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Editorial

Pharmacovigilance in the pediatric population: homework to be done in Mexico

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Pharmacovigilance (PV) is defined as the public health activity related to the identification, quantification, evaluation, and prevention of risks associated with the use of medications once they become available to the public.

The main purpose of PV is to regularly provide the most complete information about the safety of medications, making it possible to promote and execute the appropriate measures to ensure that medications available to the public present a favorable risk/benefit relationship to the general population either in private or public institutions.

The responsibility concerning PV is shared among federal and state health institutions, the pharmaceutical industry and health care professionals including physicians, nurses, pharmacists and pharmacy specialists.

It has been demonstrated that adverse drug reactions (ADRs) may be different during clinical research phases I, II and III (before the medication is available to the public). Some reactions are not identified because of their low incidence or slow development, and we must consider that initial tests are performed on reduced and controlled populations. A different situation occurs during phase IV (commercial availability) when the medication is exposed to a large population. It is then possible that new ADRs or drug interactions may take place.

ADR reports are directly proportional to the efficacy of each medication. The efficacy evaluates the overall quality of the product, including those factors that contribute, directly or indirectly, to the effectiveness and safety of the medication and its tolerance by the patient. Examples of ADRs include poor dissolution of tablets, faulty capsules, undesirable coloring in ampoules, presence of foreign bodies or precipitation in ampoules, inadequate gradation of dose-measuring cups, dose spoons or syringes. This group includes reports about the absence, decrease or increase of the expected therapeutic effect.

One of the greatest challenges of PV is the low spontaneous notification rate about ADRs worldwide, which is accentuated in Mexico and especially in the pediatric population. In general, it is accepted that

this low notification rate has different causes such as lack of time on the part of health care professionals and the time required to complete ad-hoc formats as well as the fear of documenting an erroneous prescription with the consequent lawsuits and adverse publicity.

The “homework” in our country about ADR reports in the pediatric population should be done in the short, medium and long term. The Hospital Infantil “Federico Gomez” in Mexico City has already begun a computer-assisted PV program with on-line data entry that promotes and facilitates the reporting of ADRs.¹ This program requires the creation of user-friendly software that allows rapid reporting of ADRs, sends the printed-out report to the National Pharmacovigilance Center according to that institution’s policy, uses the results to educate health care personnel at every level and creates a database available to investigators.

It is also necessary to communicate the importance of

PV in our environment in the short term. In this issue of the *Boletín Médico Hospital Infantil de México*,² there is a comprehensive review of PV in the pediatric population that includes PV concepts, current policies in Mexico, morbidity and mortality associated with PV in children, economic consequences, and the low reporting rate observed in our country compared to current international standards.

In the medium term, our plan includes beginning PV education for specialist resident physicians, publishing experiences about ADRs in our hospital, and encouraging other national pediatric centers to participate in this program in order to exchange experiences.

In the long term, we propose Mexico will be at the cutting edge of ADR reporting. In addition to collaborating with other medical centers we are able to identify those medications that should be recalled by health authorities because they compromise the health of children.

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The importance of pharmacovigilance in the pediatric population

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Abstract

In order to emphasize the importance of pharmacovigilance in children, a review was carried out with special emphasis on general and conceptual aspects outlined in the Mexican Official Norm and other documents. The different classifications from the Adverse Drug Reactions (ADR) and Adverse Drug Events (ADE) are discussed. Using the database of the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (Sweden), we analyzed up to the year 2006 the present status of the ADR reports from 82 countries. Mexico ranks in the middle classified by age groups and number of reports in

the database. The impact of ADR stands out in the general population according to morbidity, mortality, sequelae and cost considerations. The impact of ADE and ADR in newborns and pediatric patients reports the experiences of international groups. Several recommendations are mentioned that will allow a system of pharmacovigilance to be established or improved for children in Mexico. The Hospital Infantil of Mexico has initiated an ambitious program.

Key words: pharmacovigilance in children, adverse drug reactions, adverse drug events.

Introduction

The purposes of the present review are to highlight the concepts and operative components of pharmacovigilance, emphasizing the consequences of the use of medications in adults and children based on international experience. Our goal is to increase awareness among Mexican pediatricians, in particular, and health care professionals, in general, about these matters.

General Concepts

Pharmacovigilance is “the science related to compiling, monitoring, researching, qualifying and evaluating the data obtained from health care professionals and patients about the adverse effects of drugs, biological and botanical products as well as those used in traditional medicine. The purpose of pharmacovigilance is to identify data about new adverse reactions and prevent damage to patients.”¹

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The most accepted definition of Adverse Drug Event (ADE) is based on the International Conference on Harmonization Guidelines:² “it is any undesirable medical effect in a patient or in a clinical research where a pharmaceutical product has been administered that does not have an actual relationship with the treatment...” and “... any sign, symptom or unfavorable/non-intentional disease that can be temporarily associated with the use of the medical product at any dose.” This is an ample but comprehensive definition. Physicians, pharmacists, nurses and even consumers exceptionally report an ADR especially if they can link it to the use of a given medication in their daily practice. Frequently, they do not report an ADR because they think it is not related with one or more drugs.

There are five different categories for ADE³

- Adverse Drug Reaction (ADR)
- Medical Errors
- Therapy Failure/Error
- Adverse Drug Event after medication has been suspended
- Overdose

In Mexico⁴, the ADE definition includes vaccine-associated adverse events (VAAEs) and therapeutic error; however, even if the Mexican Official Norm (NOM) does not explicitly include the others, they should also be reported. ADRs are defined as “any harmful and undesired effect that presents when the appropriate dosages are used for prevention, diagnosis, treatment or function modification.”^{4,5} VAAEs are defined as “those clinical manifestations that occur within 30 days after one or more vaccines have been administered and that cannot be associated with a specific disease.”⁴ Therapeutic error is defined as “any case where the therapeutic effect is not achieved when using appropriate dosages as prescribed for humans, either with prophylactic, diagnostic, therapeutic or physiological purposes.”³ Medical errors are defined as “non-deliberate acts, either from commission or omission that result in a potential or actual damage to the patient or as a consequence of administering a medication.”⁶ The latter are considered as commission because of the confusion either during writing the prescription or when the medicine is received by the patient. Omission errors are those where the physician did not consider the possible drug interactions. ADEs, when the medication has been suspended, includes those presented when the drug is suspended abruptly

after the patient has used the medication for a long period. Overdose differs from ADR because the dosage is not usually administered for disease treatment. All these ADEs may present as an independent or combined situation.

ADR and ADE Classification

There are three types of ADRs.⁷ Type A are those generally dependent on the dose. The reaction is predictable according to the pharmacological effects of the drug and have high morbidity rates and low mortality rates. Type B reactions are not predictable from the pharmacological effects of the drug, are not dose-dependent and have a low morbidity rate and high mortality rate. Type C, which was recently described,^{8,9} includes drug reactions associated with a particular disease that are infrequent when the patient has not been exposed to the medication.

Mexican NOM classifies ADRs according to the quality of information and their probability of causing the reaction as follows:⁴

- Certain
- Probable
- Possible
- Doubtful
- Conditional/Unclassifiable
- Non-assessable/Unclassifiable

“Certain” is when a clinical event or laboratory test result occurs shortly after administering the drug and cannot be explained as a natural evolution of the disease, concomitant pathology or as a consequence of administering other drugs. There should be clinical evidence that once the drug is suspended, the adverse reaction begins to subside. The other categories are classified in descending order because of their role as the cause of the reaction. Therefore, the “Doubtful” ADR is described as an event (clinical manifestation or abnormal laboratory test result) that occurs after the last time the drug was administered that brings suspicion about its role as improbable (but not impossible). This may be explained as part of the natural evolution of the disease or because of concomitant pathologies or the combined effect of other drugs.

ADRs and ADEs are classified according to their clinical severity as follows:⁴

- Mild (when there are signs and symptoms easily tolerated that do not require treatment or increase patient's hospital stay and that might require the suspension of the drug)
- Moderate (when they interfere with patient's normal work or school activities without becoming life-threatening, require pharmacological treatment and may require the suspension of the drug)
- Severe (those that are life-threatening or may even cause the patient's death, increase hospital stay, result in persistent or significant disability, or cause alterations or malformations in newborns)
- Lethal (those where the drug contributes directly or indirectly to the patient's death)

one of the following criteria:^{4,10}

- Drugs introduced in our country in the last 2 years
- Lethal reactions
- Life-threatening reactions for the patient
- Reactions that result in hospital admission
- Reactions that increase hospital stay
- Reactions where the patient cannot attend school or work
- Reactions that produce malformations or cancer
- Reactions that cause irreversible effects
- Reactions that produce abnormal laboratory test results
- Reactions present during vaccination campaigns

ADRs can be preventable or unpreventable. Preventable ADRs are generated by diagnostic errors that lead to an inappropriate prescription, an incorrect prescription that causes overdose, those where the physician failed to warn parents about the potential risk of one or several prescribed drugs, an altered prescription by the child's parents, or an inaccurate evaluation of the drug's interaction with other medicines. Unpreventable ADRs are those not easily predictable because even if the prescription is adequate, the drugs may have an undesirable effect on one particular person, place or time and will only be identified at the time of occurrence.⁴

ADR Notification Reasons

The Mexican Official Norm (NOM) about the installation and operation of pharmacovigilance⁴ states that notification is mandatory in Mexico for institutions and health care professionals, for directors of health record systems and for those who commercialize medicines or herbal remedies, as well as for clinical research units that carry-out drug studies. However, it should be mentioned that spontaneous ADR reports by health care professionals is voluntary as occurs in most countries.

Physicians, nurses, pharmacists and pharmacy technicians are responsible for pharmacovigilance for children admitted to hospitals. They should be ever-vigilant towards ADRs. They should report these reactions even if there is no apparent cause/effect relationship and without considering whether the ADR presented at the beginning, during or after the administration of drugs, substances, biological products and vaccines that meet

The report of a suspected ADR should include expected and unexpected reactions either during medical care, clinical research studies, intensive pharmacovigilance studies and vaccination campaigns.⁴ In clinical research studies, suspected ADRs must be reported by the research centers and the sponsoring pharmaceutical company. An unexpected ADR is one that has not been described in its nature or severity in the scientific literature or in the information contained in product labeling, prescription documentation or in the registration data and that is not possible to infer according to the pharmacological activity of the drug.⁴

International ADR Report

There is a large database (WHO Collaborating Centre for International Drug Monitoring [IDM], Uppsala Monitoring Centre, Sweden) that contains information from 82 countries. We obtained the 2006 version of the database from Sten Olsson¹¹ and Prof. J. Leticia Rodriguez Betancourt in order to reorganize the data to be used for this review (see Tables 1-6).

Table 1 shows that the December 2006 database contained >3 million reports, where only 12.69% involved the pediatric population. There is a possible bias in the age proportion because the table shows the accumulated number of ADRs from the 82 countries without considering the date when the country began reporting (e.g., the U.S. began in 1968, whereas Mexico began in 1997). It does not include a rate that should have as a denominator the number of inhabitants/10,000

0/1,000,000 per year that would allow demonstrating¹² that ADRs have a similar frequency among age groups according to the number of drugs administered per group. Unfortunately, the database did not include ADRs/year and number of inhabitants; therefore, we were unable to calculate the proposed rate.

Table 2 shows only the countries with the largest cumulative number of reports by age group, which

was the U.S. However, if we calculate a rate with the number of reports per 1,000,000 inhabitants per year and country, we observe that first place is attributable to New Zealand, and the U.S. ranks in third place.⁷ The table also shows that the number of cases reported in the U.S. is very large, compared to the cases reported by Mexico by age group. Mexico has a middle position in the table among 81 other countries with 2258 cases reported. However, other Latin American countries that began reporting before Mexico (1997) and with a smaller population show a larger number of cases (e.g., Cuba). Because the information concerning the number of reports per country and age group is not easily accessible, we describe it in detail (Tables 3-6). These tables show that ADRs for pediatric population groups among countries is fairly consistent and that countries with the largest number of cases reported are the U.S., several European countries, Asia and the South Pacific, whereas the number of cases reported by Latin American countries is much lower. As an example, Table 3 shows the distribution of ADRs in newborns in 82 countries. This reveals that developed countries lead the list, which contrasts greatly with the number of reports for Latin American and African countries despite the acquired international commitment. This is probably related to a faulty search of ADRs in the pediatric population.

Table 1. Distribution of 3,086,338 ADRs in 82 countries until December 2006 according to the Centre for IDM (WHO)

Age groups	No. of ADR ^a reports	%
0-1 month	11,345	0.36
2 months-4 years	192,179	6.22
5-11 years	105,179	3.42
12-16 years	83,139	2.69
17-69 years	2,108,160	68.30
>70 years	585,855	18.98

ADR, adverse drug reaction; IDM, International Drug Monitoring, Uppsala, Sweden; WHO, World Health Organization.

^aCalculated from the database (Reference 11).

Table 2. Distribution of ADRs according to age groups for countries with the highest number of reports: the position of Mexico among 82 countries until December 2006 according to the Centre for IDM (WHO)

Age groups	Country	No. of ADR ^a reports	Position	Number of reported ADRs ^a in Mexico
0-1 month	U.S.	5,536	48	2
2 months-4 years	U.S.	65,224	41	113
5-11 years	U.S.	36,902	46	67
12-16 years	U.S.	32,332	43	56
17-69 years	U.S.	853,497	40	1763
>70 years	U.S.	238,426	39	257

^aCalculated from the database (Reference 11).

Table 3. Number of ADR^a reports in newborns (0-30 days) per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	5536	Austria	25	Bulgaria	3	Costa Rica	0
France	1841	Serbia,	22	Poland	3	Cyprus	0
Germany	757	Montenegro	21	Turkey	3	Egypt	0
UK	733	Brazil	20	Uruguay	3	Estonia	0
New Zealand	488	Italy	17	Argentina	2	Fiji	0
Canada	446	Slovakia	15	Brunei	2	Ghana	0
Australia	349	Israel	15	Macedonia	2	Guatemala	0
Sweden	236	Norway	14	Mexico	2	India	0
Thailand	101	Morocco	14	Tanzania	2	Jordan	0
Ireland	81	Portugal	14	Tunisia	2	Korea	0
Spain	80	Iran	13	Zimbabwe	2	Kyrgyzstan	0
Czech Republic	76	Chile	11	Greece	1	Latvia	0
Romania	73	Croatia	8	Iceland	1	Lithuania	0
Switzerland	53	Peru	8	Nigeria	1	Malta	0
Holland	49	Philippines	8	Oman	1	Moldova	0
South Africa	48	Finland	7	Venezuela	1	Mozambique	0
Japan	41	Hungary	5	Vietnam	1	Nepal	0
Malaysia	30	Singapore	5	Armenia	0	Russia	0
Colombia	28	Belgium	4	Belarus	0	Sri Lanka	0
Denmark	27	Cuba	4	China	0	Surinam	0
		Indonesia	4			Ukraine	0
						Uzbekistan	0
Total 11,345							

^aCalculated from the database (Reference 11).

Importance of ADEs

The information here presented was consolidated from studies carried out in adults. In the U.S.¹³ it has been considered that the combined effect of medical errors and adverse events from iatrogenic damage not associated with identified errors includes:

- 12,000 deaths per year due to unnecessary surgery
- 7,000 deaths per year due to hospital medical errors
- 20,000 deaths per year due to other hospital errors
- 80,000 deaths per year due to hospital-acquired nosocomial infections
- 106,000 deaths per year due to ADEs unrelated to errors

From the aforementioned, it may be inferred that ADEs are an important cause of morbidity and mortality. Therefore, there has been an increase in the number of studies focused on patient safety and pharmacovigilance quality control in the last decade. These events have been recognized as a high-priority project because of their iatrogenic nature and their impact on annual costs. For instance, in the U.S. it has been estimated that these vents cost between 76 and 177 billion dollars yearly, which is more than the cost of all diabetes and cardiovascular disease treatments that may reach 150 billion dollars per year.¹⁴⁻¹⁷

Epidemiological studies related to the great diversity of ADEs have found that 3-28% of hospital admissions are related to ADEs; 5-20% of patients experience one ADE

during their admission;¹⁸ patients >65 years old have a risk 2.5 times higher to develop ADE compared to the general population and seek emergency treatment that increase eight times the probability of being admitted.¹⁹ It has been estimated that 75,000 admissions in the U.S. are due to preventable ADEs that would cause 4,839 permanent injuries and 2,577 deaths.^{19,20} Of hospital admissions associated with ADRs,¹⁹ 41.5% are related to drugs that have small therapeutic windows or that require ambulatory care. Two-thirds of these admissions

could be avoided.²⁰

In outpatient consultation, prescription drugs can be associated with ADRs in 4-6% of cases. In hospitalized patients, it accounts for 16.6% of cases in Australia, 10.8% in the UK and 3.7% in the U.S. They also represent the leading cause of death in 13.6% of cases in the U.S., 8% in the UK and 4.9% in Australia.^{21,22} ADRs increase hospital stay by 1.9-2.2 days, with an associated cost of \$1,900-\$5,900 USD per patient/stay.^{17,23}

Table 4. Number of ADRs^a in children from 2 months to 4 years of age per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	65224	Chile	513	Mexico	113	Zimbabwe	17
Canada	46360	Malaysia	504	Peru	106	Ukraine	16
UK	20726	Belgium	466	Argentina	102	Guatemala	12
Australia	8876	Slovakia	460	Oman	99	India	10
New Zealand	7652	Serbia, Montenegro	459	Portugal	97	Lithuania	9
Sweden	6318	Romania	430	Latvia	72	Kyrgyzstan	8
France	5729	Bulgaria	402	Turkey	71	Mozambique	7
Thailand	5409	Switzerland	394	Greece	63	Ghana	6
Germany	3574	Norway	360	Hungary	57	Belarus	5
Spain	3484	Israel	357	Poland	54	Iceland	4
Italy	2269	Brazil	249	China	53	Korea	4
Cuba	1507	Singapore	231	Uruguay	46	Nigeria	4
Denmark	1412	South Africa	207	Costa Rica	35	Egypt	3
Ireland	1315	Indonesia	203	Armenia	32	Fiji	3
Czech Republic	1027	Iran	193	Venezuela	31	Brunei	2
Holland	1007	Morocco	172	Macedonia	25	Russia	2
Japan	841	Colombia	160	Sri Lanka	24	Cyprus	1
Austria	803	Philippines	135	Moldova	21	Jordan	1
Croatia	637	Tunisia	134	Tanzania	19	Malta	0
Finland	605	Vietnam	123	Estonia	18	Nepal	0
						Surinam	0
						Uzbekistan	0

Total 192,179

^aCalculated from the database (Reference 11).

Table 5. Number of ADRs^a in children 5-11 years old per country according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	36902	Serbia,	439	Argentina	104	Korea	6
Canada	13528	Montenegro	390	Oman	90	Ghana	5
UK	13146	Switzerland	371	Philippines	83	Nigeria	5
France	5281	Bulgaria	350	China	69	Ukraine	5
Sweden	5096	Belgium	338	Peru	69	Armenia	4
Australia	4686	Slovakia	338	Mexico	67	Estonia	4
Thailand	3819	Croatia	309	Poland	55	Iceland	4
Germany	3354	Austria	304	Greece	52	Fiji	3
Spain	2525	Chile	298	Turkey	43	Kyrgyzstan	3
New Zealand	2402	Romania	239	Uruguay	43	Moldova	3
Ireland	1643	Iran	226	Costa Rica	40	Egypt	2
Italy	1418	Colombia	207	India	29	Nepal	2
Holland	1117	Indonesia	202	Hungary	24	Belarus	1
Denmark	1005	Israel	200	Sri Lanka	23	Cyprus	1
Japan	866	South Africa	182	Venezuela	17	Lithuania	1
Czech Republic	588	Singapore	178	Brunei	16	Mozambique	1
Finland	517	Brazil	175	Latvia	15	Russia	1
Cuba	494	Morocco	159	Tanzania	13	Guatemala	0
Malaysia	455	Tunisia	158	Macedonia	12	Jordan	0
Norway	449	Portugal	138	Zimbabwe	8	Malta	0
		Vietnam	108			Surinam	0
						Uzbekistan	0
Total 105,179							

^aCalculated from the database in Reference 11

ADR in Children

In addition to the WHO IDM reports¹¹ for the pediatric population, it is worth mentioning that further information is required to better understand their relevance. Because there are few pharmacovigilance reports for the pediatric population, we describe here next to each relevant article the figures and percentages as a reference of the importance of ADRs on children during their hospital stay or in outpatient consultation and their impact on morbidity, morbidity and consequences.

