Brainstem auditory pathway of children with acute lymphoid leukemia on chemotherapy with methotrexate

Several factors can compromise the auditory pathway, including the drugs used during chemotherapy.

Both normal cells and cancer cells are destroyed from chemotherapeutic drugs, causing secondary problems such as ototoxicity and neurotoxicity.

Several chemotherapeutic drugs are used in the treatment of various types of cancer, such as cisplatin, carboplatin, actinomycin, bleomycin, nitrogen mustards (mustine), misoprostol, vincristine, vinblastine, among others.

Acute lymphoblastic leukemia (ALL) is the most common type of cancer found in young children, and may occur in adults. In a study that aimed to estimate the prevalence of hearing loss in children and adolescents with cancer, 30.8% of the 94 patients treated in 2003 and 2004 in a referral hospital in São Paulo had ALL.

Objective: Investigate the auditory pathway in the brainstem of children with acute lymphoblastic leukemia submitted to chemotherapy (by intravenous or intrathecal infusion).

Methods: Fourteen children aged between 2 and 12 years with diagnosis of acute lymphoid leukemia were evaluated. The following procedures were used: meatoscopy, acoustic immittance measurements, tonal audiometry, vocal audiometry, transient otoacoustic emissions, and auditory brainstem response.

Results: From the 14 children with normal auditory thresholds, 35.71% showed an alteration in auditory brainstem response, with a predominance of hearing impairment in the lower brainstem. It was found that 80% of the children with alteration had used intrathecal methotrexate less than 30 days and that 40% had the highest cumulative intravenous methotrexate doses.

Conclusion: Children with acute lymphoblastic leukemia submitted to chemotherapy, present auditory pathway impairment in the brainstem, with a predominance of a low brainstem.

Keywords: hearing; electrophysiology; precursor cell lymphoblastic leukemia-lymphoma; drug therapy; methotrexate; child.

RESUMO

Objetivo: Investigar a via auditiva em tronco encefálico de crianças com leucemia linfoide aguda submetidas à quimioterapia (por infusão intravenosa ou por via intratecal). Métodos: Foram avaliadas 14 crianças com idade entre 2 e 12 anos, com diagnóstico de leucemia linfoide aguda. Foram utilizados os seguintes procedimentos: meatoscopia, medidas de imitância acústica, audiometria tonal, audiometria vocal, emissões otoacústicas transientes e potencial evocado auditivo de tronco encefálico. Resultados: Das 14 crianças com limiares auditivos normais, 35,71% demonstraram alteração no Potencial Evocado Auditivo de Tronco Encefálico, com predomínio de comprometimento de via auditiva em tronco encefálico baixo. Verificou-se que 80% das crianças com alteração haviam feito uso do metotrexato via intratecal a menos de 30 dias e que 40% tinham as maiores doses acumulativas de metotrexato por via endovenosa. Conclusão: Crianças com leucemia linfoide aguda submetidas à quimioterapia apresentam comprometimento na via auditiva em tronco enCEFálico, com predomínio em tronco enCEFálico baixo.

Palavras-chave: audição; eletrofisiologia; leucemia-linfoma linfoblástico de células precursoras; tratamento farmacológico; metotrexato, criança.
Brainstem auditory evoked potential (BAEP) measurement is an objective test that captures the electrical responses to acoustic stimuli generated in the brainstem. This potential consists of seven waves with well-defined polarities. BAEPs have been used to investigate ototoxicity in cancer patients undergoing chemotherapy17-19, but the investigation of neurotoxicity with this test has rarely been explored.

METHODS

The present study was approved by the Ethics Committee of the institution under number 53924116.0.0000.0068/2016, and data collection was performed only after the parents or guardians signed an informed consent form and the children signed an assent form.

This is a clinical and cross-sectional study that evaluated 14 children (8 females; 6 males) aged 2 to 12 years (mean age, 8 years 4 months) who were diagnosed with ALL, had no infiltration into the central nervous system as confirmed by examination of the cerebrospinal fluid, and were undergoing chemotherapy. The volunteers were referred by a public reference hospital in the city of São Paulo, where they were undergoing chemotherapy and outpatient follow-up (1 individual in remission — patient 7).

The audiological and electrophysiological evaluation of hearing was performed in a teaching health center, which required patients to travel, justifying why the sample size was small.

It is noteworthy that in some cases the first assessment was revalued, since the population had complications of chemotherapy, and data collection was performed in two sessions of up to 1h30min when necessary.

