LEARNING DISABILITY AND BEHAVIOR IN TUBEROUS SCLEROSIS COMPLEX

INTRODUCTION

How are the TSC genes involved?

Tuberous sclerosis complex (TSC) is estimated to occur in one of every 6000 individuals in the population at birth (1). About two thirds of cases are "sporadic", that is "out of the blue", and neither the baby's father nor mother are found themselves to have TSC after full genetic testing. In the remaining one-third of cases, the baby has inherited either the TSC1 or TSC2 gene from their father or mother since anyone with either TSC gene has a 1-in-2 chance of passing it on to any baby they conceive. Recent genetic work has found more inherited cases of tuberous sclerosis linked to a faulty TSC1 gene, and more sporadic cases to a faulty TSC2 gene (2). In addition, the mental retardation and epilepsy associated with growths in the brain, known as cortical tubers, are less frequent in people with TSC1 mutations than in people with TSC2 mutations (3).

Parents are often only diagnosed with TSC after their child has been found to have it because they developed an obvious problem, such as infantile spasms, an early form of epilepsy. Their child can go on to develop severe mental retardation and very challenging behaviors, all related to TSC, whereas the parent is not noticeably affected. It is this wide variation in physical and intellectual abilities that is so striking in tuberous sclerosis.

Does everybody with TSC have learning problems?

A survey in the Wessex region of the United Kingdom (4), where the IQ of people with TSC was tested, found 55 percent with normal intellect and 45 percent with mental retardation, the majority of whom had profound retardation with an IQ less than 20. But people with TSC and normal intellect could be at risk of learning difficulties, and the mean IQ=93.6 of the group was slightly below the mean IQ of 105.6 for their siblings without TSC. There were also significant language deficits in normal intellect TSC children, but no increased rate of specific disorders of reading, spelling or math.

EPILEPSY, TUBERS AND MENTAL RETARDATION

How do cortical tubers in the brain affect epilepsy and mental retardation?

The faulty TSC1 and TSC2 genes produce abnormal growths of tissue in the brain as well as in other organs such as the skin or kidneys. In the brain, the major functional problems of TSC such as epilepsy, mental retardation, autism and attention deficit disorders are assumed to be associated with the cortical tubers.

Does the epilepsy cause the retardation and behavioral problems?

A common form of early seizures in TSC is infantile spasms, and these are associated with later mental retardation and autism. But it should not be thought that the epilepsy or mental retardation causes the behavior that is so characteristic of TSC. Instead, it is probable that the position and number of the cortical tubers themselves cause the mental retardation and at the same time put the child at risk of behavioral problems. The more tubers the child has, the higher the risk of having epilepsy and mental retardation. The earlier the epilepsy starts, particularly if early infantile spasms are present, the greater the risk of lower intellectual ability (4).

What is the relationship between tubers, IQ scores and epilepsy?

One study found a statistically significant relationship between the total number of tubers and IQ, with a fall of IQ related to an increase in the number of tubers(5). In addition, the study found that people with epilepsy had more tubers than those without, but this was not statistically significant. However, those with epilepsy had an average IQ of 85.8, and those without an average IQ of 105.3, which was significant. But it was not the epilepsy alone that produced the learning problems, since even after epilepsy was taken into account the number and position of the tubers remained the significant factor.
How common are behavioral problems in TSC?

It has been found that around one quarter of children with TSC will have behaviors that add up to make a diagnosis of autism, with a further quarter having fewer problems, which nevertheless satisfy a diagnosis of pervasive developmental disorder (PDD). Although the majority of autistic children with TSC will also be mentally retarded, aspects of PDD, autism or Asperger's syndrome can affect those with no learning problems. More than half of all children with TSC will also have attention and overactive behaviors that cluster together under a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

What difference does the position of the tubers make?