Of 65,864 admissions in the Children's Hospital of Columbus (Ohio, U.S.)¹⁷ there were 565 ADRs (0.85%). Voluntary reports by health care personnel were distributed as follows: 69.1% by the clinical pharmacist and 5.3% by physicians with the remainder distributed among nurses, pharmacy students, pediatric residents and others. These were all verified in clinical

files. Treatment was required to reduce ADR signs or symptoms in 72% of cases, using IV medications in 55.7% of cases. Of children, 72.9% required at least two medications to treat the ADR. ADRs were classified as unexpected in 65% of cases, 18.2% as overdose, 15.6% as overreaction and 1.9% as drug interaction. Of ADRs, 20.7% were regarded as preventable. Consequences for children aged 6 months or younger were 4.3% and required increased monitoring without harmful effects; 8.7% required surgery or presented temporary damage; 6.1% required hospital admission without permanent damage; and 19% developed a severe clinical profile. There were no actual deaths. It was estimated recently in the U.S.²⁴ that between 2004 and 2005, 158,250 children <18 years of age arrived at an emergency service as a consequence of an ADE. Of these cases, 44.9% were regarded as unintentional overdose 35%

as allergic reactions and 12.6% as ADR. The leading causes for ADRs were antibiotics in 25.2%, analgesics in 13.7% and respiratory medications in 10.6%; 1/10 patients required hospital admission or increased length of their hospital stay.

In Switzerland²⁵ during a 15-year study period, there were 5,771 ADR reports in children <16 years old among a pediatric population ~1.7 million. There were an average of 385 reports per year. The most frequent reactions were topical (24%), fever (12%) and exanthem (6.7%). The largest number of cases was reported as 63.8% for vaccination and 10.1% for systemic antibiotics. Of children, 13% suffered a severe ADR and 0.14% of deaths were related to medications. Of these cases, 9% had not recovered at the time of this study and 1% recovered with sequelae.

In a pediatric hospital in California,²⁶ there were a total of 1,087 ADRs reported during a period of 10 years, representing 1.6% of cases. Their clinical severity was classified as mild to moderate in 89% of cases and patients were admitted to the general pediatric unit and neonatal ICU. Moderate ADRs were associated with the use of penicillin, cephalosporin and vancomycin. Of ADRs, 11% were regarded as severe or lethal, being the cause of hospital admission or occurred during surgery with the use of certain anticonvulsive and antineoplastic drugs. Although 93% of ADRs were reported by health care personnel, only 29% were actually documented in the clinical file.

In countries such as Germany or Sweden, ADR occurs in children at a rate of 15-17%. Of these, 1-5% are due to the administration of unlicensed drugs to be used in

Table 6. Number of ADRs^a in children 12-16 years old per country, according to the Centre for IDM (WHO)

Country	ADRs	Country	ADRs	Country	ADRs	Country	ADRs
USA	32332	Belgium	323	Oman	65	Estonia	5
UK	13223	Cuba	318	Philippines	57	Nigeria	5
Canada	6234	Malaysia	306	Mexico	56	Zimbabwe	5
France	4520	Austria	264	Argentina	53	Korea	4
Australia	4074	Bulgaria	264	Poland	50	Lithuania	3
Thailand	3130	Slovakia	264	Portugal	46	Moldova	3
Germany	2778	Serbia,	239	Greece	37	Armenia	2
Sweden	2454	Montenegro	231	Peru	36	Russia	2
Spain	2271	Chile	231	Turkey	33	Brunei	1
New Zealand	1517	Singapore	186	Venezuela	25	Cyprus	1
Ireland	1237	Israel	179	Costa Rica	22	Jordan	1
Holland	864	Romania	167	Uruguay	21	Kyrgyzstan	1
Denmark	856	Indonesia	153	India	18	Mozambique	1
Italy	776	Iran	126	Ukraine	16	Belarus	0
Japan	555	South Africa	104	Hungary	14	Egypt	0
Czech Republic	465	Tunisia	101	Ghana	13	Fiji	0
Norway	433	Morocco	98	Macedonia	13	Guatemala	0
Croatia	400	Brazil	91	Latvia	10	Iceland	0
Finland	381	Colombia	84	Tanzania	9	Malta	0
	366	Vietnam	74	Sri Lanka	7	Nepal	0
		China	66			Suriname	0
						Uzbekistan	0

Total 83,139

^aCalculated from the database in Reference 11

the pediatric population. As for authorized medications, at least 25% of prescriptions do not meet the minimum age required on the license (off-label) with a high prevalence used on newborns.²⁷⁻³²

In 2001, during a period of 5 months in a Brazilian pediatric hospital, there were 420 ADR reports, representing a cumulative incidence of 12.5%. The skin was the most affected organ with 49% of cases, and antibiotics were associated with 53.2% of reactions. Of ADRs, 97% were classified as mild to moderate with a probable cause of 57.5%.³³

During a 1-week observation period, a regional French pediatric hospital reported that 4/260 children were admitted as a consequence of ADR and that an additional six children developed this condition during their hospital admission.³⁴

According to the findings in 63 U.S. emergency services³⁵ between 2004 and 2006, ADEs were detected in children <12 years old who were prescribed drugs against the common cold and sore throat. It was estimated that a total of 7,091 children would be treated annually because of ADEs related to such drugs, representing 5.7% of the total emergency visits when compared to other medications. The largest number of visits to emergency units was for children 2-5 years old (64%). Of these visits, 66% were due to the administration of non-supervised drugs, whereas 47% were associated with medications against the common cold and sore throat.

Of 1,689 children who attended ambulatory services in a Boston hospital³⁶ and received 2,155 prescriptions, 243 presented an ADR (14%). Of these, 23% were preventable, having a higher frequency of cases when parents had a poor understanding of English or low socioeconomic level.

The first article published in Mexico³⁷ concerning medical errors during the use of prescription drugs found, in the first review, that 53% of clinical files showed one or more errors and after corrective measures this percentage was reduced to 17.6%. It is worth mentioning that medical errors include³⁸ prescription, supply, administration, patient monitoring and drug management. Each may present different errors such as writing errors, dosage failure, administration failure, infusion time, misinterpretation by the personnel

responsible for dosage/preparation, dilution failure, labeling, drug interactions, and failure to monitor laboratory test results. Miller et al.³⁸ conducted an extensive study regarding medical errors and, after a detailed literature review, found 358 articles but included only 31 articles in their study. However, it was not possible to carry out a systematic review of all of these because most focused only on the prescription process and only a few included other information related to errors. The most important results were overall medical errors at a range between 5 and 27%. Even though not all 31 articles evaluated all aspects of errors, they found that errors occurred as follows: 4-30% were prescription errors, 5-58% were supply errors, 42-50% were administrative errors, and 1-20% were administrative record errors.

ADR in Newborns

Information available about ADRs in newborns is scarce. Newborns have several immature organs and systems that impact on their physiology, biochemistry and immunology, and this is even more noticeable in premature newborns. All these factors affect pharmacodynamics, pharmacokinetics and the metabolic mechanisms of drugs that are less efficient, rendering newborns more vulnerable to drug effects. We should also add that neonatal ICUs (NICUs) usually administer concomitant medications that are not recommended for children (unlicensed) or, when they are authorized for use in children, have not been approved for their use in newborns (off-label).^{39,40}

During a 4-month period, the NICU of a Glasgow hospital observed 105 medical errors: four were severe, 45 were potentially severe and 50 were mild. The four severe errors were caused by the administration of a dose 20 times greater than recommended. Of errors, 75% were attributable to a poor prescription process. Once specific actions were taken after the first evaluation month, the number of errors was reduced from 24.1 to 5.1/1000 of neonatal activity during a 3-month period.⁴¹

A total of 176 prescriptions involving 61 different medications were found during a 2-month evaluation period in an Italian NICU. Of these, 12% were not approved for children (unlicensed). Of the 88% approved for children (licensed), 22.7% were not recommended for use in newborns (off-label).⁴²

A systematic review of 11 studies reporting medical errors at NICUs⁴³ reveals that the largest number of errors associated with medications was 5.5/100 prescriptions in one study and the others showed ample variations explained by the different *error* definitions or by the rigor applied. The authors comment that in most of those studies there was no evaluation of the error consequences in children. These reviews identified that the most common strategies used to evaluate errors were computer-assisted methods to produce medical orders, prescription review and the presence of a pharmacist during visits; however, authors note there was scarce information contained in the review articles about the result of such strategies. A study performed during a 9-month period in a NICU at a hospital in Marseille, France focused on the frequency of iatrogenic errors in 388 admitted and studied patients during 10,436 days/patient. That study found 267 iatrogenic events in 116 patients. The incidence was 25.6/1000 days/patient of which 92 (34%) were preventable and 78 (29%) were severe. Of the events, 1% resulted in death. Iatrogenic events were related with nosocomial infections in 79% of cases, with respiratory problems representing 35% and with medications during their administration in 76% of the cases. The most important risk factors were low birth weight, gestational age, duration of hospital stay, central catheters and mechanical ventilation.⁴⁴

Another study conducted by the National University of Colombia during a 4-month period reported 20 newborns with ADRs related to the use of antibiotics and were classified as mild (65% of cases), moderate (35% of cases) and no cases as severe. According to laboratory test results, 38.1% of cases presented nephrotoxicity, 24.7% hemotoxicity, 21.6% electrolytic abnormalities and 15.5% hepatotoxicity. ADR distribution by antibiotic type was 20.6% gentamicin, 17.5% vancomycin, 16.5% amikacin, 15.5% ceftriaxone and 13.4% piperacillin with tazobactam.⁴⁵

Given the importance of studies on drug administration in newborns, it is worth mentioning the study carried out by 220 NICUs⁴⁶ in 32 states of the U.S. including Puerto Rico (1997-2004). The total number of analyzed discharges was 253,651, of which 45,192 were discarded (18%) because there was no certainty regarding administered medications. As for premature newborns with an average of 32 gestation weeks, drugs administered frequently were caffeine, citrate, surfactant, vancomycin, furosemide, metoclopramide, dopamine,

nystatin and aminophylline. In contrast, full-term newborns received ampicillin, gentamicin, cefotaxime, phenobarbital, morphine and vitamin K. After that first analysis, they evaluated which medications were the most frequently used in newborns with a mortality >20% and they found that in premature newborns the most frequently used were amphotericin B, lysosomal amphotericin and bumetanide, whereas in full-term newborns the most common drugs were clonazepam, milrinone, nitric oxide and phenytoin. Authors suggest that these findings should be further investigated in order to find possible relationships between death and the use of one or several medications.

The presence of ADRs related to drugs received by children through breastfeeding (without including abused drugs) identified that in 100 children <2 years old, 47% of ADRs were regarded as probable and 53% as possible. Of these, 63% occurred in newborns and 37% in children <2 months old.⁴⁷

Between 1997 and 2000, the FDA received 500,000 ADR reports of which 7,111 were for children <2 years old. This represented 243 deaths per year. Of these, 41% occurred during the first month of life. Exposure to the medication occurred during pregnancy, birth, or breastfeeding. Of 1902 different medications, biological products or other substances administered, only 17 were considered as the suspected cause in 54% of severe or fatal ADRs. The incidence of ADR in the newborn was ~10%.⁴⁸

Some of the most important elements for pharmacovigilance analysis are medication usage patterns in NICUs with evaluations on antibiotic tolerance and recording of ADRs as mentioned in one study⁴⁹ carried out over a 7-year period where a progressive increase of antibiotics (vancomycin and cefepime) and a significant decrease in the use of morphine was observed. Antibiotics were used to treat infectious diseases of the central nervous system, as well as endocrine, cardiovascular and gastrointestinal systems.

Regarding the use of non-approved medications in children (unlicensed) and those used outside the appropriate time range (off-label), it is worth mentioning the systematic review carried out in the pediatric population⁵⁰ where 52 studies conducted between 1999 and 2006 allow the identification of the

fact that unlicensed and off-label drugs were used with a higher frequency in the neonatal areas, followed by ICU and oncology services. The most frequent ADRs were for unlicensed and off-label drugs. Finally, in a recent publication,⁵¹ a study carried out during 2 years in a Chicago NICU revealed that with 2,304 admissions there were 61 medications used where 45% prescribed were off-label, with a higher incidence of analgesics, vasopressors and hematological drugs.

Surveillance Strategies

Because ADRs and ADEs in children represent an important health care problem and have gone beyond organizations and the public in general, it is necessary to propose different strategies in Mexico that allow a decrease in the number of ADRs for the pediatric population:

1. Specific communication of all matters related to pharmacovigilance in public and private institutions
2. Prepare well-qualified personnel to assist children during the prescription process, preparation, supply and administration of medications
3. Create a system that verifies the quality as well as correct usage of medications
4. Create an educational program using web technology including examinations
5. Create a manual (printed or digital) with specific dosages for each pediatric age, as well as dosages according to body weight and surface area where administration times are clearly specified, as well as other relevant information
6. Make a list of medications approved by Mexican Health Authorities that clearly identifies those medications not approved for use in children and the age limit for their prescription
7. Implement policies that allow identifying incomplete or incorrect prescriptions where the physician receives feedback on those errors and presents the results during relevant meetings⁵²⁻⁵⁴
8. Standardize medication dosages in children based on relevant evidence or pharmacokinetics and pharmacodynamics
9. Specify, in greater detail, adverse drug

events, adverse drug reactions, medical errors, overdose, etc.

10. Include as a medical error the processes for prescription, supply, administration, drug interaction in patient, and management
11. Use bar codes to fully identify medications
12. Establish a medications committee that defines those considered as “Basic Formulary Medications” and also specifies those that are considered as pharmacovigilant activities
13. Employ qualified pharmacy personnel
14. Establish policies to avoid, as much as possible, verbal prescriptions
15. Implement during the midterm (next decade) control systems to reduce errors such as computerized monitoring based on laboratory test results that have demonstrated high sensitivity but low specificity^{55,56} (use of other automated systems has yet to be assessed regarding their cost-benefit ratio and results published in literature are inconclusive)⁵⁷

In conclusion, as we have elucidated in each section of the current study, actions that should be carried out to comply with international norms and the Mexican Official Norm (NOM) require continued education where healthcare professionals should become involved both in the public and private sector. As we mentioned, Mexico ranks behind other countries in the control and reporting of ADRs when compared to the international community. We consider that the articles selected here are high-quality research examples and demonstrate consequences of ADEs and ADRs in the general population, including the pediatric population.

Therefore, a series of actions is suggested nationally and the Hospital Infantil de Mexico implemented one of these at the end of the year 2007 with a pharmacovigilance computerized system that allows each area to report ADRs, print them in the specific format for the NOM and send to the National Pharmacovigilance Center. The information may also be used reliably with research and educational purposes. The path is long, but we must begin the walk.

Acknowledgments

We thank Prof. J. Leticia Rodríguez Betancourt, Director of the Centro de Información de Medicamentos Institucional (UAEM, Morelos, Mexico) for providing the database from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

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Coexistence of C677T and A1298C mutations in the 5,10 methylene-tetrahydrofolate reductase enzyme in pediatric thrombotic patients

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Abstract

Background. One of the thrombophilic conditions that has been widely studied is the C677T mutation in the gene encoding the enzyme 5,10 methylenetetrahydrofolate reductase (MTHFR). The presence of the A1298C mutation in the same gene is also considered as one factor that predisposes thrombosis.

Methods. Nine pediatric patients diagnosed with thrombophilia were studied: seven males and two females with an age range from 1 month to 13 years. We performed real-time polymerase chain reaction (RT-PCR), study of the C677T and A1298C mutations in the MTHFR enzyme, G1691A mutation (Leiden) and Factor V, and prothrombin mutation G20210A. Using conventional methods the following analyses were made: activated C-reactive protein (CRPa) and protein C and S

coagulation, as well as antithrombin (AT).

Results. All patients had co-existing mutations of C677T and A1298C in the MTHFR. Only one patient was homozygous for C677T and heterozygous for A1298C. The other eight patients presented heterozygous mutations. The nine patients did not demonstrate the presence of mutations G1691A factor V (Leiden) and G20210A prothrombin or alterations in the CRPa, AT and proteins C and S.

Conclusions. Coexistence of the C677T and A1298C mutations should be considered for investigation in all patients presenting with thrombophilia.

Key words: thrombosis, methylenetetrahydrofolate reductase, Factor V Leiden

Introduction

The incidence of thrombotic events is rare in children but appears to be increasing. The Canadian Commission on Pediatrics estimates that there are 0.67 cases/100,000 children per year.¹ The cause of the thrombotic events has been attributed to a combination of several risk factors (infection, central venous line or chemotherapy). International guidelines recommend screening for risk factors such as those acquired and hereditary as

an important part in managing thrombosis.² Multiple investigations in our country have contributed to the identification of predisposing factors for thrombosis. In most cases studied, it has been identified that there is presence of multiple thrombophilic conditions when a vaso-occlusive episode occurs. These findings have also been reported by several researchers in other countries.²⁻¹⁰

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One of the thrombophilic conditions that has been extensively studied is the enzymatic activity of 5,10 methylenetetrahydrofolate reductase (MTHFR), which is involved in the metabolism of homocysteine in which the presence of two mutations, C677T and A1298C, have been identified that cause a decrease in its enzymatic activity.¹¹⁻¹⁶

In the Caucasian population, the incidence of the C677T mutation in MTHFR is ~40% for heterozygotes and 10% for homozygotes.¹⁴ There are reports that thrombophilic Mexican patients who are carriers of hetero- or homozygous states for the C677T mutation in MTHFR do not express an increase in plasma homocysteine. This does not rule out the involvement of the C677T mutation in MTHFR in the pathogenesis of thrombosis.¹⁶

The presence of the A1298C mutation in the MTHFR enzyme is also considered as a predisposing factor for thrombosis, and there are no reports in the Mexican

literature on the investigation of this mutation in patients with thrombophilia.¹⁴ Heterozygous coexistence of C677T/A1298C mutations in MTHFR has been described in some studies;¹⁴⁻¹⁵ however, there are no reports of the coexistence of these mutations in pediatric patients with thrombosis. Therefore, the objective of this work is to present nine pediatric patients diagnosed with thrombosis and, after performing various tests, to identify the most common markers of thrombophilia. Coexistence of mutations C677T and A1298C in the MTHFR gene was evidenced as the only associated genetic factor.

Materials and Methods

We described nine pediatric patients with diagnosis of thrombophilia. There were seven males and two females with an age range from 1 month to 13 years. Patients were selected by the medical staff of the Hematology Service of Hospital Infantil de Mexico Federico Gómez in Mexico City.

Table 1. Characteristics of the nine study patients

Sex	Age	Base disease	Location of the thrombosis	Diagnostic method	MTHFR C677T	MTHFR A1298C	FV G1691A	PT G20210A	CRPa	PC	PS	AT
M	11 years	None	Portal vein thrombosis	Clinical	CT	AC	GG	GG	-	-	-	-
M	1 month	Dimorphic syndrome	Atrial thrombosis, PTE	ECG	CT	AC	GG	GG	-	-	-	-
M	13 years	None	Supra-hepatic thrombosis	US	CT	AC	GG	GG	-	-	-	-
M	5 years	None	Portal vein thrombosis	US	CT	AC	GG	GG	-	-	-	-
M	5 years	None	CVA	MRI	CT	AC	GG	GG	-	-	-	-
F	12 years	AVM	Right atrial thrombosis	MRI	TT	AC	GG	GG	-	-	-	-
M	2 years	Milk protein allergy	Atrial thrombosis	ECG	CT	AC	GG	GG	-	-	-	-
M	12 years	Chronic pneumopathy & pulmonary hyperplasia	CVA	MRI	CT	AC	GG	GG	-	-	-	-
F	10 years	Coarctation of the aorta	CVA	MRI	CT	AC	GG	GG	-	-	-	-

F, female; M, male; CRPa, activated C-reactive protein; FV G1691A, factor V Leiden mutation; PT G20210A, prothrombin mutation G20210A; MTHFR C677T, mutation C677T in methylenetetrahydrofolate reductase, MTHFR A1298C, mutation A1298C in methylenetetrahydrofolate reductase, PC, protein C deficiency; PS, protein S deficiency; AT-, antithrombin deficiency; PTE, pulmonary thromboembolism, CVA, cerebrovascular accident, AVM, arteriovenous malformation; EC, electrocardiogram; MRI, magnetic resonance imaging; US, ultrasound.

Prior permission was obtained from all parents or guardians of the patients. A 3- to 5-ml sample of peripheral blood anticoagulated with EDTA was taken for DNA analysis. The extraction was performed with reagents and equipment from Roche Diagnostics (MagNA Pure Compact) according to the manufacturer's recommendations. Investigation of the C677T and A1298C mutations in the gene coding for the MTHFR enzyme, G1691A in the gene coding for factor V (Leiden) and G20210A in the prothrombin gene were performed by real-time polymerase chain reaction (RT-PCR) using the LightCycler 2.0 (Roche Diagnostics). Determination was performed of the resistance to C-reactive protein (CRP), coagulation activity of proteins C and S, and antithrombin (AT), for which a sample of peripheral blood anticoagulated with sodium citrate (3.8%) was obtained. Commercial reagents used were from Dade Behring (Sysmex CA-1500, Marburg GmbH) following the manufacturer's instructions.

Results

All patients had coexistence of mutations C677T and A1298C in the MTHFR enzyme. Only one patient was homozygous for C677T and heterozygous for A1298C; the remaining eight patients were heterozygous for both mutations. The presence of mutations of factor V G1691A (Leiden) and prothrombin G20210A were not identified in the nine patients and, similarly, they showed no alterations in CRP, AT and coagulation of proteins C and S (Table 1).

