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Original Article

Effect Of the Pandemic on Utility of Paediatric Muscle Biopsies in the Age of Genomics; a Single Centre 8 Year Retrospective Audit

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Keywords

- Muscle Biopsy
- Neuromuscular disorders
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Abstract

Background: Muscle biopsy (MBx) is one of the key investigations in children with suspected neuromuscular disorders (NMD). In cases with a wide differential diagnosis, a MBx helps with the early diagnosis and therefore prevents any delay in treatment. In children a MBx often needs to be performed under general anaesthesia.

Objective: To evaluate the effect of the Covid-19 pandemic and the advances in genetic testing have had on the total number of MBx performed at a tertiary centre between April 2014 and April 2022.

Methods: Retrospective case records of patients who underwent MBx between April 2014 and April 2022 were reviewed. Investigations including genomic testing, number of biopsies and referrals, waiting time and the final diagnosis were collected and analysed.

Results: We reviewed a total of 102 children (101 children underwent a MBx, 70 skin biopsy and 4 nerve biopsies). The average number of biopsies per year was 14.2 biopsies during the pre-pandemic period & 8.5 biopsies during the post pandemic period. This represents a 40% reduction within the last 3 years. The median waiting time from referral till the date of biopsy was 96.5 days during the pre-pandemic period (p value: 0.013, CI: 36.1-266.4) and 143 days during the post pandemic period (p value: 0.0, CI: 71.8-230.6). During the last 3 years, in 100% of the patients who underwent a MBx, a genetic test was also done at some point during evaluation. In 28.4% (29 out of 102) of the biopsies' results were specific for the diagnosis. MBx and genetic testing did not identify a diagnosis in 38% of the patients. In 11.7% of the cases (6 myositis, 6 mitochondrial, 2 Neuropathy) muscle biopsy picked up the non-genetic diagnosis or directed us to further testing.

Conclusion: The number of biopsies and referrals has significantly decreased in the last 3 years, which could be related to the pandemic and/or advances in genetic testing. The diagnostic strategy of some NMDs has been modified and the utility of MBx in this process has been questioned. The role of the MBX is never likely to disappear completely as many non-genetic NMD remain challenging and will be easily missed even with the most sophisticated genetic tests. (Word count 358).

ABBREVIATIONS

CPK: Creatine Phosphokinase; EBV: Epstein Barr Virus; IQR: Interquartile Range; LOS: Length Of Stay; Mbx: Muscle Biopsy; NGS: Next Generation Sequencing; PCR: Real-Time Polymerase-Chain-Reaction; PICU: Pediatric Intensive Care Unit

INTRODUCTION

Diagnosis of a neuromuscular disorder (NMD) can be challenging and may require extensive workup. Muscle biopsy (MBx) is one of the key investigations in children with suspected NMD. MBx facilitates morphologic, biochemical, and structural analysis of muscle for the purpose of making definitive diagnosis. When the differential diagnosis is wide, a muscle biopsy may help in identifying and narrowing the differential diagnosis. MBx is a resource-dependent procedure but it has been shown to be cost effective [1]. Muscle biopsies are also minimally invasive, but the need for general anaesthesia in children also increases the risks associated with this procedure. Even in a tertiary hospital setting, referrals for MBx are made only after a careful evaluation of the benefits (diagnostic yield) over the risk of the procedure (surgery and anaesthesia). Histopathologic findings of a muscle biopsy in ideal circumstances can be very specific for a diagnosis, however often the results of the biopsy are very nonspecific and may lead to further investigations which are usually genomic in nature. In view of the vast progress in genomic technology and medicine there is a current debate on the utility of the muscle biopsy and whether it has been superseded by other techniques.

AIM

The aim of this study was to evaluate the effect of the Covid-19 pandemic and the advances in genomic testing have had on the total number of MBx performed at a tertiary paediatric centre between April 2014 and April 2022.

METHODS

This retrospective review was conducted in children aged

≤18 years, which had MBx performed at our institution during the 2014–2022 study period. This period represents MBx which were done pre and post pandemic. Of the paediatric MBx patients identified in our centre, only those patients referred with suspected NMD or mitochondrial disease were included in the analysis. All our biopsies were performed in theatre, under sterile and aseptic conditions, under a general anaesthesia using open biopsy technique. In the UK, genomic testing for NMD is readily available using multiple panels and bioinformatics pipelines.

The demographic and clinical information about each patient undergoing a muscle biopsy was collected and recorded in an anonymized fashion. Descriptive statistics were used for the analysis.

We collected information about the investigations which included genomic testing, number of biopsies and number of referrals, waiting time and final diagnosis. This data was analysed statistically using SPSS programme.