Although behavioral problems in TSC are associated with structural brain abnormalities, such as cortical tubers, more so than with epilepsy, it is undoubtedly the case that an early onset of epilepsy can increase behavior problems, but so also can the position of the tubers. A study in the Anglia Region of the UK(6) found that if a child had one or no frontal lobe tubers with a late onset of epilepsy, or no epilepsy at all, then they made normal intellectual progress. More than one tuber in the frontal lobe and an early onset of seizures increased the likelihood of mental retardation. Similar tubers in the temporal lobe of the brain, even with early onset of epilepsy, did not predict mental retardation.

Can some kinds of epilepsy produce unusual behaviors?

Since the brain controls the sensory and behavioral functions of the body as well as the motor functions, non-convulsive seizures occur if there is epileptic activity in the parts of the brain that do not control movement. In one of these kinds of non-convulsive seizures there is often first an aura where strange sensations are felt, or there can be feelings of fear or déjà vu, or apparent hallucinations of sights, sounds, smells or tastes. Emotional outbursts of anger or uncontrollable sadness can also occur. The aura is followed by altered awareness when there can be a state of confusion that can continue for some time. If the electrical activity spreads into the part of the brain controlling movements, automatisms can occur and these are automatic repetitive behaviors such as sniffing, swallowing or fumbling with clothes. If the seizure does not progress further into an obvious tonic or clonic motor seizure, the person will instead then feel very tired and sleepy. Unless these complex partial seizures progress to obvious motor movements they can be misunderstood as behavior problems or sometimes even psychotic states such as "atypical schizophrenia".

What is non-convulsive epilepsy?

If these states go on for some time they are called non-convulsive status epilepticus. A convulsive status epilepticus episode can be easily recognized and help obtained, but the signs of non-convulsive status may not be obvious and can be mistaken for behavior problems, particularly if the person has severe mental retardation and no speech. An EEG of a person in such a state will show either continuous abnormal brain activity across the whole brain-called absence status epilepticus-or in just one part of the brain-called complex partial status epilepticus (CPSE).

What kinds of behavior result from non-convulsive status epilepticus?

In CPSE, people can appear confused and have difficulty responding to what is said to them, they seem to be half asleep, drugged or "like a zombie". Alternatively there can be changes or fluctuation in behavior for no apparent reason, such as sudden unexplained outbursts of aggression or noisy "high" behavior in someone who does not normally behave that way. Sometimes there can be strange or bizarre movements or actions. There can be a change or loss of speech with drooling or dribbling, and subtle small twitches and jerks.

These symptoms of CPSE can be more difficult to recognize if a person is mentally retarded and already has a behavior problem such as autism, but parents and caregivers who know them well are usually the first people to recognize these changes. Non-convulsive status epilepticus is more likely to occur in people whose other epilepsies are difficult to control and the states can go on for days, weeks and even months if unrecognized. An EEG will soon confirm or exclude the diagnosis and appropriate medication, such as diazepam or clobazam can be given. Although this kind of status epilepticus is not dangerous or life threatening it can have a bad effect on a person's memory or intellectual ability if it goes on for weeks and months. Some people with tuberous sclerosis who begin seizures in adult life can first appear to hallucinate or lose abilities if non-convulsive status is not recognized and treated.

Are there sleep problems in TSC?

More than 60 percent of people with TSC report sleep problems. These are also known to be associated with epilepsy that is not totally under control (7), and indeed the best indication that epilepsy in TSC is controlled is now thought to be a normal sleep EEG pattern. The major sleep disturbances found are difficulty relaxing into sleep or waking several times in the night. These problems are associated with abnormal sleep recordings on polysomnography, with many spikes instead of the slow wave patterns found in normal sleep(8). It is important therefore that a 24-hour EEG is performed if a child would appear to have controlled epilepsy but still has major sleep problems.
AUTISM AND MENTAL RETARDATION IN TSC

Is autism associated with TSC?