In conclusion, in this study we focused on the description of the coexistence of C677T and A1298C

mutations in the gene coding for MTHFR. We believe that these mutations should be investigated in all patients presenting thrombophilia and for which no predisposing factors, whether inherited or acquired, are identified. Diverse thrombophilic conditions have been identified in the described thrombophilic Mexican patients. Much research has been carried out and it has been postulated that thrombotic events have a genetic predisposition and that, depending on the number of mutations or alterations, will determine the severity of vaso-occlusive events.⁴⁻¹⁰

In Mexico, Ruiz-Argüelles et al. have made various contributions that help to understand hemostatic alterations in patients with thrombophilia.⁴⁻¹⁰ In one study with a series of 100 patients, they demonstrated that 94% of the patients studied had at least a marker of thrombophilia and 81% of the patients had two or more alterations.¹⁰ Based on various conclusions, it is recommended that the study of the greatest number of mutations or polymorphisms associated with these events be performed on all thrombophilic patients.

The risk associated with each isolated genetic defect may be relatively low, but the simultaneous presence of several mutations may dramatically increase the susceptibility to disease.¹⁸ Furthermore, both lifestyle and environmental factors may interact with one or more genetic mutations and increase the susceptibility and severity of the event. The analysis of risk factors such as acquired genetic factors combined with environmental factors has contributed significantly to the understanding of this pathology.

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Indiscriminate sale of tobacco products to minors in Tijuana, Baja California: what are we doing wrong?

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Abstract

Background: In Mexico, since 1984, the General Health Law prohibits the sale of tobacco products to minors. Nonetheless, recent surveys conducted in several Mexican cities report a prevalence of between 13 and 28% among high school students.

Methods: Ten zones from the city of Tijuana, Mexico in the state of Baja California were randomly selected from the city map. In each zone, 15 tobacco-selling businesses were then chosen. Four teams were created for the cigarette purchase attempts, each including one minor (14-17 years of age).

Results: A total of 150 purchase attempts were made. Ninety nine were successful (66%). Attempts were

significantly more frequently successful when the minor was a female, when the clerk did not ask for the minor's age or identification (ID) and when there were no signs prohibiting cigarette sales to minors in the store. In a logistic regression analysis, only the request for ID by the clerk and the clerk asking for the minor's age were significantly associated with an unsuccessful purchase attempt.

Conclusions: Two simple policies -the posting of signs prohibiting cigarette sale to minors and the store clerk asking for valid ID- could significantly reduce the sale of cigarettes to minors in the city of Tijuana, Mexico.

Key words: tobacco, sales, minors, Tijuana, Mexico.

Introduction

A recent report from the World Health Organization (WHO) indicates that, during the 20th century, tobacco consumption contributed to the deaths of 100 million people worldwide. WHO also estimated that in this century this figure could rise to 1,000 million deaths attributable to consumption of tobacco in its various forms.¹

Given that children have easy access to cigarettes, it is not surprising that most smokers begin their habit at the age of 12 years, long before the legal purchase age.² It

has been observed that the early consumption of tobacco has resulted in long-term consumption of the product, although the majority of adolescents suggest that they do not see themselves as smokers in the future.³

Wide distribution and easy access to tobacco are a vital part of the strategy of the tobacco industry aimed at young consumers. A memorandum from the tobacco company R.J. Reynolds revealed how the company's sales were concentrated in establishments that were close to schools and colleges.⁴

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Conflict of interests: none

Surveys on youth smoking conducted in Mexico in 2003 and 2004 that included >33,000 high school students in nine cities in Mexico showed that in 2003, 51.1% of adolescents surveyed had experience with tobacco, a rate which rose to 56.8% in 2006. Prevalence (they had smoked in the month preceding the survey) in 2003 was 19.9%, increasing to 24.9% in 2006. Smoking prevalence in this age group in the city of Tijuana, Mexico specifically also showed an increase from 11.5% in 2003 to 13.02% in 2006, with a similar increase for both genders.⁵

At least 80 nations ban the sale of cigarettes to children and adolescents. In Mexico, since 1984, the General Health Law prohibits the sale of tobacco products to minors (<18 years of age).⁶ Despite the legislation, the access that children have to products derived from tobacco, principally cigarettes, is a primary factor contributing to smoking in minors and is now one of our biggest public health challenges. Lack of compliance monitoring of official standards contributes to the fact that minors can easily purchase cigarettes from different types of businesses.⁶ The majority of children who smoke cigarettes purchase them at gas stations, supermarkets and grocery stores.⁷

Compliance with these laws by sellers is often evaluated through surveys. For these surveys, minors supervised by adults attempt to buy cigarettes.⁸ The rate of success in attempts to buy cigarettes by minors in this type of study has hovered between 73% in Mexico City and 98% in Juárez City.^{6,9}

The goal of this study was to evaluate the success rate in cigarette purchase attempts by minors in Tijuana, Mexico and to identify variables associated with success in such attempts.

Materials and Methods

As a first step, 10 zones were randomly selected in the city of Tijuana, Mexico using the municipal map. In each area we also randomly selected 15 businesses that sold cigarettes; excluded were bars, private clubs and adult entertainment sites where minors are not permitted entry. For the attempts to purchase cigarettes, four teams were created. Each included a minor (2 females, 14- and 17-years old and two males, 15- and 16-years old) and two adult investigators.

Attempted purchase

In the investigated business, one of the adults was searching for an article while the minor entered separately and tried to purchase cigarettes. If the retailer asked for the minor's age, the minor was instructed not to lie about it. The minor also received instruction to say he/she had no identification, if requested. The legal age for obtaining tobacco products in Mexico is 18 years of age. A successful sale was considered as the transaction in which a retailer sold a pack of cigarettes to minors. Upon leaving the store, the minor handed the pack of cigarettes to the second researcher waiting outside.

Observation procedures

The researcher who entered while the minor was attempting to purchase was actually observing the following variables: type of establishment, success or failure of the attempted purchase, signs noting the prohibition of sale of cigarettes to minors, if the retailer requested an identification from the minor or if the retailer asked the minor's age, and whether the retailer asked who the cigarettes were for that the minor was purchasing.

The second investigator then entered the business to question the retailer regarding the sale of cigarettes. The questionnaire included the following demographic information asked of the retailer: 1) Do you have children? 2) Do they smoke? 3) Do you sell cigarettes to minors 4) Do you know that the sale of cigarettes to minors is illegal? 5) Do you agree with the ban? 6) If there were no prohibition, would you sell cigarettes to minors?

Ethical considerations

The protocol for this study was reviewed and approved by the ethics committee of the Faculty of Medicine of the Universidad Autónoma of Baja California. We obtained written informed consent from the minors who attempted to purchase cigarettes and from their parents, as well as oral consent of employees to answer the questionnaire.

Statistical analysis

The association between categorical variables was initially assessed with χ^2 test (using Fisher's exact test when the number of observations per cell was required). Those variables that showed statistically

significant associations ($p < 0.05$) in bivariate analysis were included in the logistic regression analysis where the dependent variable was whether or not the purchase attempt was successful.

Results

In total, there were 150 attempts to purchase cigarettes, of which 99 attempts were successful (66%). The attempts took place in supermarkets (16 attempts), self-service shops (29 attempts), grocery stores (100 attempts) and pharmacies (5 attempts). There was no significant difference in the proportion of successful attempts when they were classified by type of business: supermarkets, 56.2%, self-service shops, 68.9%; and grocery stores, 66.3% ($\chi^2 = 0.07$, Fisher exact test $p = 0.46$).

Attempts were significantly more successful when the child was female, when the employee did not ask about the child's age, when no identification was requested, or when there were no visible notices about the ban on the sale of tobacco to minors (Table 1).

Ninety nine percent of the retailers were aware of the law prohibiting the sale of tobacco to minors; however, 97% were not in agreement with it. Forty percent of retailers said they would sell tobacco to minors if it were legal. Despite the fact that 98% of retailers said they did not sell tobacco to minors, purchase attempts were successful in 66% of cases. Only in one attempt to purchase (0.6%) did the retailer ask the minor who the cigarettes were for. We did not associate success rate of attempts to a retailer's marital status ($p = 0.68$) or whether the retailer had children living at home ($p = 0.53$).

When the attempt to purchase took place, the age of the minor was not associated with a significant rate of success. Attempts made by the minor who was 14-years old were successful in 76.7% vs. 53.3% for the 15-year old, 66.7% for the 16-year old and 71.7% for the 17-year old ($\chi^2 = 5.268$, $p = 0.15$).

Logistic regression analysis showed that only requesting an identification document by the retailer and the posters banning the sale of cigarettes to minors were significantly associated with failure to purchase.

Table 1. Bivariate analysis (χ^2 test) among factors associated with the successful sale of tobacco to minors of Tijuana, Mexico (2007)

Variable	Successful attempt (%)	Unsuccessful attempt (%)	p	OR: 95% CI
Age of employee (<25 years)	68.8	31.2	0.62	1.20 (0.57, 2.54)
Age of employee (≥ 25 years)	68.6	31.4		
Gender of employee			0.20	1.41 (0.71, 2.78)
Male	69.5	30.5		
Female	61.8	38.2		
Employee education			0.59	0.58 (0.30, 1.11)
≤ 9 years	67.8	32.2		
>9 years	63.6	36.4		
Employee use of tobacco			0.13	0.59 (0.299, 1.17)
Yes	59.7	40.3		
No	71.4	28.6		
Age of the minor			0.04	0.51 (0.259, 1.02)
Male	58.7	41.3		
Female	73.3	26.7		
ID requested			<0.001	0.13 (0.04, 0.46)
Yes	10.7	89.3		
No	78.7	21.3		
Age of minor questioned			<0.001	0.06 (0.02, 0.16)
Yes	20	80		
No	80	20		
Signs prohibiting sale of tobacco to minors			0.004	0.33 (0.15, 0.71)
Present	57.4	42.6		
Absent	80.4	19.6		

Table 2. Logistic regression analysis among factors associated with the successful sale of tobacco to minors in Tijuana, Mexico (2007)

	B	S.E.	Sig.	Exp(B)	95% CI Exp(B)
Gender of minor	-4.54	.575	.430	.635	.206-1.960
Identification requested	-4.56	.777	.000	.010	.002-.048
Signs prohibiting sale to minors	-3.91	.642	.000	.020	.006-.070
Constant	15.29	2.28	.000	4397673	

Discussion

Although prohibited by law in Mexico for almost 25 years, the rate of successful purchases of cigarettes by minors in this study was 66%, which is consistent with other studies reporting a range of 40-70% of tobacco sales to minors.¹⁰

The bivariate analysis in our sample showed a significant association between a successful purchase of cigarettes and gender of the minor, absence of signs prohibiting the sale and if the retailer questioned or not the minor's age or requested a valid identification. Similar to what was reported by Kuri et al.⁶ in Mexico City, the sale of cigarettes to minors was not associated with the personal characteristics of the retailers or the type of establishment.

As reported in the literature,¹¹ cigarettes are sold more often to females than males (73.3% vs. 58.7%; $p = 0.04$), despite the fact that gender was not predictive of a successful purchase according to the logistic regression analysis. There have been two different scenarios proposed in the literature to try to explain this difference based on gender. The first is based on the fact that females usually seem to be older than their male counterparts, facilitating the sale because they appear to be older. Alternatively, retailers may think that females smoke less than males and, therefore, are buying cigarettes for an adult, whereas in the case of males the retailers usually feel that the purchase is for that male buyer. However, our data do not determine the possibility that any of these scenarios are true because no such questions were included in the questionnaire to explore this aspect.

The attempted purchase was significantly more frequent when the establishment had no signs prohibiting the sale of cigarettes to minors (80.4 vs. 57.4%; $p = 0.004$). In the literature reported from other countries, the presence of

signs prohibiting the purchase has not been predictive as the cause for failure to make the purchase. Skretny et al. reported that community-based interventions conducted by mail in order to reduce illegal sales to minors result in an increase in the number of shops that have signs prohibiting the sale of cigarettes to minors, but this results in minimal or no impact on the sales to minors.¹²

The request of a photo ID has been reported as an effective measure to reduce cigarette sales to minors.^{13,14} In our survey, when the retailer asked for an identification from the minor, the successful attempt to purchase was significantly less frequent, and in the logistic regression analysis this variable was predictive of failure to purchase.

The Framework Convention on Tobacco Control (FCTC) is an initiative of the WHO that suggests a common agenda to coordinate efforts in combating tobacco use.¹⁵ Unfortunately, even after it was ratified the FCTC still reports no significant progress in key areas addressed by the agreement, especially with regard to the reduction of tobacco advertising or reduction of access by minors to tobacco.⁵ The Framework Convention¹⁵ specifies (Article 16) the requirement that all sellers of tobacco products must indicate in a clear and prominent location within their locale the ban on the sale of tobacco to minors and, in case of doubt, request that each purchaser of tobacco products show that they are of legal age to make the purchase.

The convention also indicates to seek a ban of sale of individual cigarettes or in small packets, which increase the affordability of such products to minors. The Convention also want to prohibit tobacco products from being directly accessible, as on the shelves of stores. The Convention states that each country adopt

and implement the appropriate government legislative, executive, administrative level, or other measures to prohibit the sale of tobacco to minors.¹⁵ However, of all the measures contained in this agreement, the latter aspect presents the weakest support in terms of evidence and the most difficult to effectively implement. This is a point in which all involved agree, including tobacco companies. To the governments of the world it seems like a sensible attitude toward the problem, to the tobacco companies it allows them to appear (falsely) supportive to international action to control the use of tobacco in minors.¹⁶

Currently there is a controversy regarding the best strategy for reducing the illegal sale of cigarettes to minors. Intervention with educational programs to those retailers who persist in selling cigarettes to minors despite the legal prohibition is a strategy that has not yielded satisfactory results. Such intervention typically highlights the negative consequences (legal and financial) to sell cigarettes to minors. This strategy had no effect in New York and was only moderately successful in California, where sales decreased by 25%. The limited success of these interventions suggests that there probably is more than a financial motive in the sale of cigarettes to minors.¹⁷ In our study, for example, most employees do not agree with the legal prohibition for selling cigarettes to minors.

In contrast, Jason et al.¹⁸ consider that the control laws on the sale of cigarettes to establish civil penalties for violations of the sale of cigarettes to minors can

successfully reduce underage access to cigarettes. Although educational methods are used to raise awareness, the illegal sale of cigarettes appears to remain high because there are no adverse consequences if the merchants continue to sell cigarettes to minors. It is probably more profitable for merchants to continue the sale of cigarettes to minors than to voluntarily obey the laws.¹⁸

A recent review on the subject shows that restrictions on the sale of tobacco products to minors can be effective, but its effectiveness depends on whether the law is strictly enforced with punitive consequences, as the voluntary agreements between government and the merchants of cigarettes are much less effective in reducing sales.¹⁹

Either way, we must be aware that the law itself will be insufficient in preventing the sale of tobacco to minors. It is well known that adolescents have multiple potential sources for the purchase of cigarettes (adults, older friends, etc.).²⁰ Perhaps the implementation of educational programs in the schools^{21,22} and home²³ settings on the harmful effects of tobacco before the children start experimenting can help reverse this gradual increase in the prevalence of smoking among adolescents in our country.

In conclusion, this study suggests that there are two simple and low-cost steps -post signs prohibiting the sale of cigarettes to minors at stores and request a valid identification from the minors- that could significantly reduce cigarette sales to minors in our city.

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Antimycotic treatment for immunocompromised patients with neutropenia and persistent fever with suspicion of systemic aspergillosis: a cost-effective analysis in Mexico

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Abstract

Background: Systemic mycosis has a great impact on medical care costs. The objective of this study was to assess the most cost-effective empirical treatment for systemic aspergillosis, evaluating amphotericin B, caspofungin and voriconazole in patients with persistent fever and neutropenia.

Methods: A decision-tree model was used to estimate expected clinical results and costs associated with the treatment for systemic aspergillosis. The study used a healthcare payer's perspective (Mexican Institute of Social Security, IMSS). Time frame was 12 weeks. Effectiveness measure was complete remission of mycotic infection. One-way and probabilistic sensitivity analyses were performed.

Results: Average total expected costs per patient for

the voriconazole treatment were US\$57,378.58, for amphotericin B US\$72,833.96, and for caspofungin were US\$49,962.37. The total expected remission rate without any adverse events was 37.0% for caspofungin, 43.6% for voriconazole and 51.1% for amphotericin B. Probabilistic sensitivity analysis showed that voriconazole would be a cost-effective treatment with 65% confidence, regardless of the willingness to pay the IMSS.

Conclusions: The results of the study agree with the recommendation that voriconazole must be the empirical treatment for systemic aspergillosis, proposed as a standard first-line antifungal drug.

Keywords: invasive aspergillosis, systemic fungal infection, antifungal agents, cost-effectiveness

Introduction

Systemic mycoses impact on the morbidity and mortality of immunocompromised children, greatly increasing the costs associated with their medical care. In some hospitals, the prevalence of invasive aspergillosis in children has been higher than that of systemic candidiasis.^{1,2} Systemic aspergillosis is a severe fungal infection that affects immunocompromised patients,

especially those who have undergone bone marrow transplant or who suffer from a hematological disease.³⁻⁶ Neutropenia and its duration are the most important risk factors for the development of fungal infections in these patients.^{3,7} Systemic mycosis may be suspected in patients with neutropenia and fever when this persists after the use of broad-spectrum antibiotics or when

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pulmonary edema or lung cysts have been identified through computed tomography. Patient's characteristics and local epidemiological data are also important factors to be considered.^{8,9} It has been recommended that patients with risk factors are subjected to empirical treatment when a fungal infection is suspected. This has been associated with an improved survival rate^{10,11} because there is a low diagnostic sensitivity (~50%) for systemic mycoses.

The incidence of systemic mycoses in the U.S. from *Aspergillus* species has increased 4.5 times yearly.¹² Despite advancements in the treatment of these infections, the mortality rate is 57%-100%.¹³⁻¹⁷

Amphotericin B was considered the primary treatment against systemic aspergillosis until 2000;¹⁸ however, its effectiveness is variable (14%-83%) and depends on the infection site and the underlying primary disease.^{4,13} In spite of the high incidence of adverse effects (nephrotoxicity), its low cost encouraged the medical community to continue prescribing it.¹⁹ Voriconazole is considered nowadays as the primary treatment against systemic aspergillosis because it presents a lower incidence of adverse effects and has a higher effectiveness rate than amphotericin B.^{18,20} Despite the increasing rate of pediatric aspergillosis, the number of studies on the subject is limited; therefore, we consider it appropriate to estimate its prevalence using available data for the adult population.²¹ It has been reported that caspofungin is indicated for patients who do not respond well to amphotericin B or voriconazole or patients who have low tolerance to these drugs.²²

The cost per patient of the empiric treatment with complete remission of systemic mycoses in patients with neutropenia has been estimated to be between \$13,674USD and \$20,024USD, in patients with cancer and neutropenia between \$8,814USD and \$13,880USD, in patients with cancer and bone marrow transplant between \$11,173USD and \$16,230USD, and in patients with neutropenia and persistent fever between \$43,183USD and \$48,962USD.²³ In the U.S., the costs associated with children hospitalized from systemic aspergillosis were >25 million USD.²⁴

We found that none of the cost-effectiveness studies on the treatment of systemic mycoses compared the three aforementioned antifungal drugs simultaneously.^{19,25-29} This comparison is important because the three

antifungal drugs are in the Mexican "Basic Formulary Medications" and it is essential to identify which offers the best cost-effectiveness ratio. According to results of other studies on initial treatments of systemic aspergillosis, the use of voriconazole in Spain reported an incremental cost-effectiveness ratio of 25,266€ when compared to amphotericin B²⁵ and 1132.18€ when compared to caspofungin.²⁹ In Germany, an incremental cost-effectiveness ratio of 62€ was reported per additional survival week when comparing voriconazole against amphotericin B.²⁷ These studies showed there are more clinical benefits when using voriconazole instead of amphotericin B or caspofungin because of its higher effectiveness in aspergillosis remission and lower incidence of adverse effects.²⁷

The main difficulty for administrators is to be certain of what is the best antifungal drug that should be prescribed, based on the available evidence of efficiency and safety, as well as in regard to associated costs, budgetary constraints and opportune costs.¹⁹ Therefore, in the present study we evaluated three possible treatments for systemic aspergillosis: amphotericin B (deoxycholate), voriconazole and caspofungin. We carried out a cost-effectiveness analysis for treatment in neutropenic patients with persistent fever using a healthcare payer's perspective and a time frame of 12 weeks.

The Mexican Institute of Social Security (IMSS) is the largest healthcare institution in Mexico and covers the health needs of ~30% of the population.³⁰ The IMSS covers only affiliated workers and their families and the covered population is equivalent to the working population in other Latin American and developing countries with similar healthcare systems.³⁰ Although most of the described studies refer to patients diagnosed with systemic aspergillosis, it is very important to evaluate the best cost-effective treatment in suspected systemic aspergillosis. The purpose of our study was to identify the most cost-effective antifungal drug for the empiric treatment of systemic aspergillosis in neutropenic patients with persistent fever.