The doses of MTX were collected using medical records, and the total dose administered intravenously and/or intrathecally until the date of BAEP measurement was obtained. Dosages, frequency, and duration of drug infusion were established according to the risk group in which the patient was entered.

A Heine® Mini2000™ Otoscope was used to examine the ear canal.

The children were subjected to acoustic immittance evaluations ( tympanometry and acoustic reflex measurements) to assess possible middle ear impairment (GN Otometrics tympanometer, model Otoflex100). Pure-tone audiometry at frequencies of 500, 1000, 2000, 4000 Hz (if possible 6000 and 8000 Hz) were used to determine auditory thresholds, and speech audiometry (speech recognition threshold — SRT — and speech recognition percentage index — SRPI, the latter performed in older children) (Grason Stadler audiometer, model GSI-61, ER-3A earphones, sound booth meeting the ANSI S3.1-1991 standard for the amount of ambient noise).

When obtaining auditory thresholds, the ages of the children were considered, and conditioned play audiometry or pure-tone audiometry using earphones were performed.

To obtain the BAEP measurements, the skin was initially cleaned with an abrasive paste, and the electrodes were fixed to the skin of the individual using an electrolyte paste and adhesive tape (micropore), according to the International Electrode System (IES) 10-20 standard11. The impedance values of the electrodes were checked and were below 5kohms.

BAEPs were measured using a click stimulus with rarefied polarity, monaurally presented at 80dBnHL, at a rate...
of 27.7 stimuli per second, totaling 2000 stimuli (Universal
Smart Box Jr274 Smart EP, Intelligent Hearing System-ER-3A
earphone for BAEP and ER-10D earphone for otoacoustic
emissions-OAEs). In cases where it was not possible to
perform conventional pure-tone audiometry or transient
otoacoustic emissions (TOAEs), the electrophysiological
threshold was obtained using the BAEP, with a normal elec-
trophysiological threshold considered to be up to 20 dBnHL21.

To obtain this potential, it was necessary for the child to
remain seated or laying in a recliner in a comfortable position
in a sound and electrically treated room.

After collection, for the acoustic immittance measures,
normal results were considered to include the presence of
a type A tympanogram pattern23 and ipsilateral acoustic
reflexes present at frequencies of 500, 1000, and 2000 Hz
between 80 and 95 dBnHL24.

Because the higher frequencies of pure-tone audiometry
are important in the evaluation of individuals undergoing che-
motherapy, the result was classified as normal when auditory
thresholds less than or equal to 15 dBnHL were observed at fre-
cuencies of 500, 1000, 2000, and 4000 Hz (children up to 6 years
of age) and when auditory thresholds less than or equal to
20 dBnHL were observed at frequencies of 250, 500, 1000, 2000,
4000, 6000, and 8000 Hz (children 7 years old or older).

The speech audiometry result was considered compati-
ble when the SRT showed a response equal to or up to 10 dB
above the mean auditory thresholds obtained in pure-tone audi-
ometry for the frequencies of 500, 1000, and 2000 Hz25
and when the SRPI showed a percentage of accuracy between
90 and 100% at an intensity of 30 dB above the SRT26.

Regarding the BAEP, the results were classified as nor-
mal and altered for each individual according to whether the
absolute latency values of waves I, III, and V, and the inter-
peak values of I-III, III-V, and I-V were within two standard
deviations, as proposed by the literature27.

Subsequently, the types of alterations found in each indi-
vidual were described: alteration in the lower brainstem
auditory pathway (increase of latency values of waves III and
V and/or the interpeak values of I-III and I-V); alteration in
the upper brainstem auditory pathway (increase of latency
values of wave V and/or interpeak values of III-V and/or
I-V); when the two alterations occurred concomitantly in the
same individual, the type of alteration was classified as both.

Results that did not meet the criteria described above
were considered altered. For results to be classified as nor-
mal, it was necessary for both ears to present results within
the normal range. Results for which at least one ear was com-
promised were classified as altered.

RESULTS

Regarding the results of the behavioral tests, two chil-
dren (1 and 6) did not have a conditioned response to the
conventional pure-tone audiometry; therefore, the TOAEs
were measured. One of the children (subject 1) did not
present a response in the TOAE test due to the intense
internal noise, while the other (subject 6) had responses at
frequencies of 1000, 1500, and 2000 Hz. Both children had
electrophysiological thresholds of 20 dBnHL bilaterally in the
BAEP measurement.

The other children showed normal results on the behav-
ioral tests.