Thirty years ago it was common for autism in mentally retarded children to be ignored and their unusual behavior put down to their intellectual delays. "All" mentally retarded children walked round on tiptoe in circles, flapped their fingers, played for hours with a piece of shining paper. Twenty years ago most clinicians dismissed the idea that you could have tuberous sclerosis and autism - tuberous sclerosis was an inherited disease due to growths in the brain, and autism was a totally different psychiatric disorder. Nowadays there are an increasing number of educational programs for autistic children, 70 percent of whom are mentally retarded, and tuberous sclerosis is one of the medical conditions most recognized as associated with both mental retardation and autism.

What affect does autism have on IQ scores?

Recent research on autism and mental retardation in children with TSC in the Anglia Region of the UK(6) found that those without autism showed a normal distribution of IQ scores in a bell curve. However, in those with autism there were more profoundly retarded children than moderately or mildly retarded children. The summation of these two groups across all intelligence scores produced the very unusual bimodal distribution of IQ that has been noted before in TSC with two peaks of scores instead of one.

How is autism diagnosed?

Whole textbooks and research groups are devoted to the study of autism (see the "Fact Sheet" titled "Tuberous Sclerosis Complex and Autism Spectrum Disorders" by Patrick Bolton, M.D.). The behaviors that lead to a diagnosis are grouped in three categories. In each category both the actual and the mental age of the person must be taken into account since autism is a developmental disorder and expressed in different ways at different stages of development. The three areas are:

Qualitative impairment in reciprocal social interaction. Does your child's head turn when they hear their name? Does your small child try to get your attention when they see something that interests them? If you point to something, do they look the way you are pointing or are they "in a world of their own"? Does your child smile when someone smiles at them? If you are hurt or sad, do they show sympathy?

Qualitative impairment in verbal and non-verbal communication, and in imaginative activity. If your child cannot speak, are they still able by body language to let you know they want something? Does your child echo back phrases they hear? Do they talk to other children as they "pretend" play together? Can you hold a "to and from" conversation with them or does such talk consist of a series of responses that are the same every time? Do they talk over and over again on the same topic? Are they aware that other adults are bored after 10 minutes of detailed description of different bus routes or the biographies of film stars?

Markedly restricted repertoire of activities and interests. Does your small child need to examine closely the picture on their glass every time you offer them juice? Does your child insist on licking the glass of the fish tank at home or is the problem one of keeping them from licking the side mirrors of cars in supermarket parking lots? Are they fully toilet trained at school but you can't get them out of the diapers at home? Will they only watch the latest video if they have first seen all the others in the order they have been brought into the house? Can they tell you about every moon landing and space capsule, but still not put the washing machine on the right cycle?

Do all people with autism behave the same way?

There are some myths about autistic behavior that don't apply as children get older. For instance, many people wrongly believe that the major criteria for autism is gaze aversion, not looking at someone when they talk to you, however brief the peek. But experiments have shown that autistic children spend less time looking at everything, however it is only the human beings that complain. In fact, many autistic children with TSC do the opposite of gaze avert, they stare for a disconcerting long time at the person talking. Their eye contact is "bizarre" rather than "aloof".

Can people with autism recognize emotions?

Another myth is that people with autism do not express emotion and/or that they do not form attachments to other people. Any parent will tell you that their autistic child has as many happy giggling sessions or temper tantrums as other children. Where they have difficulty is in recognizing that these emotions also exist in other people and this causes them problems. If you don't pick up that another person is irritated by your behavior, it is possible that you may be shouted at without understanding why, and so you don't learn from the experience. If you see someone smiling at you, but don't understand that it is in a special way that means they like you, it is difficult to make friends.

How are the problems of retardation separated from those of autism?

If the majority of children with autism are also mentally retarded, both of which conditions are regarded as developmental disorders, how do professionals tell which problem contributes most to a particular behavior? The short answer is that nothing is black or white. The most widely used test of general intelligence is the Wechsler Scales of Intelligence (WISC), which consists of many different sub-tests of cognitive ability. An ideal "normal" child shows an exact average for their age group that is even across all the sub-tests. A child with mental retardation or a gifted child will show the same even spread, although their average score will be below or above that of the "normal" child of their age.
Can autism be helped?