Methods

The cost-effectiveness analysis used a decision-tree model that represents the possible clinical events that would occur as a consequence of the empirical treatment prescribed for patients with aspergillosis, severe neutropenia and persistent fever. The model considers the adult population because the available

information is more reliable for this age group.²¹ The alternatives evaluated were voriconazole (loading dose of 400 mg/12 h on the first day of treatment), amphotericin B (loading dose of 70 mg/day, 1 mg/kg/day) and caspofungin (loading dose of 70 mg on the first day). Maintenance doses were voriconazole (200 mg/12 h), amphotericin B (70 mg) and caspofungin (50 mg).

The decision-tree model has three nodes for each therapeutic alternative (Figure 1). There are three possible results for each antifungal drug: a) complete remission without complications, b) partial remission with severe collateral effects (nephrotoxicity and possible death), c) therapeutic failure where the patient does not respond to treatment and systemic mycosis continues (possible systemic failure, multiple organ failure or death). The possibility for total remission and survival is also shown in Figure 1.

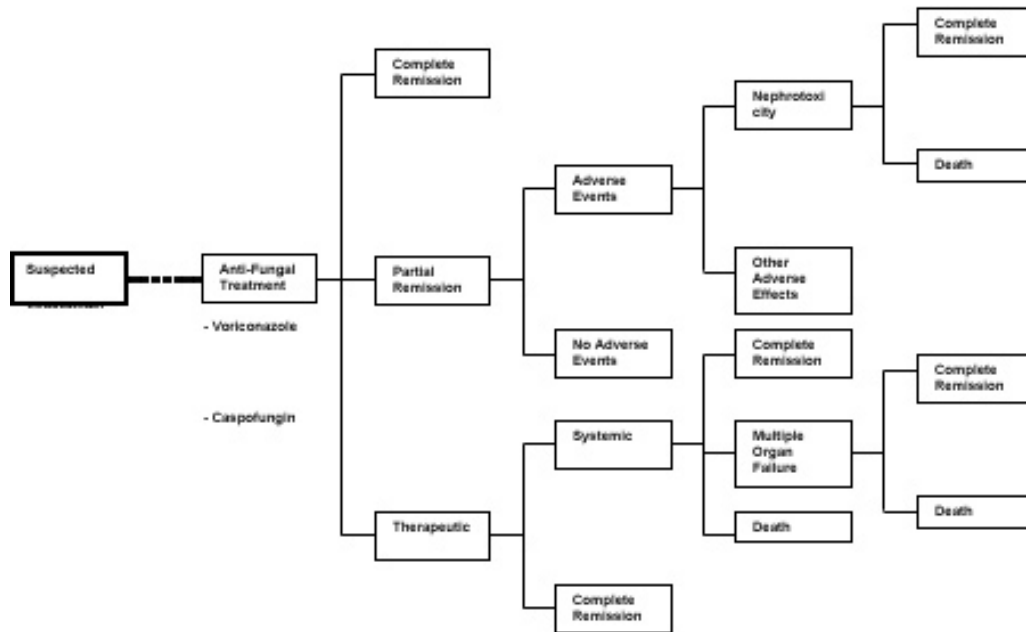
Costs

The study uses a healthcare payer’s perspective (IMSS) and therefore only considers direct costs. All costs were obtained from the financial and accounting information of the institution³¹ updated March 2004 and estimating inflation for 2008. The costs of antifungal drugs as

well as of those used to treat primary neutropenia were obtained from the IMSS website.³² The time frame used to evaluate costs was 12 weeks, assuming that during this period other clinical events could occur (clinical suspicion of aspergillosis, patient discharge, adverse effects associated with antifungal drugs, ADR treatments and even death of the patient). For this period, we considered the use of resources according to clinical events and evaluated unit costs. We applied no discounted rate because of the time frame.

In order to identify the use of IMSS resources, we assumed patients >25 years old with leukemia, lymphoma or bone marrow transplant who present severe neutropenia and, very likely, aspergillosis. We considered only the adult population in order to compare our results with other similar studies. We gathered a group of seven institutional medical experts who had experience with all evaluated drugs and we requested them to provide an estimation of resources required to handle patients and the possible clinical events described in the model including laboratory and clinical tests, hospital stay, visits from other specialists (pneumology, infectology), medicines (antifungals and others), peritoneal dialysis sessions, minor surgeries (catheter for dialysis), assisted mechanical ventilation,

Figure 1. Decision-tree model used in treatment: economic evaluation for patients with suspected aspergillosis.



This figure shows 10 possible outcomes. The probabilities used in our model are included in the Methods section. This is a summary schema of all possible outcomes and shows that even a patient who presented therapeutic failure can recover.

blood transfusions, surgical equipment and warehouse expenses. Laboratory test costs were obtained from the monthly report produced by the IMSS National Medical Center “XXI Century”.³²

Effectiveness

The effectiveness parameter was defined as the complete remission ratio of aspergillosis without adverse events. The effectiveness measure used in our study was the percentage of patients with complete remission per 1000 patients with suspected aspergillosis. In order to identify the effectiveness of studied antifungal drugs and the presentation probability of clinical events described in Figure 1, we carried out a systematic literature review between 1994 and 2004 using the Ovid-Medline, Elsevier-ScienceDirect, Proquest, Ebsco-E-Journal services and Interscience databases. We included all clinical trials in English or Spanish that tested the studied antifungal drugs on adult patients with hematological cancer/bone marrow transplant who presented persistent fever and severe neutropenia. Selected trials should include the percentages for total remission, partial remission and therapeutic failure as well as the description of adverse events such as nephrotoxicity. Only two trials met our criteria; however, it was necessary to verify other cohort studies/trials about the treatment of other systemic mycoses to identify the prevalence of complications under therapeutic failure.³³⁻⁴³

We included in our model the following data from clinical trials as follows:

Voriconazole

Herbecht et al.⁴¹ carried out a clinical trial to compare the effectiveness of voriconazole vs. amphotericin B to treat aspergillosis in patients with severe neutropenia. They included 114 patients in the voriconazole group, reporting 20% with complete remission and 38% with therapeutic failure. Severe adverse effects were documented in 13% of cases and, of these, 7% presented nephrotoxicity.

Amphotericin B

Herbecht et al.⁴¹ also reported that amphotericin B had an effectiveness of 16% for complete remission and 58% as therapeutic failure. Adverse events occurred in 24% of cases and, of these, 42% were classified as nephrotoxicity.

Caspofungin

Walsh et al.³⁵ studied 1095 patients, of which 556 received caspofungin. They reported 34% as total remission, 5% as therapeutic failure, and 5% as adverse events; of these, 2% were related to nephrotoxicity.

To complete our model we identified, using cohort studies for ICU patients with aspergillosis, that 84% of patients who presented therapeutic failure from any antifungal drug developed multiple organ failure and, of these, 50% fully recovered after a second treatment but 32% died.^{36,37}

Analysis

We carried out the analysis of empirical antifungal treatment for patients with neutropenia and persistent fever through a thorough cost-effectiveness evaluation. The cost-effectiveness analyses compared direct and indirect costs as well as savings that present two or more medical treatments to obtain a similar result in the patient's health (for instance, number of saved lives or number of patients who avoided a given disease). The net total costs of a given intervention, also known as incremental costs, are estimated and divided by the difference between clinical result effectiveness. In summary, the incremental cost-effectiveness ratios are obtained through the following expression:

$$iCER = (Total\ Costs_A - Total\ Costs_B) / (Effectiveness_A - Effectiveness_B)$$

where the incremental cost-effectiveness ratio (iCER) is obtained by dividing the net total costs (incremental costs) by the net effectiveness (incremental effectiveness) for two alternative medical treatments (A and B) (Table 1).

Sensitivity Analysis

We carried out three sensitivity analyses. Analysis of the scenario allowed us to evaluate results if voriconazole price had changed. The threshold analysis evaluated if initial model results were changed when the total remission rate was modified for any treatment. Finally, we carried out a sensitivity probabilistic analysis through a Monte Carlo simulation generating 10,000 iCER iterations obtained from distribution of parameters. We obtained acceptability curves for all studied treatments using the software Tree Age Pro 2004.

Results

We determined that the expected average cost for treating patients with hematological cancer or bone

marrow transplant who also develop systemic aspergillosis is about \$60,058.30USD at an exchange rate of 1 USD = 11.16 MXN. However, this estimation varies considerably (between \$25,441.22USD and \$119,438.18USD) according to the patient's evolution considering the following scenarios: complete remission without complications, normal aspergillosis evolution with severe consequences and even patient's death.

The results of our cost-effectiveness analysis are shown in Table 1. The average treatment cost for a patient with severe neutropenia and aspergillosis using amphotericin B is \$72,833.96USD, using voriconazole \$57,378.58USD and using caspofungin \$49,962.37USD. In a secondary probabilistic analysis we found no statistically significant differences between voriconazole and caspofungin costs (Mann-Whitney U test; $p > 0.05$), although both showed statistically significant differences with amphotericin B. As for effectiveness, the aspergillosis remission rate without adverse events was higher using amphotericin B (51.1%), followed by voriconazole (43.6%) and caspofungin (37%). This shows that caspofungin is the least expensive antifungal drug as well as being the least effective; amphotericin B is the most effective drug and also the most expensive (because of an increased nephrotoxicity probability); voriconazole is more effective than caspofungin and slightly more expensive; however, it is less expensive than amphotericin B. These data are shown in Table 1. We observed no absolute or extended dominance for any of the studied options; therefore, it was necessary to carry out a probabilistic analysis to determine the most cost-effective treatment.

With the scenario analysis we observed that if voriconazole increased its price by 25% this would be dominated by amphotericin B and caspofungin (data not shown). The threshold analysis showed that voriconazole can dominate amphotericin B when the complete remission rate is 40% because the total number of patients in a cohort of 1000 is 517 vs. 511 for amphotericin B. Voriconazole would need to have a complete remission rate (without complications) $> 35\%$ to be more cost-effective than caspofungin. This is from a deterministic point of view; however, monetary evaluation derives its conclusions from probabilistic sensibility analyses because the former results do not include uncertainty from parameters used in our model.

Voriconazole and amphotericin B used as empiric antifungal treatments could be potentially cost-effective; therefore, it is necessary to use other tools such as probabilistic sensibility analysis to determine which is more cost-effective by including uncertainty (statistical distribution of model parameters). Therefore, we developed acceptability curves (including all possible statistical probabilities for each outcome) for all three antifungal treatments in order to determine which would be the most cost-effective option according to the willingness of the IMSS to pay for each treatment. Figure 2 shows acceptability curves for antifungal treatments.

The probabilistic sensitivity analysis with acceptability curves shows that voriconazole has 65% probability of being the most cost-effective treatment, independent

Table 1. Results from cost-effectiveness analysis (Mexican pesos, 2008)

	Total expected cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Average C/E	Incremental C/E ratio
Amphotericin B	72,833.96		51.1%		142,532.21	
Voriconazole	57,378.58	- 15,455.38	43.6%	-0.075	131,602.25	206,071.73
Caspofungin	49,962.37	- 22,871.59	37.0%	-0.141	135,033.43	162,209.86

C = cost; E = effectiveness.

Incremental cost-effectiveness ratio (iCER) is calculated as:

$(\text{Cost of Treatment A} - \text{Cost of Treatment B}) / (\text{Effectiveness of Treatment A} - \text{Effectiveness of Treatment B})$ (67).

The average cost-effectiveness ratio analyzes each treatment independently and in this analysis voriconazole has the lowest ratio (more cost-effective per remission%).

of the willingness of the IMSS to pay, followed by caspofungin with 25% and amphotericin B with 10% (Figure 2). Thus, if the three drugs were used to treat immunocompromised patients, voriconazole would be the most effective and least expensive treatment (65% certainty), followed by caspofungin (25% certainty).

Discussion

Systemic mycoses can be associated with *Aspergillus* spp. in up to 58% of patients with hematological diseases in certain hospitals.⁵ Their prevalence has increased recently^{18,44,45} and they have been associated with mortality in 57%-100% of cases.¹³⁻¹⁶ A meta-analysis including 50 studies found that the mortality rate from systemic aspergillosis in patients with acute leukemia or lymphoma was 60% and in patients with bone marrow transplants reached 90%.⁴⁶

Timely treatment of systemic aspergillosis is one of the essential factors to reduce mortality rates.^{17,47} In children, delayed treatment may be related to 80% mortality, whereas timely treatment reduces mortality to 29%.¹⁷ It is important to begin empirical treatment in high-risk patients given the difficulty to diagnose systemic mycoses where there is a reasonable suspicion of the disease.⁴¹ Empirical treatment depends on several factors such as agent frequency in the population, expected result considering the primary disease, difficulty in diagnosis, drug effectiveness, drug interactions, safety and cost.²⁰

Average costs for the treatment of systemic mycosis range between \$13,674USD and \$152,140USD per patient.^{23,48,49} This significant variation depends on the patient's evolution that can have several outcomes. We considered 10 possible clinical scenarios in our study (Table 1).

We found that voriconazole was the most cost-effective option when suspecting systemic aspergillosis although there was no absolute dominance over caspofungin or amphotericin B. We found in the probabilistic sensitivity analysis that treatment with voriconazole was the most cost-effective option of the three evaluated medications with 65% of cases and independent of the willingness of the IMSS to pay.

Most studies on the subject have compared only two antifungal drugs; therefore, we decided to compare three of them.^{19,25-29} It is important to highlight that there

are very few studies where children or adolescents are involved; therefore, it has been recommended that the information obtained in studies with an adult population is applied to the pediatric population.²¹

For patients with neutropenia and persistent fever who have not responded to broad-spectrum antibiotics and who also have a high suspicion of aspergillosis, the recommended treatment is voriconazole because it provides superior clinical results with lower costs.^{19,25-29,50,51} The few studies where children were included reached similar conclusions.²¹ Our study shows that voriconazole is the most cost-effective option. We observed in the stochastic analysis that voriconazole could be chosen as the most cost-effective option with 65% certainty. It is important to remember that the model in the present study considers an empirical treatment when systemic aspergillosis is suspected. When the disease has been diagnosed, voriconazole is associated with lower costs.²⁶ On the other hand, willingness to pay thresholds are not available in Mexico or in the IMSS; however, if we adjust the parameters to those used by the British National Institute of Health (\$50,000USD) or to those recommended by WHO (<3 GDP per capita), we found that results are within acceptable levels.

Another advantage of voriconazole over amphotericin B is that 100% *Aspergillus* spp. are sensitive *in vitro*, whereas only 37.5% of species are sensitive to amphotericin B.⁵² No resistance has been reported for voriconazole by *Aspergillus*; however, there is an increasing number of fungi that are resistant to amphotericin B.^{23,53,54} On the other hand, it has been reported that antifungal drug intolerance presents faster when using amphotericin B than when using voriconazole (10 days vs. 77 days).⁴¹ Also, severe adverse drug events have been associated with voriconazole in 13.4% of cases, whereas amphotericin B has been related to 24.3%.⁴¹ Exanthema and visual impairment are the most frequent adverse events reported in children associated with the use of voriconazole.²¹

Sensitivity analysis in our study demonstrated that if voriconazole showed 40% complete remission, it would have an absolute dominance over amphotericin B and caspofungin; Denning et al.⁵⁵ and Herbrecht et al.⁴¹ reported a success rate of 48% and 52.8%, respectively, when combining complete remission and partial remission. This supports the usage of voriconazole as the first antifungal empirical treatment against suspected

systemic aspergillosis.

Studies from both Germany²⁷ and the U.S.²⁶ showed that voriconazole is the most cost-effective treatment. Results were robust and demonstrated that voriconazole was the dominant strategy in all evaluated sensitivity scenarios.²⁶

Another advantage for maintenance treatment is that voriconazole can be administered orally, whereas amphotericin B and caspofungin are only injectable.²³ This increases costs for the treatment of systemic aspergillosis because it is recommended that the patient remains in the hospital; in children, hospital stay may last for 16 days.²⁴

We used the international literature to calculate model probabilities and did not refer to the Mexican population. However, we found no reliable information in Mexico to develop our model. On the other hand, all the models (including ours) share a hospital environment approach, which gives comparable results.^{19,25-29} We consider as a possible restriction that the literature used in the model was not updated to reflect inflation for 2008. Another restriction is that antifungal drugs were not combined or alternated as a possible treatment; however, we consider this is more useful when the agent has been fully identified.^{18,20,56}

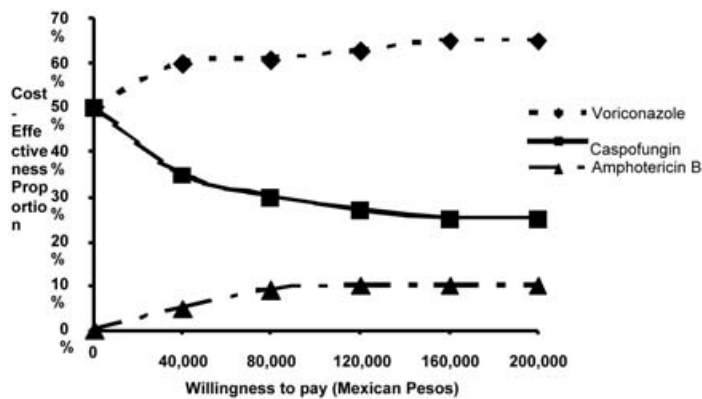
Our study evaluates the results with a time frame of 12 weeks, which is common with current cost-analysis studies.^{19,23,25-27}

One of the advantages of the present study is that probabilities included in our model were based on the average of probabilities reported in the literature, which allows the reduction of the possibility of bias because a given study may overemphasize the probability of certain events such as death, complete remission, or toxic effects in favor of or against a given antifungal drug. By using the average of probabilities, we weighed biases and could have reduced them.⁵⁷ We also included in the probabilistic sensitivity analysis the effectiveness variability reported in the literature.

With regard to recommended dosages in our study, we found that they coincide with those suggested in 2008 studies and, therefore, regard our model as current.²⁰

At the present time, the British Society for Medical Mycology recommends voriconazole as the first-choice therapy to treat systemic mycoses.⁵⁸ When it is not available, amphotericin B is also recommended and

Figure 2. Probabilistic sensitivity analysis. Acceptability curves.



The probabilistic sensitivity analysis shows that, independent of IMSS willingness to pay, the treatment with higher probability to become the most cost-effective option is voriconazole with 65% certainty. Caspofungin has only 25% probability of being chosen as the most cost-effective option. On the other hand, amphotericin B has only a low probability of being the most cost-effective option (10%). These results were obtained through a Monte Carlo simulation with 10,000 iterations.

has shown good results in children.⁴⁴ Caspofungin is recommended as a second-choice therapy and is well tolerated in children.^{58,59} Although caspofungin has reported good results against *Aspergillus* spp., this antifungal drug has shown little effectiveness against other fungi;^{58,60,61} therefore, voriconazole is a better empirical treatment for systemic aspergillosis because it has a broader spectrum against unsuspected or undetected fungi.^{16,62} Amphotericin B has been recommended over voriconazole when i) concomitant drugs with higher doses of voriconazole are being used, such as use of drugs with more interaction such as sirolimus, rifampin or warfarin; ii) there is significant hepatic damage; iii) there is high suspicion of zygomycosis; iv) when there is the presence of heart factors such as prolonged QT-interval or other cardiac risk factors.²⁰

Finally, we can highlight that in a developing country whose social security system is focused towards workers and their families, the most cost-effective option to treat a suspected aspergillosis is voriconazole. It is important to consider that the willingness to pay is affected by the probability of adverse drug events, which can be regarded as more severe, leading to choose one of the treatment alternatives.^{63,64} Nowadays, modern healthcare systems cannot adopt one therapeutic alternative considering only its effectiveness and if it is well tolerated, but they should keep in mind pharmacoeconomic parameters, and voriconazole is the best empiric treatment against systemic

aspergillosis. Nevertheless, further studies are necessary to evaluate the effectiveness of voriconazole, amphotericin B and caspofungin in the pediatric population who presents cancer with neutropenia and fever because currently available randomized trials are scarce.⁶⁵

In conclusion, voriconazole is the most cost-effective antifungal drug to treat suspected systemic aspergillosis in patients with lymphoma, leukemia or bone marrow transplant in a social security institution in a developing country. These results may be extended to the pediatric population.⁶⁶

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Epidemiology of accidental snake poisoning in the pediatric population

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Abstract

Background: In the General Hospital of Tampico, a significant number of cases of accidental snake poisonings were reported. Nevertheless, until now, there have been no reports about the clinical and epidemiological behavior and treatment protocol for accidental snake poisoning in children.

Methods: Pediatric files with a diagnosis of accidental snake poisoning from April 1994 until December 2006 were analyzed. Variables analyzed were body region affected, classification of the degree of poisoning, dose of fabotherapy administered, complications, time of the accidental poisoning and time elapsed until treatment.

Results: Of 610 patients, 171 (28%) were pediatric cases with the majority (65%) being male. The highest incidence (70.7%) was reported for the 6- to 15-year age group. The pelvic limbs are among the most affected anatomic site (55.5%). The highest

incidence occurred during the evening (47.9%) and during the spring/summer months (94%). The most severe degrees of intoxication (III–IV) were reported in 121 cases (77.7%), and 70.6% of the cases required >40 vials of antivenin (Fab) therapy. Average hospital stay was 6 to 10 days. Local infections were the main complication in 21% of the patients, and 47% of the patients arrived at the hospital after a delay of >24 h.

