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Research Article

# Underlying Organic Causes in Lebanese Autistic Pediatric Patients in a Single-Center Cohort

**EL SABBAGH Jana**[1], **MANSOUR Hicham**[1-2*]

[1]Faculty of Medicine, Saint George University of Beirut, Beirut, Lebanon.

[2]Department of Pediatrics, Saint George Hospital University Medical Center, Beirut, Lebanon.

***Corresponding Author:** MANSOUR Hicham, Department of Pediatrics, Saint George University Medical Center, Lebanon.

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## Abstract

This is a prospective observational study at a university hospital pediatric clinic between June 2025 and June 2026. During the study period, 242 new unique consults of patients already diagnosed with autism/cognitive delay were seen for neurological evaluation, 44 among which were included in the study. Among 44 analyzed children, the mean age was 6.3 ± 2.7 years and mean age at presentation was 4.7 ± 2.4 years. Presenting features were: Speech delay (93.2%), hyperlaxity (43.2%) and poor attention/hyperactivity (15.9%). Consanguinity was present in 18.2%. Lactic acidosis in (88.6%), white-matter delay on MRI in 12 (27.3%), and a positive WES finding in all 5 children who underwent testing. The most frequent treatment regimen was L-Carnitine, Coenzyme Q 10, Vitamin B2, Biotin combination. Thirty-four patients (77.3%) improved after treatment. In this selected cohort, children referred under an autism/cognitive-delay label frequently showed biochemical or clinical clues suggestive of an underlying organic disorder, and more than 75% improved after targeted mitochondrial-oriented supplementation. These findings support a more etiologic approach to selected ASD presentations rather than reliance on behavioral labeling alone.

***Keywords:*** *Autism spectrum disorder; Cognitive delay; Lactic acidosis; Mitochondrial disease; mitochondrial dysfunction; Whole-exome sequencing; Pediatrics; Lebanon*

## Introduction

Autism spectrum disorder (ASD) is one of the most common neurodevelopmental conditions in childhood, with recent global estimates placing prevalence at approximately 1 in 100 children [1]. Although ASD is diagnosed clinically based on behavior, it is increasingly understood as a heterogeneous neurodevelopmental phenotype rather than a single disease entity [2].

This distinction is clinically important because behavioral criteria can identify the syndrome, but they do not by themselves determine whether a child has an underlying metabolic disease, mitochondrial disorder, ion-channel disorder, or genetic condition presenting with autistic traits, language delay, developmental slowing, or treatment-resistant symptoms [3,4].

In pediatric neurology practice, the central question is not whether every child with ASD requires the same exhaustive work-up, but whether selected children with additional clinical warning signs are being left with a purely behavioral label. The present study was designed from this practical clinical question: among new consults presenting under an autism/cognitive-delay label, how often do we encounter a subgroup with organic clues strong enough to justify deeper metabolic and genetic evaluation.

Clinical guidelines and expert statements emphasize that etiologic evaluation is most useful when ASD or developmental delay is accompanied by atypical features such as global developmental delay, developmental regression, seizures, dysmorphism, abnormal tone, episodic decompensation, abnormal biochemical testing, neuroimaging abnormalities, unusual family history, or parental consanguinity [3,4]. These features can shift the evaluation from behavioral classification alone toward targeted genetic, metabolic, and neurologic assessment.

Interest in metabolic contributions to autism-like presentations has persisted for years. Although individual inborn errors of metabolism are rare, cohort studies show that a small but meaningful subset of children with ASD phenotypes may have diagnosable and sometimes treatable metabolic disease. Recognition of these disorders can redirect management toward dietary therapy, vitamin or cofactor replacement, disease-specific treatment, and more accurate family counseling [5-7].

Mitochondrial dysfunction is another repeatedly described biological pathway in a subgroup of children with ASD-related phenotypes. Prior studies have reported associations between ASD presentations and abnormal oxidative metabolism, including elevated lactate and other biochemical markers of mitochondrial dysfunction [8-11]. These findings do not imply that mitochondrial disease explains all ASD, but they support targeted assessment when clinical or laboratory red flags are present.

Genomic diagnostics have also changed the approach to unexplained neurodevelopmental disorders. Exome sequencing has demonstrated clinically relevant diagnostic yield and is increasingly recommended early in the evaluation of unexplained developmental delay or syndromic presentations [4].

Lebanon offers a particularly relevant clinical context for this question. Local genetic work has highlighted how shared ancestry and consanguinity may facilitate the identification of recessive neurodevelopmental disease genes. In such settings, an autism label may be the first doorway into a broader etiologic diagnosis rather than the endpoint of evaluation [12,13].

## Methods

This was a prospective observational study conducted between June 2025 and June 2026 at a pediatric neurometabolic clinic at a tertiary referral university medical center in Beirut.

During the study period, 242 new unique consults were recorded for autism/cognitive delay. A clinically selected subgroup of 45 children was identified as having lactic acidosis. One record was incomplete at the spreadsheet level, leaving 44 analyzable patients. The final analytic cohort therefore represents a high-suspicion subgroup rather than the entire autism/cognitive-delay clinic population.