Autism is a developmental disorder, so changes may occur over time. Since the behavior can be helped by a variety of special teaching programs, it is important that your child is assessed by a psychiatrist or psychologist as early as possible so that the information can be included when you decide on the most appropriate education they need. In general a structured environment and consistency between school and home is recommended. Language should be as simple and direct as possible - metaphors and ambiguities will not be understood.

There is no magic pill to cure either autism or retardation in TSC, but the best control of the epilepsy with a drug that has few side effects will certainly help lessen problems. Parents and caregivers are in the best position to understand and interpret the oddities of language that can occur since they know the child's history, and they also know how to avoid any stimuli that cause great distress such as the sound of a vacuum cleaner or dogs. As with any handicap, children can be taught to compensate for their disability, but with TSC it is also important to remember that the underlying neurological cause will be lifelong.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND MENTAL RETARDATION IN TSC

Is ADHD associated with TSC?

Attention Deficit Hyperactivity Disorder (ADHD) is defined by the problems of hyperactivity, impulsive behavior and inattention that are present in different situations. So far there has been less research in TSC on the overactive and attention related behavior as opposed to the autism, but for many parents, particularly parents of younger children, these can be the major cause of stress in the family. Although there are often severe language deficits in TSC with around 50 percent of those with mental retardation having no speech(10), this is not matched by any physical disability with 78 percent of the same group having no walking problems. So parents have to be constantly vigilant as their child wanders around creating aimless, but not deliberate, chaos. ADHD and attention problems are discussed fully in "Fact Sheets" "Attention Deficit Hyperactivity Disorder and Tuberous Sclerosis Complex" by David Dunn, M.D., and William Kronenberger, Ph.D., and "How the Tuberous Sclerosis Brain Pays Attention" by Petrus de Vries, Ph.D.

How common is hyperactivity TSC?

In a similar study of 265 children under age 17 years with TSC(11), 60 percent of those who had mental retardation were reported to be overactive as opposed to 32 percent of those who had normal intellectual abilities. The over activity reported fell to 12 percent for those people without epilepsy, and to 7 percent for those who had neither mental retardation nor epilepsy. There were similar figures for restlessness, 60 percent of those with retardation as opposed to 36 percent of those without. Again this fell to 32 percent in people without epilepsy, but still affected 22 percent of those with normal intellect and no seizures.

There can be a decrease in hyperactive behavior during teenage years, and in the study of 23 people at age 5 and age 18 (9), 61 percent were hyperactive at age 5, but only 22 percent at age 18.
How common is impulsive behavior in TSC?

Another of the criteria for ADHD is impulsive behavior and this was reported for 48 percent of the whole sample. Rates varied from 54 percent in people with mental retardation, 33 percent in those without, 24 percent in those without epilepsy and was still present in 19 percent of those with neither epilepsy nor retardation. Since the prevalence rate of ADHD in the general child population is 3 percent to 6 percent, it is obviously much higher in TSC, even among people who apparently have no intellectual problems or epilepsy.

Are there other attention problems in TSC?

It should also be remembered that children who are not hyperactive can experience attention problems and this may affect their learning ability throughout life. If a child with TSC and attention problems is also autistic, they may not be aware of the effects of these problems on their ability to keep up with other children at school. However, if they are not autistic and are of normal intelligence, and their attention problems mean they are falling behind other children in class work, their self esteem starts to fall, and emotional problems can begin. Treatment of these problems is discussed in the "Fact Sheets" mentioned previously.

AGGRESSION AND MENTAL RETARDATION IN TSC

How common is aggressive behavior in TSC?

Although parents and teachers may be aware of the mental handicaps and autism of children with TSC, the problem that will bring them in conflict with outside agencies is their aggressive behavior. Rates of aggressive behavior are high, and those reported range from 33 percent in one UK survey to 54 percent in a survey of people on the NTSA Registry. In the UK survey (10) 33 percent of people with TSC had temper tantrums or rage outbursts, 28 percent would attack other people, and 29 percent self-injure themselves. But these were almost exclusive groups, with only 5 percent who would attack both others and self-injure. For people with mental retardation these figures were higher, and 96 percent of anger control problems were in this group, 95 percent of those who attacked others and 97 percent of self-injurious behavior.