Conclusions: Accidental snake poisonings in pediatric patients have a low incidence (28%) as compared to the adult population but demonstrate a greater severity of intoxication due to the increase of the concentration of poison in a child with lower body weight. Complications are more serious, requiring a longer hospital stay. Likewise, use of a higher amount of Fab therapy is required.

Key words: accidental snake poisoning, children, antivenim.

Introduction

Mexico is one of the countries with the largest diversity of venomous reptiles; in fact, it is home for 103 species of poisonous snakes. Of these, 52 are rattlesnakes, 25 coral snakes, 19 Bothrops, 4 Agkistrodon and 3 Sistrurus.¹

Because of Mexico's geography, there is a large underreporting of patients who have been bitten by a snake. The National Epidemic Surveillance System reports an average of 3200 snake bites per year; however,

it is considered that this figure could actually be 10-fold. The states with the highest incidence of accidental snake poisoning are Hidalgo, Veracruz, Oaxaca, San Luis Potosí, Chiapas, Guerrero and Tamaulipas.²

Snake poisonings can be classified into three groups according to their toxic effects: a) proteolytic and blood coagulation (Bothrops and Lachesis); b) hemolytic and neurotoxic (Crotalus durissus Terrificus); and c) neurotoxic (Micrurus, Hydrophidae). Therefore, it is important to identify the actual snake species because

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of the different clinical presentations and poisoning levels in the patient. In Mexico's northeast area (states of Tamaulipas, Veracruz, San Luis Potosí, Hidalgo and Nuevo León) and the south of Texas, there are species of *Viperidae* (rattlesnake), *Bothrops asper* (nauyaca) and *Elapidae* (coral snake). Most of the accidents are related to *Bothrops asper*, also known as nauyaca or "four noses".

The poison of the nauyaca contains between 15 and 20 enzymes that modify capillary permeability of red cells and muscle fibers, consume fibrinogen and coagulation factors (bathracotoxin, thrombocytin), platelets (leading to a hypercoagulable state) and produce necrosis in affected tissues. The responsible enzymes for poisoning include phospholipase A2, B and C, hyaluronidases, monophosphoesterases, acetylcholinesterases, thrombolytic enzymes, etc. The initial hypercoagulable state is followed by a depletion of coagulation factors that triggers disseminated intravascular coagulation. Additionally, immune complexes are formed and deposited in renal glomeruli, producing acute renal failure. Severe poisoning cases may lead to multiple organ failure.

The General Hospital of Tampico provides medical care to the *Huasteca* area. This area has a humid and tropical climate, which is favorable for snakes and, therefore, prone to have accidental snake poisonings. Because of its central location, this hospital receives a large number of accidental snake poisoning patients from all over the *Huasteca* and has acquired important experience in the diagnosis and treatment of such events.³

The statistics of our hospital reveal that most accidental snake poisonings occur in adults (72%), predominantly in males (85%) and affect chiefly pelvic limbs such as feet and ankles (75%). Most accidents occur during the hot and humid season (spring/summer) (90%), and they significantly decrease in months with stable weather and lower temperatures.³

Our hospital has shared its experiences on the subject in several academic forums such as congresses, courses, medical journals, etc. However, there are no publications about the epidemiological and clinical behaviors or treatment of accidental snake poisoning in children. The treatment model proposed by our hospital since 1994 is based on the poisoning level of the patient when admitted to the Emergency Service (according to

Christopher-Rodning's⁴ classification) (see Figure 1), which was modified in our unit to deal with pediatric patients.

This study reports the experience acquired at the General Hospital of Tampico in the diagnosis and treatment of pediatric patients bitten by poisonous snakes.

Materials and Methods

We carried out a retrospective, observational and descriptive study. We included and analyzed all the files of children (<15 years old) who were admitted in the Pediatrics Service of our Hospital between April 1994 and December 2006, diagnosed with snake bite. The following variables were analyzed: age, sex, place of bite, poisoning level at admission, administration of antivenin (Fab) therapy, time of accident, elapsed time from accident to admission, reported complications and others.

We excluded those pediatric patients who matched the selection criteria but whose clinical file was missing or incomplete.

Results

A total of 610 patients diagnosed with snake bite were admitted at the General Hospital of Tampico between April 1994 and December 2006. Of these, 171 (28%) were pediatric patients (<15 years old); 111 males (65%) and 60 females (35%) (Table 1).

The age groups affected include children <1 year of age to 15 years of age, observing a higher incidence (70.7%) of cases for patients between 6 and 15 years of age at the time of the accident (Table 2).

The most affected body parts were pelvic limbs, chiefly toes, back of foot and distal third of the leg (55.5%) followed by thoracic limbs (43.2%) and, in a lower

Table 1. Cases according to gender

Gender	Cases
Male	60 (35%)
Female	111 (65%)
Total	171

frequency, in the neck and face (Table 3).

Table 2. Age groups

Age (years)	Cases
< 1	4
1-5	38
6-10	62
11-15	69
Total	171

Tables 4 and 5 show that most pediatric accidents occurred in the evening (47.9%) rather than in the morning (38%) and most occurred during spring/summer (94%) with a minimal incidence of cases during autumn/winter (6%).

Table 3. Anatomic site affected

Anatomic site	Cases
Pelvic limbs	96 (56%)
Thoracic	73 (43%)
Face	2 (1%)
Total	171

Table 4. Time of day for accidents

Time of day	# patients
Morning	65 (38%)
Afternoon	82 (48%)
Night	24 (14%)
Total	171

Table 5. Season of the year

Season	# patients
Spring	49 (29%)
Summer	112 (65%)
Autumn	6 (3%)
Winter	4 (2%)
Total	171

Most cases were from neighboring states of Tamaulipas, mainly Veracruz (38%) (Table 6).

Table 6. Geographical location

Geographical location	Cases
Veracruz	65 (38%)
Tamaulipas	50 (29%)
Hidalgo	30 (18%)
San Luis Potosí	26 (15%)
Total	171

The poisoning level observed at admission time was severe (III-IV) in 121 cases (77.7%), which required intensive treatment. There was a lower incidence of cases with mild poisoning levels (Table 7). Because of their poisoning level, 70.6% of cases required >40 doses of specific Fab therapy treatment (Table 8).

Table 7. Intoxication level

Intoxication level	Cases
0	4 (2%)
I	6 (4%)
II	40 (23%)
III	83 (49%)
IV	38 (22%)
Total	171

Table 8. Number of vials used

Number of vials used	Patients
1-10	8 (5%)
11-20	14 (8%)
21-30	28 (16%)
31-40	54 (32%)
>40	67 (39%)
Total	171

The average hospital stay was 6-10 days for most cases (46.7%) and >10 days in 23.9% of cases (Table 9).

Table 9. Length of hospital stay

	Cases
1–5 days	50 (29%)
6 –10 days	80 (47%)
>10 days	41 (24%)
Total	171

Infections at the bite site were the main complication in 21% of cases, followed by acute renal failure and local tissue damage (myonecrosis) (Table 10). Finally, five deaths were reported (2.9%) among pediatric patients admitted because of accidental snake poisoning (Table 11).

Table 10. Complications

	Cases
Acute renal insufficiency	24 (14%)
Myonecrosis	14 (8%)
Infections	36 (21%)
Multiple organ failure	3 (2%)

Table 11. Time of delay until hospital arrival

Hours	Cases
<1	7 (2%)
1–6	18 (10%)
7–12	28 (15%)
13–24	37 (27%)
>24	81 (46%)
Total	171

Discussion

Snake bite is a frequent entity in our region. This is because of the predominant rural activities carried out by the population who lives in the *Huasteca* area. They grow corn, and sugarcane, among other plants, and this modifies the ecosystem that triggers a migration of snakes into villages and towns. This close coexistence favors accidental snake poisoning. Also, the habitat conditions in the *Huasteca* are ideal for the development of several snake species.

There is no specific literature about accidental snake poisoning in children so it is interesting to analyze the clinical and epidemiological characteristics of an event of this type in this age group.

We found it appropriate to compare the results of our research with the actual experience acquired at the General Hospital of Tampico. We found that the distribution of accidental snake poisoning is 28% in children and 72% in adults. Adults (especially males) are more prone to present this pathology because of their work in the fields.

Level	Signs/symptoms	Doses
0	Bite without poisoning	Zero
I	Mild poisoning, mild pain, local edema <10 cm	3-6
II	Moderate poisoning, higher pain, edema >10 cm	6-10
III	Severe poisoning, abdominal level, nausea, petechiae, necrosis	16
IV	Multiple poisoning, multiple organ failure	20 or more

Figure 1. Intoxication level according to the Christopher-Rodning classification.

Boys are more affected than girls and chiefly those attending school (>6 years old). Also, children present accidents more frequently in pelvic limbs: toes, back of the foot, etc. because they tend to walk barefooted.

Children are bitten more frequently during evenings and nights, whereas adults are often bitten in the morning. This is explained by the activities carried out by each age group. Children playing in the fields are bitten by poisonous snakes during those hours where the ophidian are more active.

In general, snakes are more active in the hot seasons, and this explains why the accidents occur more frequently during the spring and summer.

It is important to highlight that children present a higher poisoning level than adults when they arrive at the Emergency Service, which is explained by the relationship between the body size of the victim and the amount of venom received.⁵ The severe poisoning level threatens the child's life and requires a more aggressive treatment, which explains the large number of doses of Fab therapy used to treat children. This was proposed

at our hospital by modifying the Christopher-Rodning poisoning classification in order to deal with accidental snake poisoning in the pediatric population (Figure 2). Also, because of a higher poisoning level, the child requires a longer hospital stay than the adult and complications in children are more serious than in adults.

mortality rate in children is 2.9%, whereas in adults it reaches only 1.4%.

In conclusion, accidental snake poisoning in Mexico represents a health problem in rural communities throughout the country. The Secretary of Health recognizes there is underreporting of this pathology because empirical remedies are used by the affected population.

The accidents occur more frequently in adults (72%) than in children (28%); however, children present more serious complications and higher mortality rates than adults.

The delayed arrival of the child to the Emergency Service after the accident may be associated with the higher complications and mortality rate. Prognosis improves substantially with the more rapid arrival of the patient to the hospital.

Finally, the physician who attends the patient bitten by a poisonous snake should diagnose the poisoning level and initiate treatment according to this level.

Level	Signs/symptoms	Doses
0	Bite without poisoning	Zero
I	Mild poisoning, mild pain, local edema <10 cm	6-12
II	Moderate poisoning, higher pain, edema >10 cm	13-20
III	Severe poisoning, abdominal level, nausea, petechiae, necrosis	32
IV	Multiple poisoning, multiple organ failure	40 or more

Figure 2. Intoxication level according to the Christopher-Rodning classification (modified for children)

Another factor that contributes to higher complications in children who have been bitten by a snake is the fact that they usually arrive at the hospital >24 h after the accident (47% of cases). Because of this late arrival, the

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Hypertensive encephalopathy secondary to acute post-streptococcal glomerulonephritis

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Abstract

Acute post-streptococcal glomerulonephritis (APSGN) is the leading cause of nephritic syndrome in children and has a broad spectrum of clinical presentation ranging from asymptomatic cases to acute renal failure and encephalopathy. Most cases are sporadic, although the disease may occur in epidemic form, mainly related to poor sanitary conditions. Hypertensive encephalopathy is a severe complication, but there is a good outcome with appropriate treatment.

Case report: We describe the case of a previously healthy 10-year-old male with a history of pharyngitis 1 week before his arrival to the emergency room. He presented with altered consciousness, partial seizures, hypertension and hematuria.

Cranial computed tomography was performed and showed no edema, mass or hemorrhage; antistreptolysin O serum titers were elevated. He was treated according to hypertensive encephalopathy due to APSGN, with a favorable outcome. Differential diagnosis should include cerebral vascular diseases, intracranial tumors, central nervous system infections and toxic metabolic disturbances.

Conclusions: APSGN should be suspected in any child with history of pharyngitis and sudden onset of hypertensive encephalopathy.

Key words: glomerulonephritis, hypertensive encephalopathy, seizures, streptococcal infections, antistreptolysin O.

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) presents as a nephritic syndrome with edema, hypertension and hematuria.¹ Patients show diverse clinical profiles such as asymptomatic, mild syndrome or significant complications such as cardiac insufficiency, acute renal failure or encephalopathy.² Hypertension is found in up to 90% of patients and 10% may have neurological symptoms, but only few present hypertensive encephalopathy (HTE). The disease is more frequent in children with recent pharyngitis or pyoderma. The prevalence of APSGN is not known precisely because patients may present a subclinical disease in 19%-50% of cases.² The incidence of this disease has decreased in developed countries in recent

years.³ Streptococcal infections have been associated with overcrowding and poor sanitary conditions, which may lead to epidemic or family outbreaks in certain groups.⁴

HTE is an acute organic brain syndrome (OBS)⁵ and is a consequence of brain hyperperfusion when the upper limit of the brain's auto-regulated vascular activity has been exceeded, leading to brain edema, petechial hemorrhages and micro-infarctions.⁶ It is more likely to appear in normotensive patients who experience a sudden increase in arterial tension, as occurs in children with acute glomerulonephritis. The clinical presentation includes acute lethargy, confusion, cephalgia, visual

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impairment (including blindness) and seizures. Seizures may be the main symptom that occurs as a focal crisis, a generalized crisis or a focal crisis with secondary tonic/clonic generalization.⁵ Severe hypertension is a rare but well-documented complication in children.⁷ The prognosis is good in general; however, without proper management, it can develop into permanent brain damage, brain hemorrhage, coma and death.^{5,6}

We describe the case of a 10-year-old male with APSGN and an unusual severe complication with favorable evolution.

Case Report

We report the case of a 10-year-old male who was previously healthy and presented fever and cephalgia of 1-week duration. The patient was attended at the general medical clinic where he was diagnosed with pharyngitis and prescribed amoxicillin (unknown dosage). When he arrived at the Hospital Emergency Room, he presented sensory system alteration, no response to external stimuli (verbal or tactile), spontaneous eye opening, right nystagmus with gaze deviation and symmetrical pupils with normal photomotor reflex. Hypersalivation was also observed with discreet clonic movements in the left arm and a general increase in muscular tone. At that time the patient had a heart rate of 120 beats/min, respiration rate of 20 breaths/min, blood pressure of 154/101 mmHg and oxygen saturation (SaO₂) of 70%. Supplementary oxygen was applied as well as IV diazepam (0.3 mg/kg), which reduced movements and gaze deviation and normalized muscular tone; SaO₂ improved to 99% and heart rate decreased to 72 beats/min with blood pressure between 145/99 and 152/109 mmHg (these were >95 percentile for age, sex, and size).⁸ Examination of the eye fundus revealed neither papilledema nor hemorrhage; cardiovascular parameters and physical examination were normal except for a discreet pretibial edema (sign of fovea positive). There were no signs of meningitis. Computed tomography (CT) revealed no edema, hemorrhages, ischemia, or hypodense or space-occupying lesions. Urinalysis from a tea-colored sample showed density (1025), pH 5.0, abundant erythrocytes, 10 leukocytes/field, blood casts negative, and other parameters were normal. Hemogram showed leukocyte count in $20.5 \times 10^3/\text{mm}^3$ with 90% segmented, 6% lymphocytes, 2% bands; hemoglobin: 12.6 g/dL; blood urea nitrogen (BUN): 15.8 mg/dL and creatinine 0.6 mg/dL; electrolytes were normal. Chest x-ray revealed cardiomegaly (level I), hilar congestion,

and clear costophrenic angles. The patient received IV furosemide (2 mg/kg) every 6 h and hydralazine (0.1 mg/kg) every 6 h to control blood pressure. He was admitted to the hospital with diagnosis of HTE secondary to acute glomerulonephritis. He weighed 34 kg (50th-75th percentile for age) and was 131 cm in height (10th percentile for age) at the time of admission.

During his hospital stay, blood pressure was controlled (95/60 mmHg) using the same treatment, but hydralazine was suspended because of dizziness, and furosemide was administered orally from the second day on. Other analyses carried out during hospitalization revealed proteinuria: 7.1 mg/m²/h (normal <4 mg/m²/h; nephritic >40 mg/m²/h); serum albumin: 3.5 g/dL (normal 3.2-5 g/dL); C-reactive protein: negative; antistreptolysin O: 1270-1350 IU/mL (normal <200 IU/mL); complement C3: 38 mg/dL (normal 80-180 mg/dL); pharyngeal culture: negative. These data were conclusive to diagnose APSGN. The patient received IM benzathine penicillin (1.2×10^6 UI) and evolved favorably with appropriate diuresis and without additional neurological problems. The patient was discharged after 3 days and prescribed furosemide for 1 week (2 mg/kg every 8 h). In the clinical follow-up after 1 month, the patient showed normal blood pressure and was asymptomatic with normal C3 levels.

Discussion

Acute post-streptococcal glomerulonephritis is the leading cause of nephritic syndrome during childhood.¹ It is a clinical entity with variable presentation, from patients being asymptomatic or with complications. The most common complications are congestive heart failure, acute renal failure and HTE.² Some authors report HTE is present in 7% of cases,⁴ although neurological symptoms such as cephalgia, nausea, vomiting and consciousness alterations may be found in up to 10% of patients.⁵ In severe cases, these symptoms may lead to seizures. In Costa Rica, encephalopathy has been reported in <1% patient series.^{9,10} In general, this complication is reversible when blood pressure is controlled and leads no sequelae.

The case reported is interesting because the seizure was subtle with discreet focal/clonic movements and consciousness alteration that could be considered as a status epilepticus because of its duration until the patient's arrival at the Emergency Room. Some authors have reported that the seizure types associated

with HTE are tonic/clonic, focal, generalized or focal with secondary generalization,⁵ which is in contrast to our case. During the patient's care at the Emergency Room it was necessary to perform imaging studies in order to document possible brain damage. Differential diagnosis should consider vascular complications such as intracranial hemorrhage, subarachnoidal hemorrhage or brain infarction as well as brain tumors and central nervous system infections (meningitis, encephalitis, brain abscess). Other causes may be toxic/metabolic (uremia, hypoglycemia, electrolytic alterations); however, the history of this patient did not lead to this group of problems. Diagnosis of glomerulonephritis was clear once CT scan was obtained with the additional revelation of hematuria. It has been reported that diagnosis of glomerulonephritis sometimes is difficult¹¹ or delayed; in the case discussed here the clinical presentation was HTE and only after hematuria was detected, we could be certain that glomerulonephritis was the cause of hypertension.¹²

In recent years, the reversible posterior leukoencephalopathy syndrome (RPLS) has been described as a phenomenon characterized by white-matter edema on parietal and occipital lobes.^{13,14} CT scan reveals bilateral hypodensity of cerebral white matter in parietal and occipital lobes, generally symmetrical in an area beyond the posterior cerebral artery, which helps to differentiate it from localized vascular lesions or strokes. Magnetic resonance helps to better identify lesions of compromised lobes. Conventional resonance studies are used for hypointense lesions (T_1) or hyperintense lesions (T_2) on cerebral white matter that sometimes also affect the gray matter. RPLS is associated with HTE in children but also appears in eclampsia, in hypertension associated with immunosuppressive therapy and in patients with renal failure.¹⁴ Visual impairment is frequently found in patients with RPLS, but this was not reported in our case. We also did not find the usual RPLS characteristics during CT scan and, because of the favorable evolution of our patient, MRI was not performed.

In patients with streptococci infection and history of neurological compromise, we should consider the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

These patients present obsessive/compulsive disorders, tics or choreoathetotic movements during a streptococcal infection.^{3,15} However, in the case presented here, there were no such manifestations. It is important to consider this during differential diagnosis of acute neurological disorders.

On the other hand, some authors report that APSGN diagnosis is defined by its suggestive clinical profile: sudden manifestation, edema, hypertension, macroscopic or microscopic hematuria associated with red blood cell casts and non-nephritic proteinuria, evidence of streptococcal infection, reduced C3 serum levels and spontaneous improvement of renal disease and complications.² It is recommended to take cultures from pharynx or from active skin lesions in order to document streptococcal infection; however, the organism is isolated in variable percentages as reported by different authors, even in patients who have not previously received antibiotics. In the case reported here, it was not possible to isolate the organism from pharyngeal culture and, therefore, the high levels of antistreptolysin O presented conclusive evidence of streptococcal infection.³ Other antibodies help to determine the infection, such as antideoxyribonuclease-B that, together with antistreptolysin O, provides the ability to identify the infection with 100% accuracy.⁴ Other serological tests include the determination of antibodies such as antihyaluronidase and antistreptokinase. Renal biopsy is not currently performed in children with APSGN because the clinical feature is sufficient to diagnose the disease. Renal biopsy is recommended only if there is rapid deterioration of renal function, complement levels remain low >8 weeks or there are clinical data that suggest another etiology (e.g. Schönlein-Henoch purpura, lupus glomerulonephritis, membranous or membranoproliferative glomerulonephritis).³

In conclusion, some authors report that diagnosis of APSGN should be considered with high suspicion in children with upper airway infection followed by sudden encephalopathy and hypertension. For example, a case was reported where urinalysis was normal, which required a more complex and expensive diagnostic approach including renal biopsy, in a potentially reversible clinical entity.¹⁶

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Cortical Adrenal Adenoma, Hypercortisolism, Cardiomyopathy, and Intrapancreatic Accessory Spleen in a 3-Month-Old Infant

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Abstract

We present a case of congenital cortical adrenal adenoma-associated endogenous hypercortisolism in a 3-month-old infant. The patient manifested polyphagia, weight gain, and changes in sleep patterns. During physical examination we found a full-moon face, bulkiness in the cervico-dorsal “buffalo-hump” region, high blood pressure, and serum cortisol of 163 µg/dL. Abdominal ultrasound revealed left adrenal tumor. During hospitalization, the patient experienced

respiratory difficulty and tachycardia, and thoracic X-ray revealed cardiomegaly. After a simple surgical procedure (venous dissection), the patient developed cardiogenic shock and died. At autopsy, adrenal tumor was found in addition to hypertrophic cardiomyopathy and intrapancreatic accessory spleen.