De-identified spreadsheet data were collected for analysis from patient clinic files. Variables available for review included current age, age at presentation, presenting features, previous treatment, reason for referral, parental consanguinity, family history of similar presentation, lactic acidosis status, brain MRI anomalies, clinical suspicion of underlying mitochondrial disease, WES result when testing was performed, mutation name when present, treatment regimen, and documented improvement after treatment.

Presenting features were recorded as the main clinical manifestations noted at presentation and included speech delay, psychomotor delay, hyperlaxity, and poor attention/hyperactivity. Previous treatment was coded as none, behavioral therapy, medication, or both. Reasons for referral were coded as autism diagnosis, no response to prior treatment, or both. Treatment regimen was reconstructed from the supplement combinations.

The main descriptive outcomes were the proportion of the subgroup with lactic acidosis, as reported in patients' files; abnormal MRI findings; WES-positive results; and documented improvement after treatment.

Continuous variables are summarized using means with standard deviations and medians with interquartile ranges when appropriate. Categorical variables are presented as counts and percentages. Because the available dataset was small, selected, and primarily intended for descriptive clinical analysis, emphasis was placed on clinically interpretable descriptive findings rather than formal predictive modeling.

This was a prospective study approved by the Institutional Review Board of Saint George University of Beirut / Research Ethics Committee of Saint George Hospital University Medical Center. Participants were enrolled according to the approved protocol, and the study used approved parental consent, child assent, and genetic consent forms in both English and Arabic. Collected data were recorded in an Excel database and analyzed after de-identification.

## Results

Over the 12-month study period, 242 new unique consults were seen for autism/cognitive delay evaluation. Of these, 45 children were identified clinically as having lactic acidosis. The spreadsheet available for final analysis contained 44 evaluable records, which formed the analytic cohort. This corresponds to 18.2% of all new consults and 97.8% of the lactic-acidosis subgroup identified clinically.

The mean age of the analytic cohort was 6.3 years (SD 2.7), and the mean age at presentation was 4.7 years (SD 2.4). Consanguinity was documented in 8 children (18.2%), while family history of a similar presentation was recorded in 2 children (4.5%) (Table 1).

Speech delay was by far the most frequent presenting feature, affecting 41 children (93.2%). Hyperlaxity was present in 19 children (43.2%), poor attention/hyperactivity in 7 (15.9%), and psychomotor delay in 2 (4.5%) (Table 2).

**Table 1.** Baseline demographic and family characteristics of the analytic cohort (n=44).

| Characteristic | Value |
|---|---|
| Current age, mean ± SD (years) | 6.3 ± 2.7 |
| Current age, median (IQR) | 7.0 (4.0-8.0) |
| Age at presentation, mean ± SD (years) | 4.7 ± 2.4 |
| Age at presentation, median (IQR) | 4.0 (3.0-7.0) |
| Consanguinity | 8 (18.2%) |
| Family history of similar presentation | 2 (4.5%) |

**Table 2.** Presenting clinical features.

| Presenting feature | n | % |
|---|---|---|
| Speech delay | 41 | 93.2 |
| Psychomotor delay | 2 | 4.5 |
| Hyperlaxity | 19 | 43.2 |
| Poor attention / hyperactivity | 7 | 15.9 |

Most children were referred because of no response to previous treatment (28/44, 63.6%), while 10 (22.7%) were referred for both autism diagnosis and treatment non-response (Table 3). Prior treatment had already been attempted in most children: behavioral therapy alone in 24 (54.5%), combined behavioral therapy plus medication in 8 (18.2%), medication alone in 2 (4.5%), and no previous treatment in 10 (22.7%). Behavioral therapy in this cohort primarily included speech therapy and psychomotor therapy. Pharmacologic treatment was heterogeneous and included a range of medications prescribed according to clinical indication, most commonly ADHD medications, as well as antipsychotic agents, antiseizure drugs, and sleep aids.

Lactic acidosis was recorded in 39 of 44 analyzed children (88.6%), and white-matter delay on brain MRI was present in 12 (27.3%) (Table 4).

WES uncovered a gene mutation in 5 children (11.4%). Genetic findings were limited to the 5 patients who underwent WES; therefore, the lack of mutation data in the rest of the cohort should be interpreted as absence of testing rather than absence of detectable variants. The documented variants were CACNA1F hemizygous (n=2), MED12 hemizygous (n=1), EP300 heterozygous (n=1), and CTCF heterozygous (n=1).

The most common recorded mitochondrial-oriented regimen was combination of Coenzyme Q 10, L-carnitine, vitamin B2 and biotin. Overall, improvement after treatment was documented in 34 of 44 children (77.3%). Notably, all five children with positive WES findings were marked as improved after treatment, although the small sample and descriptive design prevent causal inference.