In a US survey (12), using the Overt Aggression scale, which measures both verbal and physical aggression at four levels of severity-none, mild, moderate and severe-aggression was recorded for 54 percent of 353 people with TSC, but in the majority of cases it was assessed to be only mild aggression.

In the comparison survey of 23 children at age 5 and 18 (9), aggressive outbursts remained at the same level, as did self-mutilation, although destructive outburst decreased.

What contributes to aggressive outbursts?

The triggers for aggressive outbursts vary from person to person, but epilepsy, disrupted sleep, medication, lack of communication skills, autism and ADHD are all associated with this problem behavior, so the high rates are understandable. In addition, in some people these rage attacks are so unpredictable (Jeckyll and Hyde behavior) that neurologists consider they could be associated with complex partial seizures and might therefore be lessened by better seizure control. Anger management programs can help those who can understand their behavior, and other behavior management techniques such as "time out" can work for people with more limited understanding of cause and effect.

SPECIAL EDUCATIONAL NEEDS SERVICES IN THE US (by Anna Weber Byars)

There are numerous federal and state laws that govern the provision of special education services in the United States. They are based on Public Law 94-142, the Education of the Handicapped Act of 1975, which was later revised as the Individuals with Disabilities Education Act (IDEA). Each state has specific criteria for qualification for special education services as well as different classification schemes. Many children with TSC will qualify for special education under the classification of "Developmental Handicap" or "Other Health Impaired." Some children will be identified at a very young age through the Early Intervention programs; other children will have cognitive problems that will not be recognized until they start school.

An individual evaluation of the child is the first step in obtaining special education services. Such an evaluation may be initiated at the request of the parent or the classroom teacher. However, the parent must consent to the evaluation for it to occur. It typically involves intellectual testing as well as assessment of adaptive behavior and academic achievement and is done by a school psychologist. The results of this evaluation will help determine the best learning situation for the individual child. Potential learning situations include special education classes, mainstream classes with modifications, a combination of the two types of classes, and a combination of therapies (speech, occupational, physical) as needed.

The results of the individual evaluation are used to develop an Individual Education Program (IEP) at an IEP meeting attended by the child's teacher, the school psychologist, special education personnel, and the parents. The IEP document specifies the special education services to be provided, short-term and long-term goals, and the means by which progress will be measured. The IEP cannot be put into effect unless and until the parent provides written consent to do so.

The regulations and steps involved in arriving at a useful IEP are many and often complicated. There are State Directors of Special Education as well as advocacy groups in every state that may be helpful in understanding and accomplishing these steps. Organizations such as the Tuberous Sclerosis Alliance, the Epilepsy Foundation of America, and local Autism Societies provide very
useful information that helps parents in their interactions with school systems.

CONCLUSION

There are problems affecting behavior associated with tuberous sclerosis and the major ones are autism or PDD, attention deficits, ADHD and disruptive behaviors such as aggression. All these problems occur more frequently in younger children, in individuals with mental retardation and in individuals with epilepsy. Not all the problems will occur together in any one person. But when they do it is essential to obtain professional assessment of the contributions made by the various elements so that appropriate treatment or education can be given. If the professionals say they don't know much about tuberous sclerosis, give them information about it to help them understand. The days of major tranquillizers being used as chemical straightjackets should be over. There is much advice now available on autism and ADHD and what applies to individuals without TSC with these problems also applies to individuals with TSC. Use it!

By Ann Hunt, research coordinator for the Tuberous Sclerosis Association in the United Kingdom.

REFERENCES


3. Dabora SL et al, (2001), Mutational Analysis in a cohort of 224 Tuberous Sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. American Journal of Human Genetics, 68, 64-80


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