Key words: cortical adrenal adenoma, hypercortisolism, hypertrophic cardiomyopathy, intrapancreatic accessory spleen

Introduction

Cushing’s syndrome is defined as the combination of biological and clinical manifestations resulting from the presence of abnormally high and sustained circulating concentrations of glucocorticoids, whether of exogenous or endogenous production. The clinical diagnosis with a case of congenital hypercortisolism is really a diagnostic challenge because this disease is rare in infants.¹⁻³

The most common cause of this syndrome in all age groups, except infants, is the administration of exogenous synthetic corticosteroids. In later stages of life, Cushing’s syndrome is often secondary to hypersecretion of adrenocorticotrophic hormone

(ACTH).² In 80-90% of children >7 years of age with hypercortisolism, they present an ACTH-secreting pituitary adenoma.¹⁻³

Eventually ACTH is elevated due to ectopic secretion and was found to be associated with paragangliomas, Wilms tumor, neuroblastoma, and pancreatic tumors.³ In children <3 years of age suprarenal tumors are the most frequent cause of Cushing’s syndrome.^{1,4} Non-tumor processes known as bilateral suprarenal could also generate an endogenous hypercortisolism.¹⁻⁵

There are a number of very important clinical manifestations that together are suggestive of the

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diagnosis of hypercortisolism: 1) growth retardation in 100% of cases, 2) avascular necrosis of the femoral head in 4% of cases, 3) obesity or progressive weight gain in 95% of the cases, 4) asthenia and weakness in 65% of the cases, 5) hirsutism and acne in 55% of the cases, 6) “moon facies” and cervical hump.¹⁻⁵

Excessive use of steroids have effects on other organs and systems and may cause hyperglycemia, calcium alterations, osteopenia, hypokalemia, increased renin formation, muscle fiber atrophy, impaired immune function, and psychogenic disorders. Changes in heart muscle as a result of cortisol action during pregnancy and its effect on the heart at other ages noting that it favors the development of hypertrophic obstructive cardiomyopathy are also noted.⁶⁻⁹

The finding of intrapancreatic accessory spleen is a rare abnormality detected in school-age children and adolescents and more frequently in adults simulating abdominal infection and is often confused with pancreatic tumors.^{10,11}

The original treatment for hypercortisolism in cases of suprarenal adenoma is suprarenalectomy once the diagnosis has been established. The prognosis is usually good except for infants with large tumors and who exhibit hypertension, hyperglycemia, and immunodeficiency as well as respiratory infections.¹⁻⁵ We report the case of an infant with a suprarenal adenoma, hypercortisolism, and hypertrophic cardiomyopathy with a fatal evolution. On autopsy the infant was found to have an intrapancreatic accessory spleen.

Case report

We report the case of a 3-month-old male with a family history of inherited disease. The mother of the infant was an apparently healthy 21-year old. The father of

the infant was a 20-year-old drug addict (cocaine, marijuana and tobacco). The parents originated from and were residents of Hermosillo, Sonora, Mexico.

Table 1. Laboratory studies

Chemistry blood panel	16 05 06	25 05 06
Leukocytes	11,085 cells/mm ³	18,700 cells/mm ³
Segments	69%	74%
Lymphocytes	15%	23%
Hemoglobin	12.2 g/dl	10.3 g/dl
Hematocrit	33.5%	32.4%
Platelets	418,000/mm ³	321,000/mm ³
Sodium	138 mEq/L	
Potassium	3.4 mEq/L	
Chloride	96.4 mEq/L	
Calcium	10.5 mEq/L	
GSV		25 mm/h
Glucose	141 g/dl	
Urea	29 mg/dl	
Creatinine	0.5 mg/dl	
Uric acid	5.3 mg/dl	
Cholesterol	126 mg/dl	
Triglycerides	316 mg/dl	
Total proteins	6.1 g/dl	
Albumin	4.1 g/dl	
AST	40 IU/L	
ALT	100 IU/L	
FA	47 IU/L	
TB	0.4 mg/dl	
DB	0.1 mg/dl	
IB	0.3 mg/dl	
PT	13 sec	
PTT	22 sec	
Serum cortisol	163 µg/dl	

GSV, globular sedimentation velocity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fatty acids, TB, total bilirubin; DB, direct bilirubin; PT, prothrombin time; PTT, partial thromboplastin.



Figure 1. “Full moon” face, hirsutism, acne and “buffalo hump” were observed in the lateral sequence.



Figure 2. (A) Ultrasound study. In the longitudinal cut, tumor adjacent to the left kidney is observed. (B) Tumor size: 4.0 × 3.7 cm.

Perinatally, the infant was the product of a first gestation. The mother received adequate prenatal care. Birth was eutoxic, apparently with perinatal asphyxia. Birth weight was 3300 g, and the infant was breast and bottle fed.

The current condition of the infant initiated at 1 month of age. The mother of the infant noticed that the child manifested polyphagia and feeding occurred every 5-10 min. There was a progressive increase in weight, changes occurred in the face with increased volume in the bilateral malar area, dysomnia followed and eventually difficulty breathing. This was the reason for the infant being taken to a private clinic from where he was sent to the hospital for further study of possible Cushing's syndrome.

The infant was admitted with mild respiratory distress, respiratory frequency and heart rate 48 beats/min and respiratory rate of 148 min, blood pressure was 149/87, 113/79, 125/58 (systolic and diastolic >95th percentile for age) ++pallor, weight 6400 g (90th percentile), height 55 cm (5th percentile), head diameter 38 cm, and was active and reactive. It is noteworthy that the infant presented "moon facies" as well as hirsutism and acneiform lesions on the chest and arms. The infant also presented with a visible bulge in the cervicothoracic "buffalo hump" (Figure 1). Due to the clinical data and referral diagnosis, among other studies a serum cortisol level was requested and reported as 163 µg/dl.

Hepatomegaly was detected. The liver margin was found at 4 × 4 × 4 cm below the right costal margin in conventional limits.

On admission, a heart murmur and frequency of 150 beats/min was auscultated and the infant was evaluated by a cardiologist with suspicion of pulmonary stenosis.



Figure 3. Spherical left adrenal tumor is observed as compared with the normal right adrenal.

Echocardiogram was not performed. Chest x-ray demonstrated cardiomegaly, and a right apical infiltrate was found on the right apex of the lung. An abdominal and bilateral renal ultrasound was performed and showed a well-defined round image adjacent to the left kidney, 4.1 × 3.7 cm in diameter, with hypoechoic regions and with little vascularity. This was consistent with a suprarenal tumor (Figure 2).

On assessment by the Department of Oncology, a bone metastasis series was requested and reported as normal. Computerized tomography of the suprarenal area was requested, and the surgical department was requested to perform a venous cutdown for safe access during the procedure, which proved to be difficult due to the characteristics of the neck. The manipulation of the area was prolonged after which a heart rate of 158 beats/min was observed as well as increase in the respiratory rate. For this reason, an endotracheal cannula was inserted and assisted ventilation was begun. The patient was transferred to the intensive care unit (ICU).

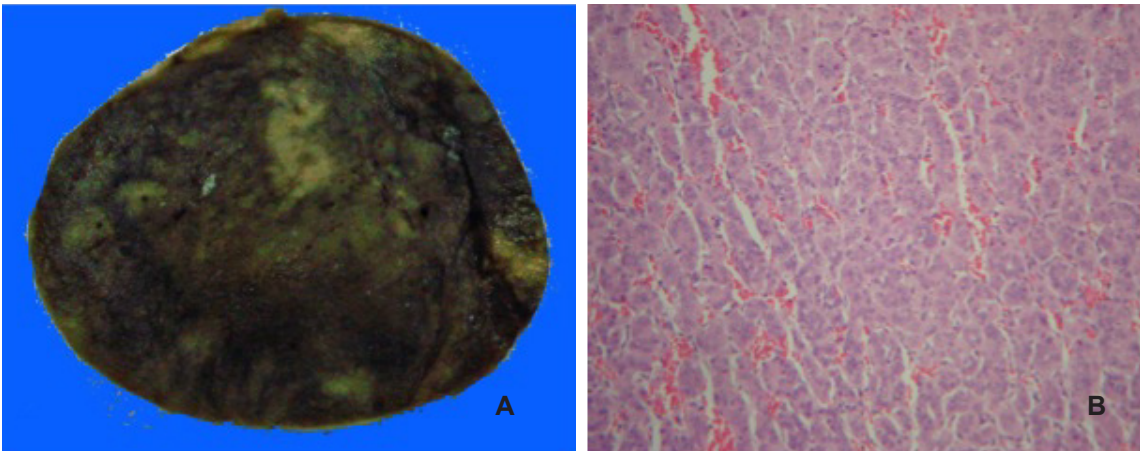


Figure 4. (A) Adrenal tumor is observed in the superficial cut with intensive congestion. (B) Light microscopy ($\times 400$); trabecular sinusoidal aspect is seen with scarce nuclear pleomorphism in 60% of the tumor and 40% of the pseudonodular aspect of sinusoidal amplification formed in the pseudopapilla.

In the ICU the patient presented with fever of 38.8°C, tachycardia, and pulse oximetry of 70%. The patient received antibiotics (amikacin, ceftriaxone) and nebulizations for the pulmonary process. There was no improvement. The patient then suffered cardiac arrest, which was reversed twice. After three episodes of cardiac arrest the patient died.

Autopsy findings

Autopsy was performed 3 h after death, corroborating morphometric findings mentioned in the medical history. Surgical wound for the venous cutdown showed some areas of hemorrhage in the peripheral soft tissues.

Left suprarenal tumor was spherical, weighed 50 g and measured 5 cm at its greatest diameter, and the outer surface was smooth with a vascularized and rubbery consistency (Figure 3). On cut, there was a solid, whitish-gray surface with several irregular foci of bleeding and capsule <0.1 cm (Figure 4).

Histologically ($\times 400$), the tumor presented a sinusoidal trabecular aspect with little nuclear pleomorphism in 60% of the tumor and the other 40% was of pseudonodular aspect or of large sinusoids that produced pseudopapillas (Figure 4).

The adipose panniculus in general was very thick, up to 1.5 cm of the abdominal wall. Histology showed a fatty aspect.

The heart increased in weight (95 g, expected 27 g) and size with a rounded apex. An increase in the thickness of the walls was demonstrated for the left ventricle (1.2 vs. 0.3 cm) and for the right ventricle (0.8 vs. 0.2 cm),



Figure 5. Characteristics of the left ventricular wall of the heart are observed.

as well as the ventricular septum decreasing the size of the cavity with restriction of the outflow tract in the right ventricle. Obstruction of the infundibulum was observed due to bulging of the septum into this cavity (Figure 5).

Inclusion nodules that histologically correspond to splenic tissue were found in the pancreas ($\times 40$). Upon closer examination ($\times 400$), pancreas and spleen tissues were observed (Figure 6).

Discussion

The cause of hypercortisolism with clinical manifestations of Cushing's syndrome is most often as a result of the administration of synthetic glucocorticoids.¹⁻³ Endogenous causes of hypercortisolism may be due to hypersecretion of adrenocorticotrophic hormone (ACTH) by pituitary or by excessive secretion of the suprarenal glands. In the case we presented, overproduction of cortisol was from the suprarenal tumor, an uncommon pathology in children <5 years of age and very rare in infants.^{10,11}

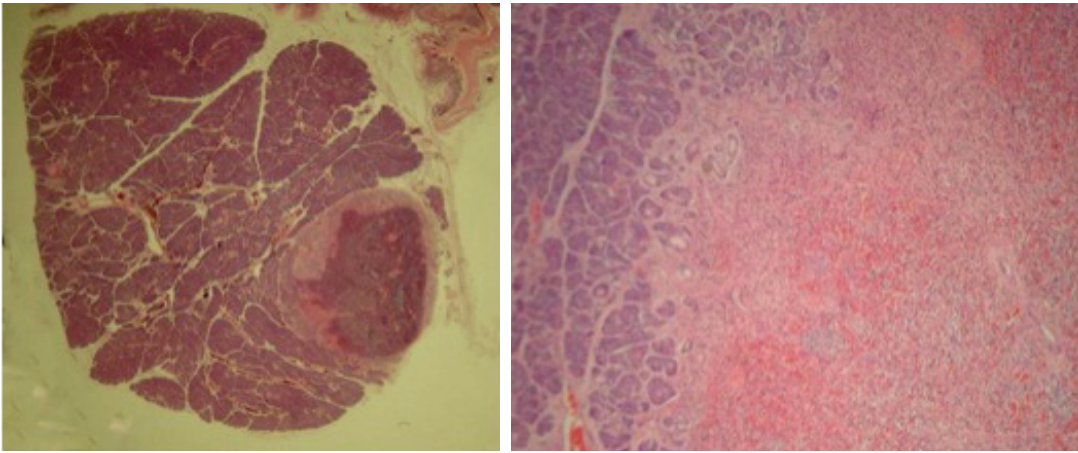


Figure 6. Histology of the pancreas with splenic tissue can be observed. Panoramic view ($\times 40$) and close-up view ($\times 400$).

Clinical manifestations in school-age children may be very florid, with very characteristic presentation and with no doubt in diagnosis; however, in other patients the clinical signs may be evident by growth failure and obesity, delaying the diagnosis.¹⁻⁵

In the case of the patient presented here, the principal manifestation was polyphagia with the infant virtually demanding food 24 h/day. The mother complained of fatigue because she stated that the 4 weeks prior to admission to the hospital she hardly rested at night because the infant slept very little and she observed him to be apneic. The child's weight was 6400 g, within the percentile for his age, with height in the low percentile, plethoric changes in facies, and thickening of the chest and upper extremities that the mother attributed to obesity due to overfeeding at the breast.

In this 3-month-old patient, on admission to the hospital physical examination may have easily pointed to Cushing's syndrome with the "full moon" characteristics of the face, hirsutism, acneiform lesions in the chest and arms, as well as a "hump" and bulging of the superior segment (trunk) in the cervicodorsal region (Figure 1). All the physical changes found were as a consequence of the persistent and intense action of the glucocorticoids, which favored the accumulation of fat in the abdomen, chest and face, condition central obesity. With the action of other compounds such as growth hormone and β -adrenergic receptor antagonists, these induce lipolysis, facilitating increase of triglycerides and free fatty acids. Thinning of the extremities is usually observed with proximal weakness. Decrease in protein synthesis leads to atrophy of the muscle fibers, a circumstance accentuated by the decrease in potassium.¹⁻⁵

Other skin changes that tend to be present such as capillary fragility, ecchymosis and hematomas and red stria in the abdomen and thighs were not found in this infant, and only mottling of the skin was demonstrated.

During the course of the patient's evolution, arterial hypertension was noted. Increase in blood pressure is due to the secretion of renin and mineralocorticoids. In hypercortisolism, the renin substrate is increased, inducing as a consequence the pressor response of angiotensin and catecholamines, and sodium retention, facilitating the expansion of extracellular volume.¹⁻⁵

There are laboratory studies to establish the diagnosis and help to discern between hypophyseal or suprarenal origin. These include serum cortisol level, free cortisol in the urine, determination of 17,hydroxycorticosteroids that has been substituted by free cortisol in the urine test in order to obtain better sensitivity, suppression test with nighttime dexamethasone, cardiac rhythm of cortisol, plasma ACTH, metopirone stimulus test, vasopressin and analogue stimulus test, corticotrophin-releasing hormone stimulation test, and catheterization of inferior petrosal sinuses. Some of these tests are available only in third-level hospitals in Mexico. Imaging laboratory studies include ultrasound, computerized tomography, and magnetic resonance. These studies are performed based on age and clinical evidence, and all are of tested usefulness.^{1-6,13}

In the case presented here, the following tests were performed: blood tests, liver function tests, electrolytes, cholesterol, triglycerides, urea, and creatinine. Alterations were found in glucose (141 mg/dl),

triglycerides (316 mg/dl) and serum cortisol (163 µg/dl).

With regard to the imaging studies, skull x-ray was normal. Chest x-ray demonstrated right apical lung infiltrate and global cardiomegaly. Ultrasound of the suprarenal area demonstrated a tumor in the region of the left kidney (4.1 × 3.7 cm in diameter) with scarce vascularity and hypoechoic regions. Using the diagnostic tests and clinical examination, diagnosis of functioning suprarenal tumor was made. The patient's evolution did not allow further tests to be performed.

Surgical consultation was requested for venous cutdown and for scheduling of tomography and magnetic resonance. Prior to surgical intervention, however, after manipulation of the cervical area with the intent of placing the venous cutdown catheter, the polypnea that was observed on admission worsened, and it was necessary to place the infant on a ventilator.

Systemic arterial hypertension, elevated levels of cortisol and cardiac changes noted on chest x-ray were probably related to myocardial injury that on autopsy showed heart muscle changes with predominant left ventricular hypertrophy. Myocardial damage was related to an excess of cortisol with a direct local effect on myocardial growth due to an increase in the protein/DNA relationship, which perhaps begins in the intrauterine stage. This tends to lead to a systolic and mainly diastolic function of the heart, which progresses to cardiac insufficiency, as was the case with this patient. On the other hand, cardiac muscle hypertrophy

was the result of the arterial hypertension present from intrauterine stage. The cardiac muscle hypertrophy itself produces an alteration in the organization of myocardial fibers, which also leads to hypertensive myocardial hypertrophy. Of this pathology, two variants are known: dilated and hypertrophic, as was the case with this infant.⁶⁻⁸

Taking into account the infant's age of 3 months and the significant suprarenal tumor mass (50 g) and the possible beginning of hypercortisolism from the intrauterine stage, in addition to arterial hypertension, it may have contributed to injury of the myocardial fibers that in turn caused obstructive hypertrophic cardiomyopathy. Due to all of the above causes, added to the stress generated by the surgical procedure, the pneumonic process may have been precipitating factors for triggering cardiogenic shock, which led to the death of this infant 10 days after his hospital admission.

It has been reported in the literature that suprarenal tumors weighing >100 g are a poor prognostic factor in the early stages of life. According to the Sandrini classification, it may correspond to stage I suprarenal adenoma.^{1,2,4, 9,10,12-16}

Regarding the autopsy findings on the presence of intrapancreatic accessory spleen, it is an observation of embryonic development that in later stages of life is often confused with pancreatic tumors and, sometimes, with abdominal infections and episodes of acute pancreatitis. In this case it was an accidental discovery that did not influence the patient's evolution.^{8,11,17}

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Trichinosis: clinicopathological case

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Case Report

We present the case of a 9-year-old male with clinical characteristics of abdominal pain, decreased bowel movements, vomiting, edema, pale skin and drowsiness.

Family history reported apparently healthy parents (31-year-old mother and 37-year-old father not currently living with family). There was a maternal uncle with hepatitis of unspecified type and the stepfather was addicted to cocaine.

There was no presence of previous personal pathology. The family originated from and currently lives in the Federal District. Their socioeconomic status is low and they live with two dogs. The child was breast fed for 2 years and began solid food at 3 months. The child was the product of a second unplanned, unwanted pregnancy. The mother received irregular prenatal care and experienced urinary tract infection during the second trimester of pregnancy. The infant was born via Cesarean section due to failure of progression of labor. The infant demonstrated normal breathing and crying at birth with unknown Apgar score. The child had chicken pox at the age of 2 years. The mother reported toxic exposure a week prior to admission.

The recent disorder is described as follows. The infant had a 15-day evolution with colicky-type pain located in the mesogastrium with moderate intensity and without irradiation or exacerbations and yielded partially to unspecified treatment. There were loose bowel movements without blood or mucus, occurring five to seven times during a 24-h period. There was vomiting of gastrointestinal contents for 13 days preceded by nausea. There was 7 days of edema.