The BAEP results showed that of the 14 children evalu-
ated, 35.71% (1, 2, 4, 8, 11) had some type of alteration, and
the predominant type was auditory impairment in the lower
brainstem (80%) (Tables 1, 2 and 3).

We also observed that 60% of children (1, 2, 4) who pre-
vented altered BAEPs were younger than 5 years old and that
80% of the children (1, 2, 8, 11) with alterations had received
MTX intrathecally less than 30 days before (Table 1).

The 40% of children (1 and 8) who had abnormal BAEP
results had the highest cumulative doses of MTX adminis-
tered intravenously (8000 mg, subject 1; 7600 mg, subject 2)
and intrathecally (72 mg, subject 1; 99 mg, subject 2) (Table 1).

DISCUSSION

Although data from the literature4 show that ALL occurs
more frequently in males, in the present study, our sample
included mostly females. This may have occurred because
the sample number was small.

Conductive impairment was only observed in children
younger than 5 years (3 years 7 months), while upper airway
impairment was present in both younger and older children.
This hindered the measurement of OAEs; therefore, this proce-
dure was performed only in children who did not undergo pure-
tone audiometry. These findings are consistent with reports in
the literature of individuals undergoing chemotherapy who
have both complaints of otitis and upper airway infection4.

Chemotherapeutic drugs do not differentiate normal
cells from cancer cells; therefore, several types of normal cells
are destroyed, causing secondary problems1, such as ototox-
icity6. The results of the behavioral tests obtained in the pres-
ent study showed that the peripheral hearing of children at
the frequencies conventionally evaluated was not impaired
by chemotherapy because all children had thresholds within
the normal range for their age.

However, analysis of the TOAEs for subject 6 (Table 1)
showed responses at frequencies of 1000, 1500, and 2000 Hz
and no response at frequencies of 3000 and 4000 Hz (higher
frequencies) bilaterally. Due to the absence of response to the
3000 and 4000 Hz frequencies, the electrophysiological
threshold was obtained using the BAEP, which was 20 dBnHL
bilaterally. The medical records showed that this individual
had been undergoing chemotherapy for several months, and
one of the drugs used was vincristine at a dose of 4.400 mg.
which, according to the literature, is considered an ototoxic drug. These findings suggest that alterations occur in the cochlea and are first detected by the TOAE responses and later by the auditory thresholds obtained in pure-tone audiometry, which would explain the electrophysiological threshold of 20 dB HL bilaterally. In a study involving auditory monitoring in patients undergoing chemotherapy, the TOAE results showed that a response to frequencies of 1000 and 2000 Hz was observed until the end of treatment, while a progressive increase in the absence of responses to frequencies of 3000 and 4000 Hz was observed during treatment.

In the present study, we found that 5 (35.71%) of the individuals who underwent audiological and electrophysiological assessment of hearing (Tables 1 and 2) showed impairment in the auditory pathway in its most central portion, demonstrating the importance of peripheral and central auditory assessment in this population.

According to the BAEP results, the five individuals mentioned above had some type of alteration, and the predominant type was auditory impairment in the lower brainstem (Tables 1 and 2). These findings suggest possible impairment by MTX, as the literature emphasizes that this drug can cause adverse effects, such as neurotoxicity. In addition, studies have reported that neurotoxicity can occur in an acute, subacute, or chronic form and can be observed after intrathecal or intravenous administration of MTX. In the present study, it was also observed that the majority of children with alterations had used MTX intrathecally less than 30 days prior.

Other authors have further reported that acute and subacute forms of neurotoxicity may occur during ALL treatment, generally manifesting as neurological signs. In some cases, neurotoxicity is transient and benign, and in other cases, it can be severe and debilitating, leading to permanent neurological deficits.

Because BAEP measurement was not performed prior to MTX administration, and follow-up was not performed, it was not possible to determine when auditory nerve impairment and/or brainstem impairment occurred or the duration of such impairment. According to the literature, the mechanism by which MTX causes neurotoxicity is not fully understood.

