Letters to the Editor

'Intrathecal baclofen use in children with spasticity – a physicians' survey'

SIR–The use of intrathecal baclofen (ITB) during the past two decades has resulted in major advances in the management of complex spasticity.[1] There is increasing use of ITB in children for managing spasticity in a number of conditions, with evidence for effect across a range of functional domains.[2] However, significant complications have been reported.[3,4] These can be broadly divided into three groups: (1) mechanical; (2) central nervous system effects from dose excess or withdrawal; and (3) infections. In conducting a multicentre survey, our primary aim was to describe the experience of individual physicians with ITB management in children, specifically with regard to extent of use and complications noted.

A survey was conducted of physicians working with children with physical disabilities. This was mailed to 165 physicians randomly selected from the membership register of the American Academy for Cerebral Palsy and Developmental Medicine, and to an additional 35 physicians identified as ITB users on the basis of articles authored in the literature. The questionnaire asked for single choice responses and requested information in four key areas: (1) demographics; (2) patient selection factors; (3) frequency of actual complications; and (4) beliefs about potential complications and access to safety data. Those physicians not currently involved with ITB were asked only to fill out section (4).

Eighty-five physicians (43%) completed the survey; 69% of the overall sample was involved in the use of ITB. Of the ITB users, 40% had between 2 and 5 years' experience and 44% had more than 5 years' experience. Seventy-six per cent of respondents were working in centers where up to 50 implanted pumps were managed in the previous year. In describing their role in the phases of management, 91% responded that they were involved in preoperative assessment of the child's suitability for the device. Nineteen per cent were involved in the operative implantation and 73% in the ongoing care of recipients, including long-term follow-up.

When asked about a single minimum age criterion in identifying suitable candidates, 24% indicated that the child should be older than 5 years, 32% indicated older than 1 year, and 39% believed that a minimum age was not relevant to the selection process. With respect to the child's weight, 37% believed a minimum of 10kg was acceptable and 46% indicated a minimum weight of 20kg. Respondents were also asked to indicate what degree of motor impairment would describe a suitability for ITB on the basis of the descriptions of gross motor ability from the Gross Motor Function Classification System (GMFCS)[5] for Levels III, IV, and V. Forty-two per cent of respondents would consider a child who ambulated with assistive mobility devices (Level III) for ITB. Sixty-seven per cent would consider a child with very limited ambulatory skills who relied more on power mobility (Level IV), and 91% would consider a non-ambulatory child (Level V).

In order to improve recall and facilitate analysis the frequency of events were grouped in the following manner: rare (<5% of recipients); infrequent (5–15%); common (16–25%); very common (>25%). Dose-related events in the postimplantation period were reported as rare by 75% of respondents and infrequent by 24%. Mechanical and infection events were reported in the following frequencies: rare 41.5%, infrequent 41.5%, common or very common 17%. Baclofen withdrawal events were rare in 65%, infrequent in 27%, and common in 8% of respondents' experience. No difference in reported complications was found on the basis of experience or activity (number of pumps inserted and managed per year).

Those surveyed were asked about what rates they may anticipate of life and non-life threatening complications in children of GMFCS Levels III, IV, or V. Respondents indicated that they would tolerate the highest rate of both life and non-life threatening events in the most severely impaired children (GMFCS Level V) compared with those less impaired ($p<0.005$). When asked whether they believed that the overall safety of ITB had been adequately established in terms of the current evidence, almost equal numbers replied yes (43%) and no (44%) and a small number (13%) did not know. An overwhelming majority (96%) of respondents indicated that an international database for ITB-related safety and complication issues would be essential or useful. No difference was seen in terms of responses to section 4 between ITB users and non-users.

To our knowledge, this is the first survey on the use of intrathecal baclofen specifically in children. We deliberately chose to explore the complications issue in this survey as there is little known about this from a systematic perspective. Currently there are no universally agreed guidelines on the optimal selection and management of children with ITB. The responses on selection factors indicate that there is a large degree of variability in the decision-making process. One-third of respondents indicated that ITB withdrawal events occur in more than 5% of recipients. ITB withdrawal can be difficult to diagnose, may be life-threatening, and, importantly, is largely preventable.[6] To our knowledge, there has been no reporting on ITB withdrawal in children other than by case report.[7–9]

We asked all respondents, regardless of their current use of ITB, what they believed to be acceptable cut-off rates for complications in children of varying motor severity based on GMFCS. Our hypothesis was that more physicians would consider accepting higher complication rates in the more severely impaired child, possibly as the need for benefit from ITB in a more motorically impaired child is greater than for a less impaired child. The results indicate that most physicians would accept higher rates of both life and non-life-threatening complication in GMFCS Level V children compared with Level III or IV ($p<0.005$). This finding is challenging: are quality of life issues more important than safety issues to some physicians and families in deciding whether or not to choose ITB?