This study was classified as an audit/ quality improvement project and therefore did not need institutional ethical approval.

RESULTS

We identified from our records 102 children who underwent biopsies for suspected NMD. 101 children underwent a MBx, 70 underwent a skin biopsy and 4 had a nerve biopsy. The average age of biopsy was 6.4 years with a range of 3 weeks to 17.8yrs. 63.7% (65) were male. No perioperative complications (such as malignant hyperthermia, rhabdomyolysis or failed extubation) were noted in any patients. 42% of the patients needed one general anaesthesia to complete the whole workup. All of the obtained biopsy specimens were deemed adequate for histologic examination and did not suffer from any sampling issues. More details are shown in [Table 1].

The average number of biopsies taken per year was 14.2 during the pre-pandemic period (2014 to 2019) and 8.5 during the post pandemic period (2020 to 2022) (Figure 1), which represents a 40% reduction. The average number of biopsy referrals per year was 14.2 during the pre-pandemic period and 9.4 during the post pandemic period, which represent a 33.8% reduction (Figure 2).

Table 1: Demographic characteristics

Characteristics	Number = 102
Age	6.4 years (3weeks-17.8yrs)
Gender: n (%) • Male • Female	 65 (63.7%) 37 (36.3%)
Investigations: n (%) • CPK • Cerebrospinal fluid analysis • Metabolic panel • Respiratory chain	 96 (94.1%) 53 (52%) 79 (77.5%) 94 (92.2%)
General Anaesthesia (GA): n (%) • One GA • Two GA • Three or more GA **The remained patient was intubated in PICU	 42 (41.2%) 38 (37.2%) 21 (20.6%)
Biopsy Type: n (%) • Muscle • Skin • Nerve ** One patient underwent nerve Bx without MBx	 101 (99%) 70 (68.6%) 4 (3.9%)

The median waiting time from referral till the date of biopsy was 96.5 days during the pre-pandemic period (p value: 0.013, CI: 36.1-266.4) and 143 days during the post pandemic period (p value: 0.0, CI: 71.8-230.6), an increase of48%. During the last 3 years, in 100% of the patients who underwent a MBx, a genetic test was also done at some point during evaluation as shown in [Table 2].

There were 29 (28.4%) patients with definitive abnormal pathologic findings. The remaining 73 patients (71.6%) showed nonspecific histologic changes that were insufficient for making a definitive diagnosis.

In 8 patients (7.8%) whose histopathologic findings facilitated a diagnosis of inflammatory process (6 myositis, 2 neuropathy), immunomodulation treatment was given with improved outcome. In 6 patients (5.9%), MBx identified problems in the respiratory chain system which prompted further investigations for mitochondrial diseases. MBx and genetic testing did not

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Genetics %	70%	83.30%	84.6	94.40%	88.80%	85.70%	100%	100%	100%
Number	7/10	15/18	11/13	17/18	8/9	12/14	7/7	11/11	2/2

Table 2: Number of genomic testing and percentages in each year.

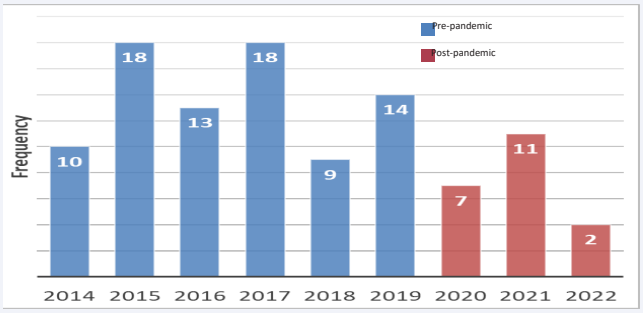

Figure 1 Numbers of biopsies done per year pre and post pandemic.

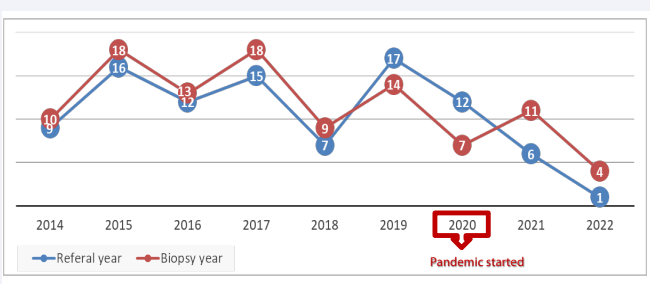

Figure 2 Frequency of referrals and biopsies over time pre and post pandemic.

identify a pathologic diagnosis in 39 patients (38%). The case load by condition category was as in (Figure 3).