**Table 3.** Reasons for referral.

| Reason for referral | n | % |
|---|---|---|
| No response to previous treatment | 28 | 63.6 |
| Autism diagnosis | 6 | 13.6 |
| Both: no response to previous treatment and autism diagnosis | 10 | 22.7 |

**Table 4.** Key biochemical, imaging, genetic, and response outcomes.

| Variable | n | % |
|---|---|---|
| Lactic acidosis | 39 | 88.6 |
| White-matter delay on brain MRI | 12 | 27.3 |
| Patients with positive WES findings (among 5 tested) | 5 | 11.4 |
| Documented improvement after treatment | 34 | 77.3 |

## Discussion

As outlined in the introduction, ASD is a behaviorally defined but etiologically heterogeneous presentation. The present cohort illustrates this point in a selected tertiary-clinic context: children referred for autism/cognitive delay may carry additional signs, particularly lactic acidosis and treatment non-response, that should prompt consideration of an underlying organic disorder rather than reliance on behavioral labeling alone.

This study points to an important clinical reality. Among children referred to a university hospital pediatric clinic with a label of autism or cognitive delay, there is a subgroup with a particularly high number of organic red flags. These children were not part of a typical, unselected ASD population. Instead, they represented a more concerning group characterized by lactic acidosis, poor response to treatment, and clinical suspicion of mitochondrial disease. Even so, the findings remain important because they reflect real referral patterns in pediatric neurology practice.

The first major observation is how often behavioral labeling coexisted with broader developmental and systemic clues. Nearly all children in the analytic cohort had speech delay, and many also had hyperlaxity, abnormal MRI findings, or prior treatment failure. These patterns matter because when a child presents with more than isolated social and communication difficulties, clinicians should consider whether an underlying biological process may be contributing to the overall clinical picture [3,4].

The second major observation is the diagnostic relevance of targeted metabolic and genetic thinking. The literature suggests that universal metabolic screening in all non-syndromic ASD is low yield, but selected screening becomes more defensible when red flags are present [5-7]. Our cohort fits the latter scenario. Although not directly comparable to broader neurodevelopmental cohorts, the fact that mutations were identified in the 5 patients who underwent WES highlights that exome sequencing can be highly informative in carefully selected patients with unexplained or syndromic developmental presentations [4].

The treatment findings are also worth noting. More than three-quarters of the cohort were documented as having improved after mitochondrial-targeted supplementation. Prior literature has similarly described symptom improvement in selected metabolically characterized ASD cohorts after targeted interventions, although the quality of evidence remains heterogeneous [6,10].

The presence of consanguinity in 18.2% of the cohort strengthens the relevance of this work in Lebanon and similar populations. Lebanese and regional studies have emphasized that consanguinity and shared ancestry can increase the yield of discovering recessive neurodevelopmental disorders. In such settings, the threshold for genetic and metabolic evaluation should arguably be lower when autism is accompanied by developmental delay, poor response to standard therapy, seizures, MRI abnormalities, or laboratory signs such as elevated lactate [12,13].

Our findings fit within a broader literature describing a treatable subset of autism-associated metabolic disease. Greek and Iranian cohorts have shown that selected children with ASD can harbor diagnosable inborn errors of metabolism, including creatine disorders and urea-cycle defects, some with important implications for management [6,7]. Similarly, the mitochondrial literature has described elevated lactate and other biochemical markers in a subgroup of children with ASD-related phenotypes, reinforcing the idea that autism can sometimes be the surface manifestation of altered cellular energy metabolism [8-11].

This study has important limitations. The dataset was small, single-center, and highly selected. The source spreadsheet was missing several variables that would have strengthened a more complete etiologic analysis, such as sex, developmental regression, seizure burden, detailed laboratory values, standardized neurodevelopmental scores, precise MRI findings, and duration of follow-up. In addition, improvement was recorded only as a binary variable and was not based on a validated assessment scale. There was also a small discrepancy between the 45 children clinically reported to have lactic acidosis and the 44 rows available for analysis in the spreadsheet, which suggests a minor issue with data completeness. Finally, because the cohort was specifically selected based on suspicion of mitochondrial disease, the findings cannot be generalized to all children with ASD.

Despite these limitations, the study offers a useful clinical message: when autism is accompanied by treatment resistance or additional neurological, biochemical, or systemic clues, the evaluation should move beyond behavior alone. The goal is not over-testing, but smarter testing in the right child, early enough to matter [3,4].

## Conclusion

In this prospective study at a university hospital Neuropediatric clinic, nearly one in five new consultations for autism or cognitive delay belonged to a subgroup with lactic acidosis that warranted further investigation for an underlying organic cause. Within the 44 analyzable children in this selected cohort, neuroimaging abnormalities, WES findings among those tested, and substantial clinician-documented post-treatment improvement were common enough to justify continued emphasis on etiologic work-up. In selected pediatric patients, the autism label should therefore be viewed as a starting point for investigation rather than the end of diagnosis.

## Conflict of Interest

The authors declare no conflicts of interest.

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