While most physicians had access to information on complications in ITB, responses were split on whether respondents believed that ITB is a safe procedure. Does this suggest that broader concerns exist as to ITB as a procedure, or that physicians need more information on which to make an informed judgment? Beyond data obtained from reports published in peer-reviewed journals, a single manufacturer of ITB pumps collects information from centres using ITB. In the face of limited free availability through journals, the question of whether a third party should collect and disseminate safety-related information on ITB, in the form of an international registry, is an important issue. This would create a more transparent reporting and access system for ITB safety information and could allow greater use of data in determining optimal and at-risk candidates. The need for

greater access to education and strategies on pump problem solving has been raised previously.[10]

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James Rice MBBS FRACP FAFRM[a]*
Maureen O'Donnell MD FRCPC[b]
Robert Armstrong MD FRCPC[b]

[a]*Paediatric Rehabilitation Service, The Royal Children's Hospital, Parkville, Australia.*
[b]*Division of Developmental Paediatrics, University of British Columbia, Vancouver BC, Canada.*

**Correspondence to: james.rice@rch.org.au*

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'Age of menarche in females with autism spectrum conditions'

SIR–Studies in typical populations show that the timing of pubertal development has important behavioural and psychosocial consequences.[1] In children with autism spectrum conditions (ASC), puberty may produce changes in symptoms. Some studies report that between one-tenth and one-third of children with ASC experience deterioration and aggravation of symptoms soon after entering puberty; this may be particularly the case for females.[2] Given the potential impact of the pubertal transition on symptom severity and the possibility that females with ASC share some of the same vulnerabilities that arise from early or delayed maturation in the general population, a better understanding of puberty timing in these individuals is needed.

In this letter, we report the results of a cross-sectional survey of age at menarche in women with ASC. We focused on menarche since this is a very salient event, and can be recalled accurately many years later. Data were available for 38 women with an ASC, diagnosed by psychiatrists using *International Classification of Diseases-10th revision*[3] criteria. Their mean age was 31 years 6 months (SD 9y 10mo; range 18y 11mo–57y 9mo). Specific diagnoses were available for 35 of the women. Ten were diagnosed with autism, two with high functioning autism, and 23 with Asperger syndrome. Several also had comorbid diagnoses including severe learning disability,* Tourette syndrome, attention-deficit disorder, dyslexia, dyspraxia, epilepsy, depression, and anxiety. They were recruited via the National Autistic Society (UK), specialist clinics, and adverts in relevant newsletters/web-pages. Data from an age-matched comparison group of 38 females without ASC were also collected (mean age 32y 2mo [SD 9y 1mo]; range 19y–36y 5mo). This was not significantly different from the group with ASC, $t(74) = -0.10$, $p = 0.92$, $d = 0.07$. All women were asked the following question: 'How old were you when you had your first period?'. They were asked to indicate age in years and months. They were also asked 'What date was it (month/year)?' If participants answered both questions, recalled age was used in the subsequent analysis as this is remembered more accurately. In four women with classical autism the participant's mother responded; analyses were run with and without these cases. Participants were excluded if they reported having a hormonal condition that could influence the variable being tested, such as thyroid gland abnormalities, diabetes, and anorexia. Three women were removed from the ASC group for exclusionary conditions. Because timing of menarche differs among ethnic groups,[1] only participants with a Caucasian background were included in this study. The reported study was approved by the Cambridge Psychology Ethics Comittee. Informed consent was obtained in all cases.

Three of the women in the ASC group had their first period at a very late age (20y 3mo, 20y 1mo, and 20y). One woman in the control group had a delayed age at menarche (17y 8mo). This represents a significant minority of the women with ASC. Even excluding these women, a *t*-test showed that women with ASC, on average, began their periods at a later age than the women in the control group (13y 4mo vs 12y 7mo respectively), $t(69) = 1.95$, $p = 0.055$, $d = 0.45$. Levene's test[4] indicated equal variance. The probability of a type I error was maintained at 0.05. A significant difference was also found when participants whose mother's responded were excluded, (13y 6mo vs 12y 7mo), $t(67) = 1.95$, $p = 0.02$, $d = 0.60$. The cause of this delay remains open to investigation.