Table 1. Characterization of the sample as the use of methotrexate, BAEP result, cerebrospinal fluid collection, and the child's age.

| Individuals | age | intravenous MTX cumulative dosage | intrathecal MTX cumulative dosage | BAEP | cerebrospinal fluid collection | Result Liquor (neoplastic cells) |
|-------------|-----|-----------------------------------|-----------------------------------|------|-------------------------------|---------------------------------|
| 1           | 3a6m| 7600 mg                           | 3800 mg                           | 54   | 72 mg                         | low brainstem 7 negative        |
| 2           | 4a3m| 1447 mg                           | 740 mg                            | 6    | 48 mg                         | low brainstem 11 negative       |
| 3           | 4a4m| 2700 mg                           | 1400 mg                           | 38   | 36 mg                         | negative                        |
| 4           | 4a4m| 1800 mg                           | 200 mg                            | 67   | 36 mg                         | low brainstem 103 negative      |
| 5           | 5a2m| 710 mg                            | 150 mg                            | 31   | 48 mg                         | 19 negative                     |
| 6           | 3a3m| 2229 mg                           | 1100 mg                           | 65   | 64 mg                         | 3 negative                      |
| 7           | 6a8m| 4390 mg                           | 330 mg                            | 102  | 60 mg                         | 193 negative                    |
| 8           | 10a8m| 8000 mg                          | 5000 mg                           | 43   | 99 mg                         | low brainstem 8 negative        |
| 9           | 12a6m| 5000 mg                          | 5000 mg                           | 6    | 30 mg                         | 1 negative                      |
| 10          | 11a | 2250 mg                           | 250 mg                            | 15   | 24 mg                         | 27 negative                     |
| 11          | 10a5m| 1160 mg                          | 920 mg                            | 36   | 45 mg                         | high brainstem 7 negative       |
| 12          | 9a7m| 2300 mg                           | 200 mg                            | 9    | 84 mg                         | 9 negative                      |
| 13          | 11a6m| 4550 mg                          | 25 mg                             | 2    | 24 mg                         | 19 negative                     |
| 14          | 12a8m| 2690 mg                           | 30 mg                             | 79   | 15 mg                         | 18 negative                     |

MTX: methotrexate; BAEP: brainstem auditory evoked potential.
understood, and more than one mechanism may be involved, but MTX has been shown to have an immediate effect on nerve tissue. The findings of our study suggest that this effect occurred because children exhibited impairment of the auditory nerve/brainstem at 1, 7, and 13 days after administration of MTX.

It was not possible to establish the minimum (or exact) amount of drug likely to impair the lower brainstem region using the results of this study. However, we found that 40% of children who had abnormal BAEP results received the highest cumulative doses of MTX intravenously (8,000 mg, subject 1; 7,600 mg, subject 2) and intrathecally (72 mg, subject 1; 99 mg, subject 2) (Table 1), which are doses considered to be high according to the literature.

In addition, the location and degree of toxicity that MTX causes in the central nervous system are difficult to establish, but in the present study most of the impairment occurred in the lower brainstem. The only study found in the literature that used BAEPs to evaluate the central auditory pathway of individuals undergoing chemotherapy showed that these individuals exhibited an increase in the interpeak I-III value. This result is suggestive of impairment in the lower brainstem auditory pathway.

Studies of BAEP measurement in individuals receiving MTX were not found in the literature; however, in a study that assessed motor evoked potentials, delayed conduction of the stimulus in the peripheral motor nerve as well as impairment of the central nervous system were observed after intrathecal MTX administration.

It is known that, ABR waves I, III, and V are the largest and most frequently observed waves when compared to waves II and IV that may not be present even in normal individuals. Thus, the present study opted for the analysis of waves I, III, and V and their interpeaks I-III, III-V, and I-V. Normal wave I latency values were observed in all evaluated individuals, and the same was not observed for waves III and V and / or interpeaks I-III, I-V, III-V.

As most children in the present study exhibited alterations in the lower brainstem, it can be inferred that a deficit in nerve conduction of the acoustic stimulus was present in the region proximal to the brainstem of the auditory nerve (wave II) (although the values were not obtained), which is part of the final structure of the peripheral auditory system, that interfered with the latency value of wave III, or there may have been a deficit in the cochlear nucleus region (wave III) located in the brainstem — the first structure of the central auditory nervous system.

In the present study, another important finding was the observation that children younger than five years old were the most susceptible to chemotherapy because most had some type of impairment in the auditory pathway. These findings corroborate a previous study that showed that children and elderly people undergoing chemotherapy are most susceptible to auditory alterations.