DISCUSSION

In this study, we aimed to find out the utility of MBx in children with suspected NMD in an eight year cohort. During this time, genomic testing has become common and more reliable than ever before. Towards the latter part of this time period, we were able to assess the effect of the Covid 19 pandemic on our ability to undertake biopsies.

Although major limiting factors for muscle MBx are its invasiveness and the need for general anaesthesia, these are not considered as an absolute barrier to requesting MBx, as it is minimally invasive and easily tolerated by the patient with a very low rate of complications. In our cohort, no perioperative complication in any included patient was noted. A study by Shapiro et al, [2]. reviewed 877 paediatric patients and revealed relative safety in performing a biopsy as no one exhibited signs or symptoms of malignant hyperthermia, rhabdomyolysis, cardiac arrest, or postoperative deterioration of weakness.

During the pandemic, the waiting time for MBx increased by 48% in our centre, which is comparable with other health care organizations in Europe where elective surgery waiting time increased by as much as one-third [3].

A MBx can give us a preliminary diagnosis for treatable conditions in a timely fashion, while the genetic testing may take a long time to reach the final results. When differential diagnosis is wide, a muscle biopsy can be recommended in the early stages of care in order to prevent deterioration in treatable conditions. We found that in 8 patients (7.8%) the histologic analysis of phenotypical variants of non-genetic diseases is important for guiding and redirecting management. For example, by ignoring MBx from the diagnostic pathway of inflammatory myopathies, the diagnosis of juvenile dermatomyositis will be easily missed even with the most advanced genomic testing [4]. Meanwhile, MBx identifies problems in the respiratory chain system which prompted further investigations for mitochondrial diseases [5].

Our study showed pathologic diagnosis in 28.4% patients. This finding is consistent with findings from other studies

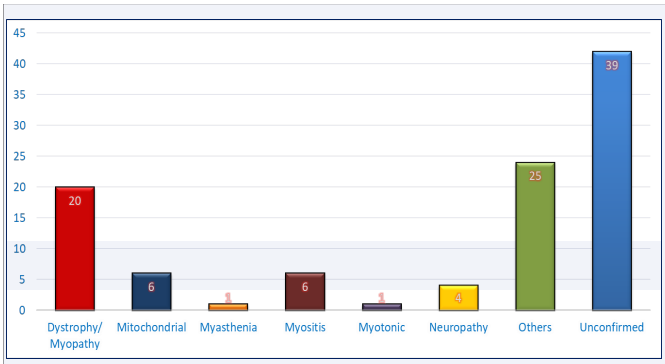

Figure 3 Frequency of diagnostic classification.

reported in the literature. Yang, et al. [6], showed the pathologic diagnosis alone led to a clinical diagnosis in 33.9%. Also, Thavorntanaburt et al. [7], found that 36% of cases ended in a specific clinical diagnosis.

The histological findings in the MBx play an important role in categorizing some of the NMDs, esp. congenital myopathies, which will help to establish the genotype-phenotype correlation and allow for a discussion of the prognosis with the family [8].

Relying solely on genomic testing to establish a diagnosis of NMD has its limitations and pitfalls. This is due to poorly established genotypic–phenotypic correlation and the presence of genetic heterogeneity in many muscle diseases [9]. A Muscle biopsy may confirm the pathogenicity of new gene variants, guide cost-effective molecular studies, and provide phenotypic diagnosis in doubtful cases [10]. In addition, limitations of genomic data in certain understudied populations or an adopted child with unknown parents are all restrictive factors for the diagnosis of NMD solely based on genetic testing.

STUDY LIMITATIONS

This study had some limitations. It is a retrospective study with the associated patient-selection bias and a relatively small size population from a single centre. In addition, our institution is a tertiary referral centre with various subspecialists, such as muscle pathologists, paediatric neurosurgeons, paediatric anaesthesiologists, and paediatric neuromuscular specialists. Therefore, MBX procedure availability, safety, results interpretation and the availability of other investigation tools including genetic testing may be different from other centres with different resources and expertise.

CONCLUSION

The number of biopsies and referrals has significantly decreased in the last 3 years, which could be related to the pandemic and/or advances in genomic testing. Even in the genetic era, MBx continues to be a useful and beneficial diagnostic tool in evaluating children with suspected NMD either as a primary diagnostic tool or a complementary to the genomic testing. MBX is never likely to disappear completely as many non-genetic NMDs remain challenging and will be easily missed even with the most sophisticated genomic tests. In addition, MBx will help in categorizing the NMD subtypes when there is a genetic heterogeneity.

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