One possibility is the influence of prenatal androgen. It has recently been suggested that high testosterone may be a risk factor for autism.[5] Our results are compatible with this theory in that female rhesus monkeys exposed to high levels of androgens early in gestation experience delayed menarche.[6] Females with ASC show other markers of high testosterone including a low 2nd to 4th digit ratio, potential somatic hypermasculinization,[5] and a more masculine pattern of play (Knickmeyer et al. unpublished).

Another major candidate is body mass index (BMI). Females who are obese tend to enter puberty at an earlier age than their peers, while strict training in activities such as sports or ballet dancing delays menarche.[1] Children with autism often have dietary abnormalities which could affect

North American usage: mental retardation.

their BMI. Stress is also thought to affect menarche, but due to the highly subjective nature of this phenomenon, it is difficult to study. Given that our study included no clinical controls, our results could reflect stress associated with having a clinical condition. Females with cerebral palsy and females with severe cognitive impairment may also have delayed puberty.[7,8] However, females with Down syndrome experience menarche at an earlier age than the general population. Age of menarche shows no deviation in fragile X syndrome.[9] The factors producing this variation across conditions merit further study, but may include activity level (acting through BMI) as well as physiological factors specific to the conditions. Individuals with clinical conditions may have taken medications which alter their metabolic or endocrine status, thereby affecting timing of menarche.

In conclusion we found a significant minority of women with autism have an extremely late onset of menarche. We have since been contacted by another woman with autism who, at the age of 26, has never experienced menarche. Even excluding these extreme cases, menarche was delayed in women with ASC compared with age-matched controls by 8 months. Whilst intriguing, our findings are limited in that they included only a single ethnic group and relied on participants recalling their age at menarche and self-reporting exclusionary clinical conditions; the study was also of a relatively small sample size. A comprehensive study of pubertal development, which takes account of nutritional status, medication, and other variables relevant to pubertal development in women with ASC, is needed before any strong conclusions can be drawn. Our results suggest that such a study would be worthwhile.

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Rebecca C Knickmeyer[a]*
Sally Wheelwright[b]
Rosa Hoekstra[c]
Simon Baron-Cohen[b]

[a]*Department of Psychiatry, University of North Carolina-Chapel Hill, Neurosciences Hospital, Chapel Hill, NC, USA.*
[b]*The Autism Research Centre, Departments of Experimental Psychology and Psychiatry, University of Cambridge, Cambridge, UK.*
[c]*Department of Biological Psychology, Vrije Universiteit, Amsterdam, the Netherlands.*

**Correspondence to: rebecca_knickmeyer@med.unc.edu*

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'Ferritin as an indicator of suspected iron deficiency in children with autism spectrum disorder: prevalence of low serum ferritin concentration'

SIR–Children with autism spectrum disorder (ASD) often have limited iron intake[1] as shown by Latif et al.[2] who found children with ASD to have a high prevalence of low serum ferritin levels, a widely-used screening test for depleted iron stores.[2–4] The cut-off values used for low ferritin differ across centers (<6ug/L to <22ug/L2[5–8]), limiting its accuracy for detecting the presence of iron deficiency. The World Health Organization[9] reports a geometric mean of normal ferritin levels of 34ug/L whilst Milman et al.[7] reported a mean of 38.5ug/L. The American Association for Clinical Chemistry uses a range of 6 to 24ug/L (1–5y) and 10 to 55ug/L (6–9y).[6] The National Health and Nutrition Examination Survey (NHANES)[5] chose the ferritin level cut-off that fell near the fifth centile for age.

