Muscle Biopsy in Hypotonic Schizophrenic Children: A Preliminary Report

by Sheila Cantor, Cynthia Trevenen, and Ray Postuma

Abstract

Two hypotonic boys, aged 7 years, 3 months and 7 years, 7 months, who possessed sufficient speech to demonstrate a severe thought disorder and who differed markedly in their activity levels, were subjected to a biopsy of the quadriceps muscle. The biopsies revealed atrophy of type 2 muscle fibers, as well as variability in the size of these fibers. The findings could be compatible with a denervation phenomenon.

The hypotonia and doughy muscle tone of schizophrenic children was first described by Bender (1947, 1953). Fish (1961, 1962) has studied infants at risk for schizophrenia and has described hypotonia in high risk infants as early as the first month of life. Meltzer (1972, 1976) and Meltzer and Crayton (1975) have reported abnormal muscle biopsies both in chronic adult psychiatric patients and in their first degree relatives.

The Patients Studied

Case 1. This boy, the youngest in a sibship of four, first aroused concern in his parents when he was late to develop speech (compared with his three older siblings). The pregnancy, birth, and delivery were uncomplicated, despite a birth weight of 10 lbs. Early development was well within normal limits, and nothing extraordinary was noted by either the child's parents or his pediatrician before he was 18 months of age. Between 18 months and 5 years, 9 months, a child development clinic, a behavior modification therapist, and a special education language program all attempted to improve the child's disturbed behavior. When the child did begin to talk, much of his speech was incoherent, echolalic, and dominated by television and radio commercials. Affect, interpersonal relationships, and language were all described as severely disturbed.

At age 5 years, 9 months, the child was admitted to a psychiatry ward for assessment. His general health was reported to be good, and he had had no previous hospital admissions. Neurological examination did not reveal any focal neurological signs. The child was noted to be hypotonic; ankle jerks were brisk; all other reflexes were difficult to elicit. Review of systems and physical examination revealed no other significant abnormalities. On the Bruninks-Oseretsky Test of Motor Proficiency, the boy fell within the first stanine (i.e., 99 percent of boys his age could perform this test better). His highest points of functioning were visual-motor, while tests measuring balance, strength, upper limb coordination, upper limb speed, and response speed were all significantly below the norm for his age level.

At the time of biopsy (age 7, 3 months) there was much symbolic speech, as well as neologisms and the frequent repetition of unrelated words or phrases. Speech was sometimes used for meaningful communication. Affect was flat except for outbursts of spontaneous giggling or crying. There was facial grimacing, and the boy often appeared to be hallucinating. Intellectual func-

1 This study was approved by the Ethics Committee at the University of Manioba. Informed consent was obtained from the children's parents. The parents were told that their children were suffering from a chronic mental disease of unknown etiology and that the muscle biopsy might contribute to knowledge about the disease, although the children would derive no immediate benefit from the procedure. The children are receiving occupational therapy to help improve their motor functioning.

Reprint requests should be sent to Dr. Cantor at Health Sciences Centre, Department of Child Psychiatry, 685 Bannatyne Ave., Winnipeg, Manitoba, R3E OW1, Canada.
tioning was very uneven. Although the boy expressed affection toward his family and his therapist, he isolated himself from his peers. Eye contact was fair.

This child's parents are eastern European immigrants and are the only members of their family who are in Canada. As far as they know, there is no family history of mental illness or mental retardation. The boy's three siblings are functioning well in a regular school program. The father, who has a grade 5 education, is presently working as a supervisor for a roofing company. The mother has an elementary school education and is a housewife.

Case 2. This boy's parents believed that there was nothing wrong with him except that he was "a little slow to adjust to new people and new situations," "stubborn," and "slow to learn." When the boy entered school, at age 5 years, 2 months, his kindergarten teacher noted that he would communicate with no one other than his sister and that all speech was incoherent except for a few negative phrases such as "leave me alone" and "no." The teacher referred the boy to the school psychologist.