### Table 3. BAEP latency values obtained in the sample.

| Individuals | age | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left |
|-------------|-----|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|
| I           | I-III | V | I-III | III-V | I-V |
| 1           | 3a6m  | 1.75 | 1.45 | 4.20 | 4.15 | 5.90 | 5.90 | 2.45 | 2.70 | 1.70 | 1.75 | 4.15 | 4.45 |
| 2           | 4a3m  | 1.70 | 1.65 | 3.95 | 4.10 | 5.70 | 5.85 | 2.25 | 2.45 | 1.75 | 1.75 | 4.00 | 4.20 |
| 3           | 4a4m  | 1.60 | 1.45 | 3.80 | 3.80 | 5.65 | 5.55 | 2.20 | 2.35 | 1.85 | 1.75 | 4.05 | 4.10 |
| 4           | 4a4m  | 1.65 | 1.55 | 4.05 | 4.00 | 5.85 | 5.70 | 2.40 | 2.45 | 1.80 | 1.70 | 4.20 | 4.15 |
| 5           | 5a2m  | 1.60 | 1.50 | 3.80 | 3.80 | 5.75 | 5.65 | 2.20 | 2.30 | 1.95 | 1.85 | 4.15 | 4.15 |
| 6           | 3a3m  | 1.60 | 1.55 | 3.75 | 3.80 | 5.60 | 5.65 | 2.15 | 2.25 | 1.85 | 1.85 | 4.00 | 4.10 |
| 7           | 6a8m  | 1.85 | 1.70 | 3.70 | 3.85 | 5.70 | 5.75 | 1.85 | 2.15 | 2.00 | 1.90 | 3.85 | 4.05 |
| 8           | 10a8m | 1.25 | 1.25 | 3.95 | 3.85 | 5.70 | 5.80 | 2.70 | 2.60 | 1.75 | 1.95 | 4.45 | 4.55 |
| 9           | 12a6m | 1.55 | 1.55 | 3.85 | 3.75 | 5.70 | 5.65 | 2.30 | 2.20 | 1.85 | 1.90 | 4.15 | 4.10 |
| 10          | 11a   | 1.65 | 1.45 | 3.75 | 3.75 | 5.80 | 5.50 | 2.10 | 2.30 | 2.05 | 1.75 | 4.15 | 4.05 |
| 11          | 10a5m | 1.75 | 1.75 | 3.90 | 3.90 | 6.00 | 6.00 | 2.15 | 2.15 | 2.10 | 2.10 | 4.25 | 4.25 |
| 12          | 9a7m  | 1.75 | 1.65 | 3.75 | 3.70 | 5.60 | 5.55 | 2.00 | 2.05 | 1.85 | 1.85 | 3.85 | 3.90 |
| 13          | 11a6m | 1.75 | 1.55 | 3.65 | 3.70 | 5.50 | 5.50 | 1.95 | 2.10 | 1.80 | 1.85 | 3.75 | 3.95 |
| 14          | 12a8m | 1.75 | 1.75 | 3.85 | 3.85 | 5.70 | 5.75 | 2.10 | 2.10 | 1.85 | 1.90 | 3.95 | 4.00 |

BAEP: brainstem auditory evoked potential.
Although MTX is considered neurotoxic, it is important to highlight that there is interindividual variability, which may be due to genetic susceptibility, having as participants the following genes involved: megaline, glutathione S-transferase, cross-complementation group’s excision repair 1 and 2, acylphosphatase 2, and mutations in mitochondrial S-transferase, cross-complementation group’s excision repair participants the following genes involved: megaline, glutathione which may be due to genetic susceptibility, having as par-
tant to highlight that there is interindividual variability, we can infer that the findings of brainstem auditory pathway impairment in the present study might have been caused by the administration of MTX in this population.

Because the auditory nerve is responsible for the tono-
topic organization of frequencies (low and high)\(^3\) (wave II of the BAEP) and the cochlear nucleus is responsible for listening in noisy conditions\(^4\) (wave III of the BAEP), impairment in one of these regions, even if temporary, especially in young children, can compromise the development of speech and language and impair their social interaction (family, school).

Although this population is difficult to assess due to the complications of chemotherapy, behavioral assessment of auditory processing would be indicated in individuals with alterations in BAEP, as well as in those with complaints and normal hearing thresholds, aiming at a better direction in the therapeutic treatment and stimulation of impaired auditory skills.

The present study demonstrated that BAEP measurement is a useful tool in the evaluation of individuals undergoing che-
motherapy, which demonstrated the importance of peripheral and central auditory evaluation in this population, in addition to audiological monitoring during chemotherapy. Thus, thera-
peutic strategies can be implemented early to decrease future impairments in this population who are undergoing acquisi-
tion and development of speech and language.

Further prospective studies with a larger number of individuals and with BAEP measurements conducted prior to chemotherapy should be performed to better define the auditory impairment of these patients.

In conclusion, children with ALL undergoing chemother-
apy exhibit impairment of the brainstem auditory pathway, and the main impairment was located in the auditory pathway in the lower brainstem.

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