In this retrospective chart review, all 96 children (78 males, 18 females) who had undergone an ASD diagnostic assessment at the tertiary level Child Development Centre (1998–2003), located in The Hospital For Sick Children, Toronto, Canada, were included, regardless of their nutritional history. In our center's population of children with ASD, although the ferritin level was initially measured only in those whose nutritional history suggested risk for iron deficiency, the frequent finding of low ferritin levels led to the clinical practice of routine measurement of serum ferritin concentration in 1998 during all diagnostic assessments of children with ASD in order to screen more formally for iron deficiency. In the current study, ferritin levels were recorded and mean corpuscular volume (MCV; <80fL[10]) and haemoglobin (Hb; <110g/L in 2–4-year-olds and <120g/L in 5–10-year-olds[10]) were used as measures of iron deficient erythropoeisis because ferritin by itself does not indicate the severity of iron deficiency once iron stores are fully depleted.[11] To compare the prevalence of low ferritin in children with ASD to that of iron deficiency in the general population, we used the same cut-off values as those described in the Center for Disease Control and Prevention (CDC) recommendations to prevent and control iron deficiency.[3,12] Their data were drawn from NHANES,[5] using a cut-off of <10ug/L for preschool children (age 1–5y) and <12ug/L for school-aged children (6y and older). A weakness of our design was the lack of multiple markers available for iron deficiency; these could have been beneficial because ferritin lacks a uniform reference range in the literature and ferritin can become falsely elevated by physiological fluctuations.[11,13] χ^2 test or Fisher's exact test were used to test the difference between two proportions, two-independent sample *t*-tests or Mann–Whitney *U* tests were used to test

differences in means between two samples, and Pearson's correlation was used for patterns of association between continuous variables.

The mean age of the 61 preschoolers (1–5y) and 35 school-aged children (6–10y) was 5 years 5 months. Median ferritin was 17.1ug/L (range 2.5ug/L–49.2ug/L). Two preschool children had an outlying ferritin level (168.4ug/L and 175.5ug/L). Ferritin did not appear to differ with age (preschool children [17.2ug/L], school-aged children [16.6ug/L]; $p=0.61$).

Ferritin was low in 1/12 of 1–2-year-olds with ASD, similar to the 7% prevalence of iron deficiency reported in the general population at that age;[5,12] it was also low in 7/49 of 3–5-year-olds, more than double the 5% typical prevalence,[5,12] and in 7/35 of 6–10-year-olds, fivefold greater than the 4% typical prevalence.[5,12] MCV was low in 48% (44/91), associated with median ferritin 17.4ug/L; Hb was low in 19% (17/91). A ferritin level above 12ug/L was present in 34/43 of those children with low MCV and in 16/17 of those with low Hb. Lower ferritin values were correlated with higher ADOS[14] communication scores ($p=0.005$), indicative of more severely impaired communication, which could reflect more restricted diets in impaired children, or that behavioural difficulties are exacerbated by iron deficiency.

Assuming low ferritin indicates iron deficiency in this population, this study confirmed a much higher prevalence of iron deficiency in children with ASD than in the general population. This may be associated with more severe ASD impairment. The high rate of microcytosis supports the presence of iron deficiency, but its associated high prevalence of ferritin above cut-off values suggests that ferritin measurements may miss some children with iron deficiency and supports the need for multiple markers.[13] In conclusion, children with ASD represent a high risk group for iron deficiency, and need close monitoring, even at school-age, in accordance with the CDC[3] recommendation to screen populations at risk for iron deficiency.

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Cara F Dosman MD[a]*
Irene E Drmic MSc[b]
Jessica A Brian PhD[c]
Ambikaipakan Senthilselvan PhD[d]
Mary Harford RN[c]
Ryan Smith[c]
S Wendy Roberts MD[c]

[a]*Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, Alberta;*
[b]*Department of Psychology, York University;*
[c]*Child Development Centre, The Hospital For Sick Children, University of Toronto, Toronto, Ontario;*
[d]*Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada.*

**Correspondence to: carado123@hotmail.com*

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'Interobserver reliability of visual interpretation of electroencephalograms in children with newly diagnosed seizures'

SIR–Stroink and colleagues recently addressed the important question of interobserver reliability in electroencephalograms (EEGs) of children with newly diagnosed seizures and concluded that 'the reliability of the visual interpretation of EEGs in children is almost perfect as regards the presence of epileptiform abnormalities'.[1] The methods of this study should make us skeptical of the generalizability of this conclusion.

First, their case mix differs from the typical clinical case mix. The authors selected two groups of EEGs from their first seizure/newly diagnosed epilepsy study. In the first group, 56 of 72 (78%) had been read by the first EEG reader as abnormal. In the second, 37 of 39 were interpreted abnormal. In standard clinical practice, EEGs are ordered in a much more diverse mix of patients. Even in comparable first seizure or epilepsy patients, the proportion of EEGs that will show abnormalities is far lower. So, conclusions drawn on the basis of this case mix may not be generalizable to all situations where EEGs are performed in children.