This boy was born in a rural community. The pregnancy and delivery were described by the family physician and by the family as "easy and normal." Neither the family nor the family doctor had noted anything extraordinary in the boy's early development. He had suffered no major illnesses and had never been admitted to the hospital before his admission for psychiatric evaluation at age 5 years, 6 months. During his first hospital admission, no overt psychosis was noted, but the boy was observed to be very anxious and withdrawn. It was suggested to his school that every effort should be made to develop a warm and trusting relationship with him. The initial diagnosis was "Withdrawing Reaction of Childhood."

One year later, the boy was readmitted to a psychiatric ward at the request of the school because of his extremely slow academic progress. By this time, the boy had developed mannerisms, and his teacher now believed that he was hallucinating because he talked to himself and at times turned his head as if in response to someone. His gait was awkward and stilted. Frequently the boy would run across the room on his toes, flapping his hands and clapping them together. Speech was often mumbled and incoherent, especially when he was running and talking to himself. On neurological examination, no focal neurological signs were elicited. The boy's physical appearance was markedly asthenic, and he was hypotonic. No other abnormalities were noted on physical examination. Although the Bruninks-Oseretsky Test of Motor Proficiency was not administered to this boy, it was noted that he was unable to hop, climb, throw a ball, or tandem walk. In general, both his gross and fine motor skills were very immature.

At the time of biopsy (age 7 years, 7 months) much of this boy's speech was symbolic in nature. Although echolalia was rare, there was senseless repetition of words and phrases, and alliterative speech was common. The boy's anxiety level was very high, and he frequently walked on his toes in an agitated manner. The boy was attached to his family, but actively avoided other interpersonal relationships. Grimacing was frequently observed. Intellectual functioning was very uneven. Affect tended to be flat and anhedonic, except when the boy was very anxious.

This boy's father has been diagnosed as a schizotypal personality. He has lived all his life in a farm community, voluntarily isolating himself from interpersonal relationships. The boy has two siblings—an older sister who is functioning normally in school, and a younger sister, whose speech development has aroused some concern. No other family history is available.

Both boys are pale, have doughy musculature, and a visibly reduced muscle mass. The pupils of both boys were frequently dilated, especially during hallucinatory episodes. The electroencephalograms were normal in both boys, and karyotypes revealed no abnormalities. The two boys differ markedly in their physiological appearance; case 1 is well over the 97th percentile for height and weight, while case 2 is markedly asthenic in appearance (25th percentile for weight). Both boys demonstrated poor postural tone, were markedly awkward at running, skipping, and jumping, could not ride a bicycle or climb in an age-appropriate manner. A broad-based gait was noted in both boys. The two boys differed in their preferred activity level, with case 1 tending to be hypoactive, while case 2 often displayed agitated hyperactivity.

Case 1 had been on Mellaril, 25 mg daily, until 1 month before surgery; case 2 had been off all medications since 6 months before the muscle biopsy. Both boys had been diagnosed as psychotic by more than one psychiatrist, and both had been symptomatic for more than 1 year.

Procedures

Under general anesthesia, open biopsies were taken from the proximal third on the rectus femoris muscle (far from the tendon) in both patients and processed for light
A third sample was rapidly frozen in isopentane previously cooled to -160°C in liquid nitrogen. From the frozen tissue, 10 micron thick sections were cut and stained with hematoxylin-eosin, periodic acid Schiff (PAS), oil red 0, and the modified Gomori Trichrome. Stains for reduced nicotinamide-adenine dinucleotide tetrazolium reductase (NADH-TR) and adenosine triphosphatase (ATPase) at pH 9.4 and after acid preincubation were also performed (Dubowitz and Brooke 1973).

In each muscle sample stained for ATPase, an equal-sized area was randomly selected, photographed, and printed at a constant magnification (x 100), and each muscle fiber within this photograph was measured. Thus, although the total area of muscle tissue measured was identical for each child, the number of fibers present in a given photograph depended upon the size of the individual muscle fibers. Histograms were then constructed according to the technique described by Dubowitz and Brooke (1973). The muscle fibers were classified only as type 1 or type 2, with no distinction being made between type 2a and type 2b fibers.