At the time of admission, the patient appeared to be the chronological age reported. He was pale with dry mucous membranes. He had normocephalic appearance with appropriate hair, skin and outer ears. His eyes were symmetrical with sclerotic, icteric tint. Thorax was normal with well-ventilated lungs. His abdomen was soft, non-painful upon palpation, with increased peristalsis, and without ascites. He had normal male genitalia. The patient was admitted on April 13 and on April 14 there was probable sepsis and treatment was initiated with 150 mg/kg/day of cefotaxime and 22.5 mg/kg/day of amikacin. He presented with cardiorespiratory arrest for 3 min, which reverted with two cycles of compressions and one dose of epinephrine (0.01 mg/kg/dose). He was intubated and epinephrine

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and norepinephrine infusion were begun. Base solutions and support measures were left in place, and later there was a course of hypoglycemia and significant pulmonary congestion. On April 16 an abnormal EEG was observed with severe dysfunction and a pattern of attenuation. There were concentrations of platelets and IgG identified. He continued with fever and signs of systemic inflammation. Cefotaxime and amikacin were discontinued and 60/mg/kg/day of peropenem was started. He presented with hemodynamic instability with hypotension unrelated to the lack of volume, decreased urine output and venous reserve expenditure and increase of lactate. Hydrocortisone was suspended and mannitol was started every 12 h. Pulmonary echocardiogram showed a pressure of 55 mmHg and ejection fraction of 66%. From April 18 to April 19 he continued with a tendency to hypotension, oliguria, 66% hypoxemia and hyperlactatemia. We increased norepinephrine and dobutamine. Alveolar recruitment was performed with improvement in oxemia. CT scan showed cerebral edema. The abdomen demonstrated abundant free fluid in the cavity. Bone marrow aspirate was done by a hematologist with histiocytes and hemophagocytosis, which were negative for neoplastic infiltration. Gammaglobulin and total parenteral nutrition were begun. On April 20 there was severe rhythm dysfunction with low voltage slow wave outbreaks of widespread bifrontal predominance. He continued with fever peaks and aminergic support continued as well as mechanical ventilation. The results were favorable. We ruled out Epstein-Barr virus, cytomegalovirus, and hepatitis A. On April 24 the patient had low-voltage delta activity without reactivity and widespread severe dysfunction. Blood culture was positive for *Staphylococcus epidermidis*.

On April 27, plasmapheresis was performed without complications with a Mahurkar catheter with total replacement of 2200 ml. The patient continued with hypotension, and norepinephrine and ventilator settings were increased for the hypoxemia. The patient was placed on a high-frequency ventilator. Hemodialysis was performed with hydration restriction. The patient continued with hypotension and hypoxemia, and he did not receive any food; edema accumulated in the abdominal wall. The placement of a nasogastric tube was accomplished to drain bile. The patient's evolution continued to decline and we were unable to remove the aminergic support or ventilator. He presented bleeding and cardiorespiratory arrest with no response

to advanced resuscitation maneuvers.

Radiological studies (Dr. Rocío Enríquez García, Department of Radiology)

The first diagnostic study was a simple-phase CT performed on April 13 where we observed the brain parenchyma, which showed an appropriated differentiation of the gray and white matter, in the ventricular system. Basal cisternae are found with amplitude and preserved morphology. Actually, in this study we did not find any injury or alterations. We also combined reconstructions where we observed both coronal and sagittal sections. In comparison to the study on April 18 where a simple-phase CT and contrast was carried out, we found the same features without alterations in brain parenchyma. These are the contrast studies where unaltered vascular structures were seen; subarachnoid area did not show any bleeding or other anomalies. We also did not observe cerebral edema because the amplitude of the ventricles as well as the ventricular system were within normal limits. We also performed an axial section CT scan with contrast medium of the abdomen where we found an overall increased size of the liver with decreased density. Vascular structures were normal in course and caliber and there was no dilation of the bile duct. There was vessel morphology and no changes were demonstrated in the parenchyma. Both kidneys were functioning properly and contrast medium was eliminated. We observed the ureters, and there were feces in the bowels. The patient was not adequately prepared for the procedure and should have received an oral contrast or kept on a liquid diet in order to view the intestinal wall, although there is apparently no change. Our attention was focused on the free fluid in the parietocolic space of the left side. We also observed the bladder, which was not distended due to the placement of the catheter. In regard to the CT scan, we observed a striking increase in hepatomegaly, a reduction in density showing an inflammatory process and free fluid that may be a result of liver damage. In the coronal sections we observed the free flow of liquid along with hepatomegaly. In regard to the CT, vascular structures were well preserved and we did not find any vena cava or aorta alterations.

Case Discussion (Dr. José Luis Romero Zamora, Department of Infectious Diseases)

The discussion this afternoon concerns the case of a 9-year-old male who was hospitalized in our institution for 17 days. The patient is a native and resident of the Federal District. With no additional reported

type of relevant epidemiological data, the patient is from a dysfunctional family with emphasis on the characteristics of separated biological parents. The patient lives with a stepfather addicted to cocaine and with an uncle who has liver disease, characteristic of hepatitis. First, I wish to raise the diagnosis of social family dysfunction. This is significant for the resulting risk of child abuse and neglect that can happen, among other dysfunctional situations. The battered child syndrome affects all areas with physical or emotional contact with toxic or other specific drugs or relevant drug addiction. We know that the patient was breastfed until the age of 2 years. It should be mentioned that features of pediatric nutrition essential to remember during the first few months and days of infancy are the nutritional properties of breast milk along with the emotional qualities that are fundamental. To emphasize, it is recommended to breast feed for only the first 6 months of life. Any longer period of breastfeeding does not meet the conditions for adequate food both in quantity and quality. There is also a history that the patient was receiving treatment for attention deficit disorder. There is no further data or information to comment on. We do not know if the patient received group or psychological counseling. It is possible that he may have received a combination therapy based on some unknown drugs that may be stimulants as prescribed by a psychiatrist. This patient was initially admitted with gastroenteritis that may have been a secondary infection from various causes, probably bacterial, but a virus may have also been involved. The clinical development may also have been caused by parasites that may be contracted by the susceptible host either by mouth or skin. The problem may also be caused by fungi or intoxication from either food or another source. Without further information to sustain or to rule out these etiologies, we can only assume the cause is probably an infectious gastroenteritis. The patient was dehydrated with a fluid and electrolyte imbalance based on a determination with a hyponatremia of 120 mEq/L, hypo-osmolar hypochloremia of 87,000 mEq/L with metabolic acidosis, and hyperlactatemia of 3.9. It is known that in patients with diarrhea and vomiting, loss of chlorine is more significant in the nasogastric fluids because it contains 1.5-3 times more chlorine than sodium. This leads to hyponatremic dehydration, which is important because it relates to defects in the ability of dilution of the kidneys. In relation to vomiting and diarrhea, this condition may be caused by depression, resulting in extracellular fluid depression that stimulates the release of anti-diuretic

hormone at the expense of osmolarity. In patients with extracellular fluid deficit for >3 days, the rate is 60%, whereas intracellular fluid deficit is ~40%. Our patient's persistent dose of sodium is equivalent to 120,000. We support the possibility of hypotonic dehydration. It is important to note that most likely the patient showed poor response to the administration of fluids or had difficulty becoming properly hydrated. Our patient showed signs of developing a systemic inflammatory response to mixed neurogenic hypovolemia when less dehydrated. This provokes urgency for administering fluids, installation of a central venous catheter for adequate monitoring, central venous pressure and promotion or facilitating fluid administration. From the medical history this was not immediately performed and we are aware that the patient had a type of diarrhea that persisted for at least 15 days prior to hospitalization at our institution, apparently without inflammatory characteristics. According to the clinical files, the patient presented with hypotension probably associated with sepsis, a systemic inflammatory response syndrome that frequently is involved in an infectious etiology. This inflammatory response syndrome is apparently refractory to fluids, which warrants the use of adrenaline and nonadrenaline vasopressor amines. At that time the patient had a cardiac arrest. The type of cardiac arrest is unknown, whether with asystole or with electrical activity and without pulse, which is vague. We do not know whether vasopressor amines for management of hypotension is associated with induction as part of the intubation protocol in rapid sequence or in relation to the hypotension refractory to administration of intravenous fluids or a complication arising from the same procedure. Due to the placement of a central access, our patient's course with cardiogenic shock showed a poor response to furosemide. Because hypotonia persisted, the patient was administered dexamethasone and had a poor response to the amines, and there was a tendency for hypertension to persist. This led us to raise the possibility of probable adrenal insufficiency. Our patient's history also is in accordance with the clinical course of moderate to severe pulmonary hypertension. This is based on the above findings showing an ejection fraction of 66%. When performing the echocardiograph during monitoring of the patient's evolution, hemoglobin, leukocytosis, and thrombocytopenia were all low, and this led us to suspect sepsis. We should raise this possibility due to the very high rate of bacterial etiology, especially with a pattern evident from the beginning of this diagnosis

as part of the treatment approach for this patient. A complete study protocol for sepsis should have been done. As an infectious disease physician, I know the commentary will be self-critical in order to present the clinical information as clearly as possible by our team. Based on the information presented, a third-generation cephalosporin (cefotaxime-aminoglycoside) was indicated. From the provided information, I cannot really prove the presence of infection. Because of the frequency and analysis of the information, it may possibly be a type of bacteria. Regardless, I reaffirm that I am unable to confirm infection. What was referred to from the start was the possibility or the idea of a type of infectious bacterial agent. This would often be considered as empirical antimicrobial therapy; however, following the matching principle, this precisely meets our goal of empirically searching for the possible bacterial-type agents. This may have been gram-negative bacteria, and with the evolution and clinical history, gram-positive foci may not have been present at first. As we return to the empirical concept, it would be worth taking into account that the scheme using cefotaxime described in the literature may adequately cover a range of agents, including gram-positive foci. In reality, this is not true because cefotaxime does not provide adequate coverage for gram-positive foci. Current data of our patient showed thrombocytopenia, which may be secondary to several factors. One may be type of infection, which in this case may be autoimmune.

However, the thrombocytopenia could provide the data for splenomegaly, evident alterations such as the presence of collateral venous network, a sign of a cogwheel, etc. Subsequently, the patient began to show neurological signs, so an electroencephalogram was performed. He presented with cortical and subcortical dysfunction. These alterations may be related to metabolic or digestive diseases or from damage from these factors. However, I recognize that the most important characteristics reported in the literature with regard to these studies would be the presence of triphase wave-type. Continuing the evolution of our patient, on April 17 the persistence of fever was mentioned, with signs of systemic inflammatory response. The antimicrobial schedule was changed to carbapenem, specifically meropenem, in order to expand coverage. Carbapenem adequately treats gram-negative and some anaerobes but does not have adequate coverage for gram-positive coccus, but rather a broad spectrum antimicrobial in relation to the virus, especially of

hepatotropic type, such as herpesvirus, adenovirus, parvovirus B19, hepatitis viruses A, B, C, D, G, F, and others and principally bacteria such as *Salmonella*, *Escherichia coli*, or parasites such as *Leishmania* and *Plasmodium*.¹⁻⁶

In conclusion, this patient followed a course of hemophagocytosis manifested by all the data appropriate in the clinical history. Catheter-related infection are *S. epidermidis*; type A encephalopathy, initially grade I/II, posteriorly grade IV; liver failure, probably secondary to autoimmune hepatitis; and acute respiratory distress syndrome. My final diagnoses were the following conditions: diarrheal syndromes, anemia, hemophagocytosis, encephalitis and cholestasis, along with dehydration with hydroelectrolyte imbalance. Cause of death was multiple organ failure affecting the liver, kidney, lungs and brain.

Commentary

Dr. Ricardo Muñoz Arizpe (Department of Nephrology)

In regard to nephrology management of fluids, I have the impression that this patient had either second-level lupus nephritis or a primary drug-induced nephrotoxicity, which also caused hepatotoxicity. We do not know which of these he had, but all data indicate that it was one of these. In drug intoxications, lupus immunologics may be positive, antinuclear antibodies, low complement including anti-DNA, which is very specific for lupus, in some intoxications it can also be altered. Therefore, this is the reason for the confusion. The patient was admitted with impaired renal function, not glomerular but tubular filtration. Our attention is directed towards the fact that the patient had no oliguria, although he was dehydrated, and continued to urinate >1 L (almost 1½ L). Therefore the patient lacked the capacity to concentrate urine, which mostly indicates a drug-induced tubular-interstitial nephritis. Secondly, it is very difficult to discuss the management of fluids and electrolytes because we have no evidence of renal function. There is a determination of creatinine and three urinary electrolytes, which did not lead us to any answers. This determination cannot be interpreted with the absence of urinary creatinine, which would at least give us the determination of the fraction of excreted urinary electrolytes. Our conditions are not helpful. We would have primarily needed a general urine exam, which we did not have. Secondly, we needed a collection schedule for determination of urinary osmolar output of clear water, creatinine, and

24-h protein urine collection in order to discern if there is proteinuria. If it were a tubular type it would lead us to drug intoxication or point us to lupus nephritis with a glomerular type of proteinuria or to a liver/kidney syndrome that is a diagnosis of exclusion and related to alteration of the renin-angiotensin-aldosterone system. In this case I think it would be an acute tubular necrosis and not a liver/kidney syndrome. The patient later was sent for plasmapheresis, but we do not have any indications for such. He then received hemodialysis, which was not indicated, and we do not have any reason for the creatinine elevation. It is not an indication for dialysis. There must be very precise indications for hemodialysis, and in this case the patient had hypoglycemia, hypotension, and hemodynamic instability. Hemodialysis was a contraindication and we should have resorted to other alternatives. I would suggest that if the dialysis was necessary (because renal failure can also be conservatively managed), peritoneal dialysis should have been used, not with Tenckhoff but with an application of an acute atraumatic catheter. If this is not available in the hospital, then we must acquire it to avoid the bleeding problem. The other absolute contraindication for hemodialysis is that we must heparinize the patient systemically and the patient was bleeding, another contraindication for hemodialysis with regional heparinization with the use of protamine. This is not indicated in the medical record and, therefore, does not exist here. Hemodialysis was contraindicated and I believe that we should have approached the patient in another manner.

Pathological Findings

Dr. Maria Sanchez Escobar Algeria (Department of Pathology)

This patient had no previous biopsy. The most relevant information of the exterior habitus and of the opening of the gap was that he was an obese male weighing 39 kg when the average weight for a child of his age is 26 kg. He showed generalized edema including multiple petechiae and generalized cyanosis. We found a liter of yellowish fluid in the peritoneal cavity along with 50 mL of fluid in the right pleural cavity and 100 mL of the same liquid in the left pleural cavity. In a cross-section of the tongue, we can see part of the intact epithelium without alterations. In skeletal muscle we found part of a salivary gland, muscular fibers were dissected by infiltrated inflammation consisting of neutrophils, eosinophils, histiocytes and numerous cysts containing parasitic larvae (Figure 1).



Figure 1. Cyst with larva of *Trichinella spiralis* reaction surrounding larva constituted by Hematoxylin & eosin (HE) x30

This cut corresponds to the trachea where we observe part of the tracheal cartilage and the paratracheal muscles, which are located in the neck. These cross-sections showed the same encysted larvae. There was also a granulomatous reaction to these foreign bodies. We could also observe extensive inflammatory infiltrate consisting of lymphocytes, histiocytes and multinucleated giant cells in all muscles that correspond to the neck, abdominal wall, tongue and diaphragm. The same encysted mature larvae were found, some cut transversely, with intense inflammatory reaction in the

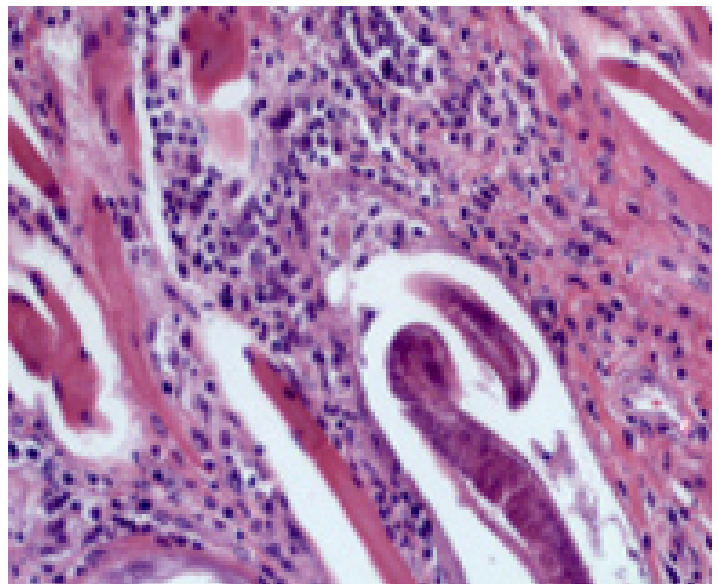


Figure 2. Inflammatory lymphocytes, plasma cells and giant multinucleated cells. (HE x20)

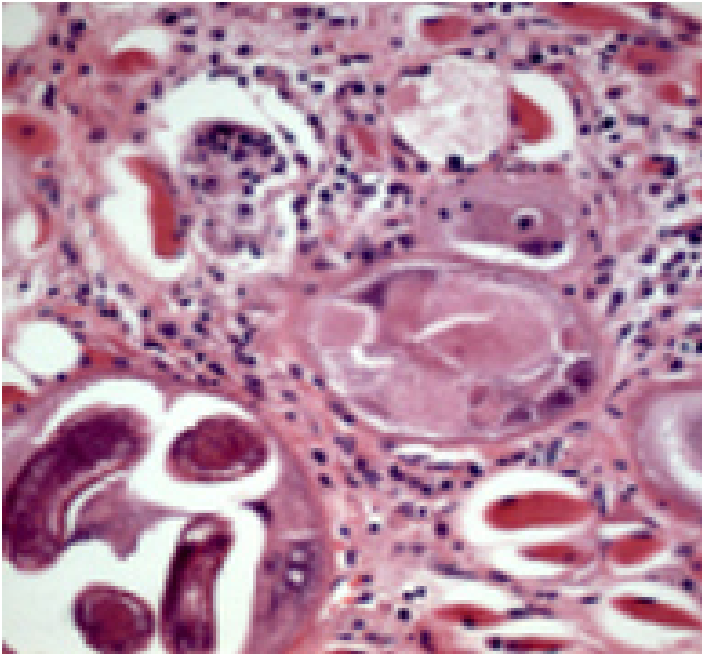


Figure 3.
HE x20 Schistocytes and degenerated larvae.

tissues (Figures 2).

Here we clearly see encapsulated adult larva with a hyaline capsule. Morphological characteristics of the larva are as follows: three-section body, anterior, middle and posterior. In the anterior part we can see part of its digestive tract, the esophagus and intestine and a cord constructed by mucosal cells, which constitute the schistosomiasis. In the posterior part are the reproductive organs of the parasite, and in this cross-section we see the same characteristics and can distinguish a section of its intestine and esophagus. Morphologically, due to

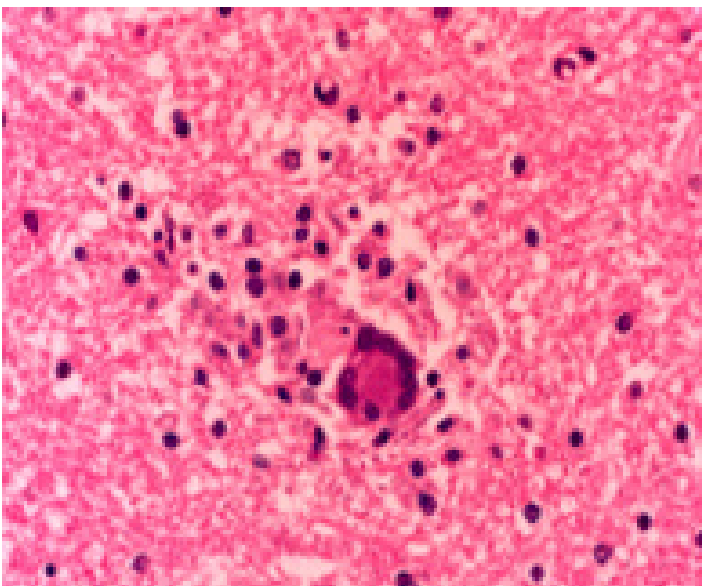


Figure 4.
HE x20 Encephalitis with chronic granuloma surrounding larva fragments.

the presence of larvae in skeletal muscle, this parasite appears to be *Trichinella spiralis*. Here we can again see another cross-section of the larva and observe the structure called schistocytes (Figure 3). These form a cord along the entire body of the larva. Some larvae had also started to degenerate. This is important because I believe that the principle disease is an infection from trichinella. Looking at the average life of the larvae, after 1 or 1½ months of infection, encysted larvae begin to undergo calcification, and here is where we observe the well-preserved larvae with intense inflammatory reaction (Figure 2). This is an acute process with ~1 month of evolution.

In the central nervous system, the brain had a weight according to what we expected. There was an area of congestion in the meningeal vessels, both at the base area as well as in the convexity.

In different cross-sections we can observe the basal ganglia. They present small areas of infarction and mild dilatation of the ventricular system. Different histological cross-sections showed encephalitis constituted by inflammatory infiltrate at the expense of lymphocytes, histiocytes and neuronophagia. There are fragments of larvae as well as multinucleated giant cells. This patient had encephalitis secondary to a parasitic infection (Figure 4).