Second, these authors are experienced clinical neurophysiologists who have been collaborating in epilepsy research for years. Thus, one would expect them to have worked to reduce interobserver variation, and that over time a convergence in EEG interpretation would occur. This may partly explain the high level of agreement. However, there is no reason to think

that neurologists trained at a wide variety of institutions for varying periods of time would currently achieve this high level of agreement in interpreting EEGs.

In fact, evidence from other large studies shows that interobserver reliability is much lower than the authors report. If the reliability of EEG reading is 'almost perfect' in children, one would expect that the test characteristics of EEGs would be highly consistent across studies in children. However, our meta-analysis of studies involving over 2000 children showed sensitivity ranged from 33 to 91% and specificity from 13 to 80%. Moreover, the readers' interpretation threshold varied, and this significantly influenced the predictive accuracy of EEG for seizure recurrence.[2] In the community setting, we found, in reviewing 2500 EEG interpretations by six experienced clinical neurophysiologists, that the probability that an EEG would be interpreted as epileptiform varied significantly depending on the neurologist reader.[3] Taken together, these results show that agreement in visual interpretation of EEGs across centers and within a single community is not 'almost perfect'.

For diagnostic purposes, it is worth noting that classification of epilepsy syndromes includes more specific interpretations of the type and location of epileptiform discharges than Stroink et al. required for their study. When neurologists' readings on more specific epileptic findings are compared, agreement is also lower. In a random sample of 255 neurologists asked to read 10-second samples of 12 EEGs, among the 100 who agreed to participate there was wide variation in interpretations of particular EEG findings.[4]

The authors have done a commendable job in showing us that it is possible for visual EEG interpretations in selected situations to have high agreement. However, there is more work to be done before we can tell our patients and colleagues that neurologists interpret EEGs consistently.

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Donald L Gilbert MD MS
Cincinnati Children's Hospital Medical Center, USA.

Correspondence to: donald.gilbert@cchmc.org

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'Stroink et al. reply'

SIR–We thank Dr Gilbert for his valuable comments, however, we feel that the object of our study was somewhat different from the studies of Gilbert et al.[1,2] They investigated the value of electroencephalograms (EEGs) of children requested during daily practice[1] and performed a meta-analysis of the prognostic value of EEGs in studies of children with epilepsy or a first seizure.[2] Gilbert et al. concluded that a large variation exists in the conditions of children referred for EEG and a large interreader variation because of diverging specificity and sensitivity of the EEG between studies. We investigated the interrater reliability of the EEG in children diagnosed with epilepsy by experienced paediatric neurologists. We think that our results do not conflict but agree with most of the findings of Gilbert et al.[1,2]

A seizure and epilepsy need to be diagnosed on the basis of the history of the events and, if available, on (home) videos. EEG may support the diagnosis of epilepsy only if the clinical suspicion of epileptic seizures is already high. The interictal EEG should be used predominantly to classify epilepsy syndromes and to help choose the right drug when treatment is indicated, and it may have prognostic value in some specific circumstances.[3] The diagnosis of epilepsy based solely on EEG results without adequate knowledge of the clinical signs of seizures, or rejection of this diagnosis because of normal interictal EEG findings, are frequent mistakes, as shown in the literature.[1–5] If paroxysmal events are not straightforward epileptic seizures by history, one has to consider alternative diagnoses, wait until the events become clearer in time, request a home video if possible, request a video-EEG, or refer the child to an experienced paediatric neurologist or epileptologist. Thus, an EEG should be obtained only if the clinical suspicion of epileptic seizures is high, as was the case in our study,[8] and not when children present unclear events or non-epileptic complaints.[1–5]

Two of the five clinical neurophysiologists in our study were co-authors of our paper. None of these five was a member of our study group DSEC. However, they are all full-time, board-certified clinical neurophysiologists with a great deal of experience. This has probably influenced our results, as has the selection of the children. Moreover, in daily practice the quality of EEG reports and consequent diagnosis and classification of epilepsy in children depends on regular discussion between clinicians and clinical neurophysiologists. This method of working may alone be an important factor in improving the interrater reliability, as Gilbert remarks. Another factor causing diverging EEG results, not mentioned by Gilbert, may be the interval between seizure and EEG.[3,6] A longer interval lowers the chance of epileptiform discharges. We only performed an interrater study for EEG abnormalities and did not study syndrome classification (we published such a study earlier[7]). Epilepsy classification depends on the results of the EEG in combination with the clinical symptoms. For example, if a clinician requests an EEG because of seizures with diminished consciousness, automatisms, and postictal confusion and the EEG shows centrotemporal spikes with a normal background pattern, the EEG findings do not match the clinical symptoms; they are probably coincidental and do not contribute to a classification.

