable outcome[1].

EDUCATIONAL APPROACHES: At present, the best available evidence points to the importance of appropriate educational interventions to foster the acquisition of basic social, communicative, and cognitive skills and the relation of such interventions to ultimate outcome. Behavior modification procedures may be helpful in increasing appropriate and decreasing inappropriate behaviors and may facilitate involvement in educational programming[6].

It is clear that early and continuous intervention is highly desirable; some reports have noted sustained improvement following intensive early intervention[16] .Autistic children learn best in a highly structured setting in which the opportunity for the child to disengage from others is kept to a minimum and the teacher intrudes when the child is engaged in solitary activities[1].

Educational interventions are best provided on a year-round basis; the usual pattern of summer school vacations is typically not well tolerated by autistic children[6].

PSYCHOTHERAPY: Psychotherapy is not usually indicated for the affected autistic child, although it may be useful in higher-functioning individuals. In such cases, therapy should be carefully focused and supportive in nature[17].

PSYCHOPHARMACOLOGİCAL TREATMENT: In a subgroup of autistic children with target symptoms, such as temper tantrums, aggressiveness, self-injury, hyperactivity, and stereotypies, appropriate psychoactive agents may be an important part of a comprehensive treatment program. Workup studies recommended prior to beginning drug treatment are examination for abnormal movements, including rating on Abnormal Involuntary Movement Scale (AIMS), weight, blood pressure and pulse rate, complete blood cell count and differential, tests of liver and renal function (blood urea nitrogen 'BUN', creatinine), electrocardiogram (ECG), urinanalysis, and other laboratory studies as needed (e.g., electrolytes,

blood levels of psychoactive drugs monitored). Periodic drug withdrawal (every six months) is recommended to assess whether there is continued need for treatment[1] .

Although none of the pharmacological agents used in the treatment of autism and related conditions have proven curative, certain medications, particularly the major tranquilizers, have been shown to have an important, limited role in the management of certain cases[18] .

It was hypothesized that the stereotypies and hyperactivity seen in many autistic children were a function of increased dopaminergic activity. That was the rationale for the use of antipsychotics, which block dopamine receptors, in autistic children. In individually regulated doses of 0.25 to 4.0 mg a day, or from 0.016 to 0.217 mg/kg a day, the high-potency antipsychotic haloperidol proved more effective than placebo in reducing target symptoms. Side effects of sedation and neuroleptic-induced dystonia were seen at doses above therapeutic doses. No negative effect on learning or cognition was found, and in two studies haloperidol was shown to facilitate language development and learning in the laboratory. In one study that assessed the interaction of haloperidol and behavior therapy, the combination of the two treatments was superior to either treatment alone in facilitating speech acquisition. The efficacy of haloperidol is maintained over time, and the drug is especially effective in children who are angry, irritable, and emotionally labile[1] .

Careful double-blind studies using haloperidol have demonstrated enhanced learning and improved behavioral adaption. The major tranquilizers may act to decrease activity levels, increase relatedness and task involvement, and increase accessibility to remediation programs. Individuals who receive major tranquilizers or other pharmacological treatments should be carefully monitored for side effects, and the agents should be used in the lowest effective dose for the shortest possible period of time. Oversedation should particularly be avoided [2,6] .

In nonsedating dosages, haloperidol in controlled studies reduced withdrawal, stereotypies, and hyperactivity. But, in a long-term study, dyskinesia occurred in 27percent of children. It resolved after cessation of drug. Another high-potency antipsychotic, pimozide, in daily dosage that should not exceed 0.3 mg/kg because of potential cardiotoxicity, may be more effective than haloperidol in decreasing maladaptive behaviors in treating hypoactive or normoactive autistic children. Risperidone also has been beneficial in anecdotal reports[1,19] .

Studies of additional agents, e.g., fenfluramine (which reduces blood levels of serotonin), or naltrexone have not revealed particular benefit [1,2,20,21] .

The nonspecific increases in activity levels, autistic individuals sometimes exhibit may be taken to suggest a trial of stimulant medications. In general, stimulants worsen behavioral functioning; this result is not surprising, given that stimulants can induce stereotypies in animals by facilitating the action of the neurotransmitter dopamine. More recently, an open trial of methylphenidate, optimal daily dose range, 10.0 to 50.0 mg, in nine autistic children resulted in a marked decrease in hyperactivity without major side effects[1,6] .

Antidepressants, such as fluoxetine, imipramine, desipramine, and the mood stabilizing agent, lithium, have been used in treating individuals with autism with some success. These drugs may be particularly helpful in addressing depressed mood, anxiety, and obsessive-compulsive symptoms that are sometimes evident, particularly in high-functioning individuals with autism or Asperger's disorder[2,22]

Antianxiety medications such as buspirone and propranolol have also been used, particularly in children who display a great deal of anxiety or agitated behavior[1,22] .

Clonidine has been used in some children with autism to reduce high levels of hyperactivity, impulsivity, distractibility, and acting-out behaviors. In one recent double-blind, placebo-controlled study, it was found to be superior to placebo in decreasing certain problem behaviors. The transdermal administration of clonidine at a mean dosage of 0.005 mg/kg a day was associated with a decrease in stereotypies, withdrawal, hyperactivity, and

clonidine at a mean dosage of 0.005 mg/kg a day was associated with a decrease in stereotypies, withdrawal, hyperactivity, and temper outbursts in nine autistic male patients aged 5 to 33 years. Anticonvulsants, such as phenytoin and carbamazepine, are used to treat children with autism who suffer from seizures. These medications may also be effective in decreasing aggresive behavior and episodic behavioral outbursts, particularly in children with seizure disorder[1,22] .

Recent reports have suggested the potential usefulness in autism and related conditions of other agents, e.g., those used in treatment of compulsive behavior[23] .

A recent double-blind, placebo-controlled crossover study found clomipramine to be superior to both desipramine and placebo in decreasing obsessive-compulsive symptoms, anger, and core autistic symptoms, including withdrawal and abnormal object relations. The sample consisted of 7 autistic individuals aged 6 to 18 years. The mean dosage of clomipramine was 129 mg a day (4.3 mg/kg a day)[24] .

However, in a recent pilot study conducted on eight hospitalized children, aged 3.5 to 8.7 years, clomipramine yielded therapeutic changes in only one child. Untoward effects were numerous and included acute urine retention, constipation, and behavioral effects indicating toxicity; the daily dosage ranged from 2.50 to 4.64 mg/kg, mean, 3.14 mg/kg a day[1] .

Another double-blind, placebo-controlled trial of fluvoxamine was reported by McDougle and colleagues[25] . Fluvoxamine was found to reduce perseverative symptoms and aggression and to improve language use and general functioning. The authors emphasized that the results pertain only to adults and that they have observed untoward behavioral effects (irritability, agitation) in some children treated with serotonin reuptake inhibitors.

A second double-blind, randomized study in crossover design by the same authors, closely related to the former study, evaluated the behavioral effects of a reduction in the availability of the serotonin precursor tryptophan and the authors concluded that an acute reduction in tryptophan availability might exacerbate maladaptive behavior in some autistic adults, and that their findings provided further evidence of dysregulated serotonin function in autism[26] .

A study assessing the benefit of fluoksetine in the treatment of children and adults with autistic disorder and mental retardation also had resulted promisingly[27] .

CONCLUSION

Educational approaches, behavior therapy and either haloperidol or serotonin reuptake inhibitors, in different patient groups, may be beneficial in the treatment of autistic disorder. And also, we should expect significant advances in our understanding and treatment of autism in the foreseeable future.

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