Results

On routine hemotoxylin-eosin stained sections, no light microscopic abnormalities other than variation in fiber size were noted in case 2. In case 1, variation in fiber size was more marked. There were a few fibers with multiple internal nuclei, and scattered atrophic muscle fibers (figure 1) were noted throughout the biopsy. Ultrastructurally, no abnormalities were evident in muscle fibers; however, no intramuscular nerves or muscle spindles were present in the sample.

ATPase stains revealed a mosaic distribution of type 1 and type 2 fibers in both muscle biopsies (figures 2a and 2b). The marked variation in the size of the type 2 fibers in case 1 (size range 20-61μ) was confirmed while case 2 (size range 11-41μ) showed less variability. Both histograms (figure 3) demonstrated a significant atrophy of type
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2 fibers (i.e., the difference between the type 1 mean fiber size and the type 2 mean fiber size is greater than 12 percent of the largest type 1 fiber [Dubowitz and Brooke 1973]).

Serum creatine phosphokinase (CPK) levels were within normal limits and consisted of 100 percent muscle CPK.

Discussion

It is widely accepted that neural influences determine many of the biochemical features of muscle, including their enzyme profiles and their glycogen content. However, the exact nature of the trophic influence of the nerve on the muscle fibers is uncertain (Guth 1968). The selective atrophy of type 2 muscle fibers is one of the most common abnormalities associated with muscle pathology. It has been seen in such diverse disorders as corticospinal tract disease, mental retardation, myasthenia gravis, parkinsonism, rheumatoid arthritis, and as a result of simple disuse (Brooke and Engel 1969a, 1969b; Edstrom and Nordemar 1974). Although its significance is not well understood, the selective involvement of type 2 fibers suggests that some trophic factor, probably neural in origin, is deficient in all of the above conditions. The twin-peaked histogram is not a feature seen in myopathies, but is characteristic of denervation. The smaller atrophic fibers are believed to represent a population of denervated fibers (Brooke and Kaplan 1972).

The rounded and polygonal atrophic muscle fibers seen in these muscle biopsies do not resemble the scattered angular atrophic fibers described by Meltzer (1976) and Meltzer and Crayton (1975) in adult schizophrenics. The changes that they reported were more marked in

**Figure 3. Histograms for cases 1 and 2**

- **Case 1**
  - Type 1
  - Type 2

- **Case 2**
  - Type 1
  - Type 2

Case 1 shows marked variability in the size of the type 2 fibers, while case 2 shows less variability, but there is still a definite twin-peaked configuration rather than a Gaussian distribution.
the peroneus brevis muscle than in the quadriceps muscle. Our study was of the quadriceps muscle, which may in part account for the differences in findings. In addition, since the children biopsied in our study were not only psychotic but also had evidence of a moderate neuromuscular dysfunction, they may be on a continuum with only a select group of adult schizophrenic patients (that is those who demonstrate some neuromuscular dysfunction and whose thought disorder is chronic).

The possibility of a disuse atrophy cannot be completely ruled out. However, the contrasting activity levels of the two children—one hypoactive, the other hyperactive—mitigates against a disuse atrophy being the cause of our findings.

Heterogeneity has been a major stumbling block in schizophrenia research. A homogeneous subgroup could facilitate research greatly. It is hoped that the investigation of children who are both schizophrenic and hypotonic may lead to the selection of a relatively homogeneous subgroup of schizophrenic patients for study.

References

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The Authors
Sheila Cantor, M.D., is Assistant Professor, Department of Psychiatry, University of Manitoba, Winnipeg, Manitoba, Canada; she was formerly Child Psychiatry Fellow, Bellevue-New York University Medical Center, New York, N.Y. Cynthia Trevenen, M.D., is Assistant Professor, Department of Pathology, University of Manitoba. Ray Postuma, M.D., is Assistant Professor, Department of Surgery, University of Manitoba.