Gilbert has previously shown that EEGs are regularly requested unjustifiably without a high suspicion of epileptic seizures and even for other reasons, and that prognostic value varies widely between studies. We showed that the interobserver reliability of EEG descriptions can be high with the use of criteria for EEG abnormalities, when EEGs are requested by experienced physicians for children with a high suspicion of epilepsy and are seen and read by experienced, certified clinical neurophysiologists.

Much work needs to be done in teaching physicians and clinical neurophysiologists treating children with paroxysmal events on how to improve the quality of diagnosis and treatment of these children. Preferably, only a few selected physicians in a general paediatric practice will see children with possible epilepsy, to gather enough experience and training within this field. EEGs should be read by experienced clinical neurophysiologists who discuss the results with the clinicians. In case of doubt, the child should be referred to an experienced paediatric neurologist or epileptologist.

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Hans Stroink MD[a]*
Robbert-Jan Schimsheimer MD PhD[b]
Al W de Weerd MD PhD[c]
Ada T Geerts MSc[d]
Willem F Arts MD PhD[d]
Els A Peeters MD[b]
Oebele F Brouwer MD PhD[e]
C Boudewijn Peters MD PhD[f]
Cees A van Donselaar MD PhD[f]

Departments of Paediatric Neurology at:
[a]*St Elisabeth Hospital, Tilburg;*
[b]*Medical Centre Haaglanden, the Hague;*
[c]*Dutch Epilepsy Clinics Foundation, Zwolle;*
[d]*Erasmus MC, Rotterdam;*
[e]*University Medical Centre, Groningen;*
[f]*University Medical Centre, Utrecht, the Netherlands.*

**Correspondence to: H.Stroink@Elisabeth.nl*

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'Genetic testing for myotubular myopathy despite muscle biopsy without centrally located nuclei'

SIR–I commend your journal and authors de Goede et al. on the fascinating article 'Muscle biopsy without centrally located nuclei in a male child with mild X-linked myotubular myopathy'.[1] The authors described a male with a congenital myopathy, who lacked a more specific diagnosis despite various tests including repeat muscle biopsy (which did not show centrally located nuclei). Years later, the child's mother learned that her cousin's son had a clinically similar myopathy where muscle biopsy indeed did show centrally located nuclei, prompting genetic testing which, in both children, was positive for the same *MTM1* (myotubularin) mutation, thus making the diagnosis of X-linked myotubular myopathy (XL-MTM) in both.

This is a landmark article, clearly showing the growing importance of genetic testing for myotubular myopathy (MTM) and other forms of centronuclear myopathy (CNM). Many other cases in practice and in the literature have shown that a conclusive diagnosis of XL-MTM cannot be made merely based on centrally located nuclei on muscle biopsy, which looks similar in congenital myotonic dystrophy as well as among the various different forms of MTM/CNM. Meanwhile, family histories are limited by memory, undisclosed paternity, and lost contact with relatives. Further, the clinical presentations show substantial variability and overlap among these myopathies. Thus, we have known for years that myopathy patients with centrally located nuclei need genetic testing to more definitively diagnose the specific myopathy. However, this article presents a novel revelation that MTM/CNM genetic testing is indicated even in myopathy cases where the muscle biopsy does not show centrally located nuclei.

The knowledge gained from this single article has the potential to shift substantially the diagnostic algorithm in congenital myopathies, leading to increased genetic testing and more accurate diagnoses. This, in turn, would allow for more accurate genetic counselling for affected families and relatives, as well as an increased likelihood of appropriate patient identification for research studies and eventual gene-specific treatments. I praise the authors and this journal, and I hope that the medical and research community worldwide will take note of this article's importance and implications.

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Patrick M Foye MD
University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, USA.

Correspondence to: Patrick.Foye@umdnj.edu

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