The heart showed a significant pericarditis (Figure 5). The pericardium was bleeding, dull, and in different cross-sections we found an extensive myocarditis

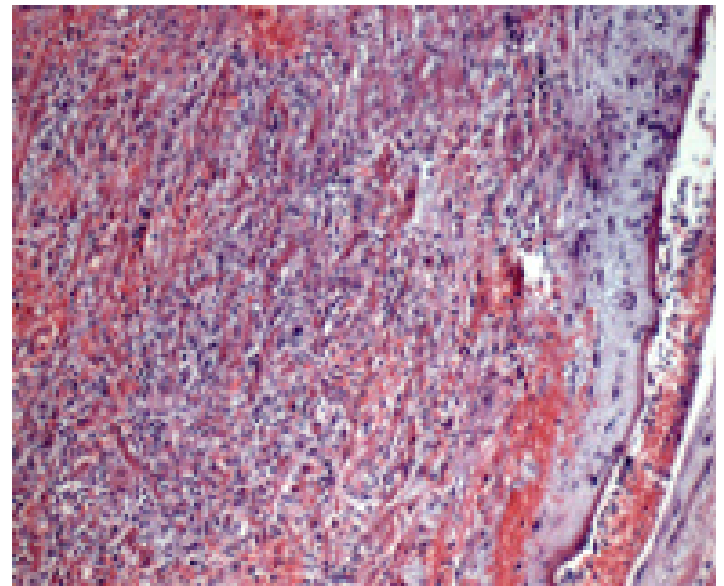


Figure 5.
HE x10 Pericarditis with extensive acute and chronic necrosis.

with inflammatory infiltrates consisting of neutrophils, histiocytes and eosinophils. Here we can see part of the pericardium and how it extends to the myocardium. There is necrosis of muscle fibers of the myocardium. In another cross-section at a higher magnification, some multinucleated giant cells are also visible as well as the presence of histiocytes, corresponding to the small intestine where there is a flattening of the mucosa and congestion. From a histological point of view, in both the cross-sections of the small intestine as well as the colon, we observed only congestion of the mucosa, lymphoid hyperplasia and congestion of lymphatic vessels. The parasite enters the digestive tract through undercooked meat, and by way of the gastric juices travels immediately into the small and large intestines. Larvae are generally not found in the small intestine because they usually migrate through the lymphatic vessels and the venous system to the skeletal muscle, as already mentioned, mainly to the tongue, neck muscles, diaphragm and abdominal muscles. In this cross-section we can see dilation of blood vessels.

At a high magnification we view extensive inflammatory infiltrate with predominance of eosinophils, neutrophils and mononuclear cells. *Trichinella* infection is found in 4 to 6% of the autopsies, 1-2% present serious systemic infection, and <1% die. The severe phase of infection is 6 to 8 days with a similar course to that of our patient. This is in relation to the amount of larvae ingested. I believe that this patient ingested a massive amount of larvae; the stage of muscle invasion is during the second week when the myalgia appears. These data offer a poor prognosis in this patient with myocarditis and encephalitis, which led to his death. The cycle of infection occurs during weeks three to four. Other important findings were that the lungs had a weight within that expected. Macroscopically, in the various

cross-sections we observed areas of congestion and dilation of the vascular system. The trachea showed slight loosening of the mucosa. The patient had extensive pneumonia in both lungs. We could see destruction of the parenchyma and inflammatory infiltrates in the pleura. Hence, he had pneumonia and pleurisy.

The esophagus showed numerous well-defined ulcers predominantly in the middle and lower third and in the esophagogastric junction (Figure 6). Histologically, what was found was esophageal epithelial ulceration in addition to the presence of secondary cytopathic changes due to viral infection (Figure 7).

In what appears to correspond to a virus from the herpes group, the larynx and trachea showed loss of epithelium and presence of granulation tissue and inflammatory infiltrate. The liver was extremely enlarged from a macroscopic view (Figure 8). It did not show necrosis, but the most important finding was hepatomegaly. Histologically there were no data

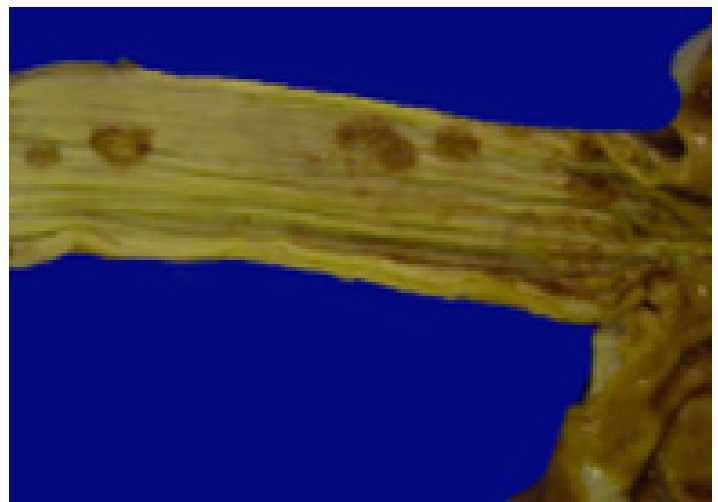


Figure 6.
Macroscopic photograph of the esophagus with numerous well-defined borders.

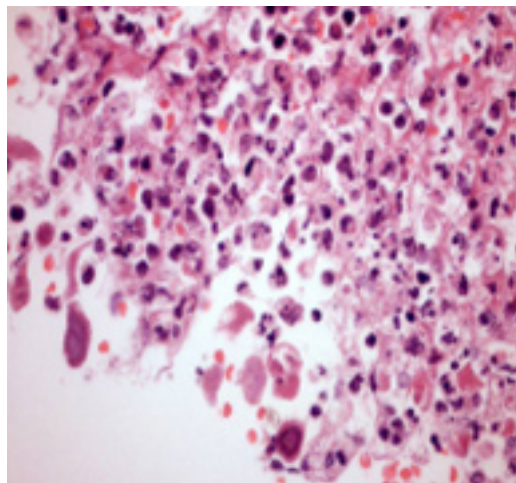
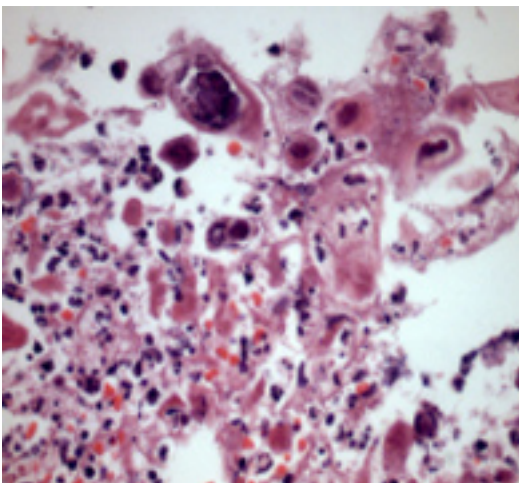


Figure 7.
HE x40 and x20. Ulcerated esophageal mucosa with cytopathic changes and intranuclear inclusions of herpesvirus type.

of inflammatory infiltrate at the level of the portal spaces or submassive hepatic necrosis. What this child presented was an extensive panlobular steatosis (Figure 9). The spleen was extremely enlarged with a prominence of lymphoid tissue. Histologically, the patient presented active lymphoid tissue, congestion of the red pulp and hemophagocytosis. In the kidneys we found data of acute tubular necrosis. There were no data showing glomerulopathy although cytoplasmic vacuolation was found in some tubular epithelial cells, corresponding to a tubulointerstitial nephritis or part of an acute tubular necrosis. The thymus showed diminishment of lymphoid tissue and significant dilation in addition to calcification of Hasall corpuscles. Organs of the mononuclear phagocytic system showed no abnormalities histologically. Both T- and B-lymphocytes were present. Postmortem cultures were positive for the following: right and left lungs, liver and spleen (yeast), small intestine (*Stenotrophomonas maltophilia* and *Pseudomonas fluorescens*), hemocult and colon (*Enterococcus faecium*).

The final diagnoses are as follows:

Primary disease: Trichinosis that affected the patient's tongue, skeletal muscles of the neck and abdomen, diaphragm, myocardium and central nervous system

Concomitant alterations: Acute pneumonia with yeast and pseudo-hyphae of *Candida* sp.



Figure 8.
Macroscopic photograph of the liver

Pleuritis with yeast and pseudo-hyphae of *Candida* sp.

Acute ulcerated esophagitis with secondary changes to infection from herpesvirus group.

Ulcerated acute laryngitis

Hepatomegaly (2400 vs. 828 g)

Panlobular macrovesicular steatosis

Splenomegaly (120 vs. 83 g)

Secondary macrophage activation

Thymus involution

Anatomic shock data: Acute tubular necrosis, acute alveolar damage, and multivisceral congestion

Final remarks

From Dr. Romero:

Dr. Campuzano, on April 20 of last year, there is a note from a physician who no longer works at this hospital, but his signature appears. Seven days after the death of this patient you were insisting that it was necessary to discard the possibility of parasites. What is your reflection 1 year later?

Reply from Dr. Roberto Campuzano:

What we should take into account is the importance of assessing the patient or offering a suggestion as to the diagnostic approach because it implies that we did not overlook such considerations. The possibility existed that histopathological studies were not performed or not finalized for obviously unknown reasons in order to document the possibility of infection. Therefore, not only was there a delay in diagnosis, but it definitely

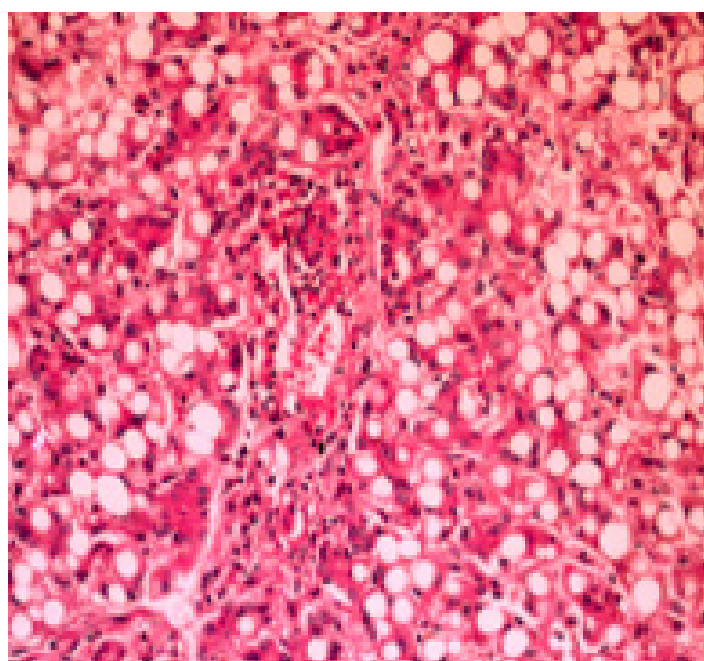


Figure 9.
HE x20. Liver with panlobular macrovesicular steatosis

contributed to the deterioration of the patient and to his fatal demise. The reflection would be that if we are requesting a study to attempt to document an infectious process, it should be conducted in a timely manner.

Dr. Romero:

My thoughts are that if you had concerns about some diagnostic possibilities, you must not question yourself but rather carry out the necessary studies at that specific time.

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Clinic for integral care of the abused child: implementation of a national strategy in education, research and treatment

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Abstract

The importance related to the topic of child abuse and neglect is considered. We focus here on the medical, social and legal aspects of this problem. It is easily understandable that the World Health Organization sees it as a global public health problem in view of its consequences: physical and emotional for the child and economic and social for the family and the community. In order to address this situation, the authorities for the pediatric community must develop

a strategy for interdisciplinary, interinstitutional and even international overall care within the framework of standard professional activities in clinical care, teaching, and research. The clinical program for integral care of child abuse and neglect at the Mexican National Institute of Pediatrics, a third-level pediatric hospital, has been developed during the past 10 years.

Key words: child abuse treatment, integral care, interinstitutional, international.

Introduction

Child abuse is also referred to in the medical community as the Battered Child Syndrome (BCS). Unfortunately, its prevalence has been recognized for many years and has important medical, social and legal implications. It was first recognized from a description made by Kempe.¹ Although the problem had already been studied by Caffey,² other medical professionals later described and classified this problem.³⁻⁸

In Mexico, this problem has been partially addressed.⁹ Various medical groups and particularly pediatricians have conducted investigations regarding this matter and communicated their findings to other physicians.

They have also developed strategies for management, research and educational activities related to this problem.¹⁰⁻¹⁶

It is very difficult to assess the overall frequency of child abuse because there are situations that make accurate reporting of cases very difficult.

Among these difficulties is underreporting when not all types of incidents of child abuse are included in medical and legal files among different institutions. There are also many included unreported cases.¹⁷ Despite these limitations, there were three million complaints registered in the U.S. in the year 2005 and, of these, one

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million were classified as child abuse.¹⁸

In Mexico, cases are reported to the National System for Integral Family Development (DIF), Office of the Attorney General of Mexico (PGR), Office of the Attorney General of the Federal District (PGJDF)¹⁹ or the Clinic for Integral Care of the Abused and Neglected Children of the National Pediatrics Institute (CAINM).^{20,21} According to these reports and comparing them with data from other countries, we are able to infer that up to 10% of children or adolescents suffer some type of abuse and only 10% of cases receive proper care.²²

Considering the complexity of the problem, it is necessary to avoid any political, social, religious or economic bias when addressing this matter. Therefore, it is evident and mandatory to create a strategy to address this problem from different perspectives.

In most national or international pediatric hospitals, children are usually assisted by pediatricians and specialist pediatricians in critical medicine or other specialties, but usually not by experts in children abuse. In most cases a professional not directly related to health care deals with child abuse such as the social worker,²³ psychologist²⁴ or an attorney²⁵ in institutions like DIF through their PREMAN program.²⁶ In local and national offices of Attorney Generals, cases are addressed through the Family Violence Care Units (UAVIS) and others such as nongovernmental organizations that develop diverse programs related to sexual abuse of children,²⁷ homeless children,²⁸ drug addiction and alcoholism in children and adolescents,²⁹ etc.

In the National Pediatric Institute of Mexico (INP), child abuse has been studied since the 1980s by the Department of Internal Medicine and their first experiences were published.³⁰⁻³²

The opportunity to create a team dedicated exclusively to address this pathology arose when we realized the need to provide integral care to victims of child abuse. Therefore, the Clinic for Integral Care of Abused and Neglected Children (CAINM) was founded in 1997 and has been recognized by the Postgraduate Division of the Faculty of Medicine of the National Autonomous University of Mexico (UNAM).

Even though other international institutions occasionally consider an interdisciplinary, interinstitutional and

international approach, the CAINM includes it from its foundation with the purpose of addressing the medical, social and legal problems considering management, research and educational approaches.³³

The ultimate goal is to establish a program that allows the development of three fundamental activities in medicine: medical care, teaching and research. This includes the analysis of each case as part of a model of integral care with interdisciplinary and international approaches. This program would be replicated in other states throughout Mexico.

The initial experience of the work of CAINM shows that two out of three children who received care at the Clinic are not abused again during the first 3 years after they have been discharged.³⁴ Although these results are satisfactory, the personnel at the Clinic still search for results where patients and their families obtain better medical, social and legal opportunities.

New personnel who arrive at the Clinic and the greater experience gained by the founding group enrich the future outlook in several disciplines (Figure 1).

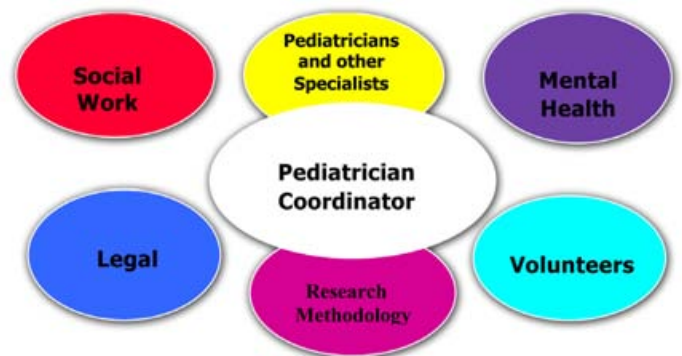


Figure 1. Clinic for Integral Care of Abused and Neglected Children.

Although the characteristics of this teamwork at a specialized pediatric hospital are not easily replicated nationally, we consider this a requirement in order to care for the abused child and the family.

We consider that when implementing this program, it should include pediatricians, psychiatrists, psychologists, social workers and attorneys.

It is essential that all team members are knowledgeable with the subject and have the appropriate qualifications along with the right attitude to share their knowledge with other colleagues. This multidisciplinary group

should be able to carry out research projects in medical, social and anthropological fields in their own community. Therefore, it is highly likely that the outcome of their work can be used to differentiate the subtleties between upbringing, discipline, “community traditions” and child abuse.

It is frequent that, in general medical centers, the family physicians handle child abuse cases and we consider that they will require additional information on the subject as well as the implementation of reference strategies in order to make the best decisions for each case.

The leadership skills developed by the teamwork specialists will depend on their interest and information regarding the subject.

It is advisable that a pediatrician be responsible for medical and surgical matters when managing these patients because there are several diseases whose characteristics are similar to those of child abuse. This group includes accidents,³⁵ osteogenesis imperfecta,³⁶ renal rickets,³⁷ human papillomavirus infection,³⁸ etc.

The allied health group comprises professionals from the fields of social work, mental health, infirmity and nutrition. Each will be able to analyze some characteristics of the victim, the family, social and school environment, the psychoemotional status of the patient and families that will all contribute to establishing an accurate diagnosis.

Legally, attorneys will establish the link between physicians and allied health personnel with the appropriate authorities who will determine the legal status of the patient, the aggressor (if any) and the family.

The involvement of other professionals related to children and adolescents is very important because their support eases the diffusion of the topic, the timely reporting of cases and, under special conditions, development of clinical, social and epidemiological research programs.³⁹

We present the program of Integral Care for the Abused Child together with interdisciplinary, interinstitutional and international intervention strategies as well as other classification parameters. The strategies of this teamwork are regulated by the “Quality Management

System” program.⁴⁰

Mission

To detect, care, rehabilitate, and prevent any form of violence against children and adolescents.

Vision

To become the team leader who takes care, rehabilitates and prevents abuse against children and adolescents in Mexico and throughout Latin America.

Goal

To create a new culture in health where improved treatment towards children and adolescents is characteristic of families and society in general.

Purpose

To develop care, educational and research protocols aimed toward the detection, integral care and prevention of child/adolescent abuse and neglect through an interdisciplinary, interinstitutional and international strategy.

The following purposes are also considered:

Resolution of child abuse in the largest number of cases and the shortest possible time

Development of prevention strategies considered an essential requirement to halt the recurrence of the problem

Quality systematic diagram

The methodology and organization established at CAINM is aimed to provide quality service according to overall best practices. Therefore, the National Pediatric Institute of Mexico (INP) created a systematic diagram describing the pathways for the care of children and adolescent who have suffered any form of abuse.

This systematic diagram contains the basic characteristics and specific functions of suppliers, customers and service providers as shown in Figure 2.

Description of the three basic activities of the program

Assistance activities

Purpose

To aid the victim to recover optimal physical and mental health as the primary goal of all team members

To provide to all family members social and psychological orientation to reduce damage to the

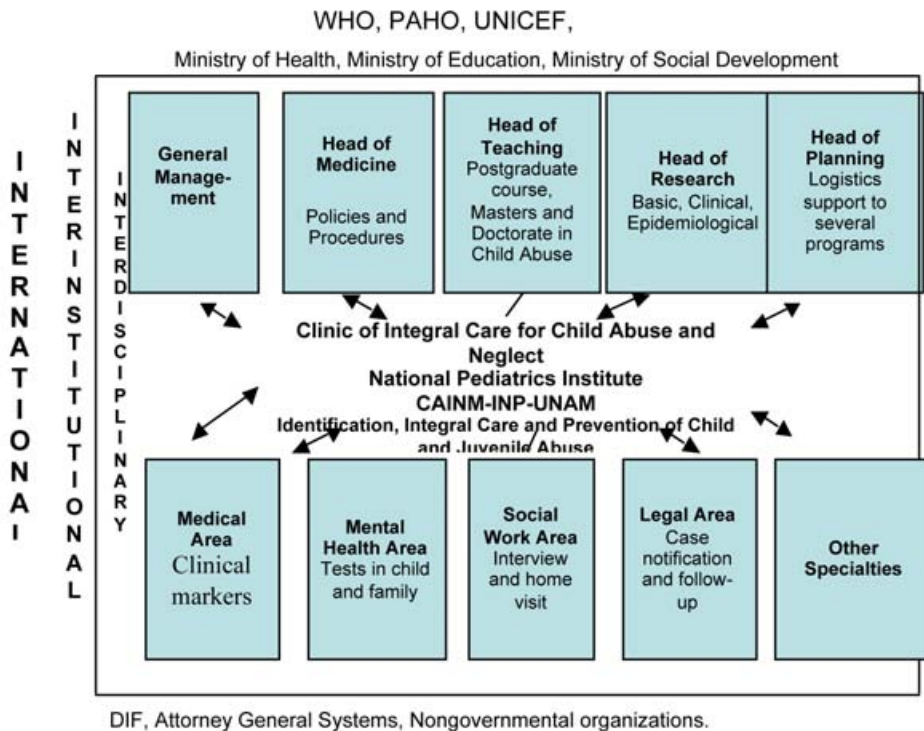


Figure 2. System diagram at CAINM for integral care of abused or neglected children and adolescents.

family structure and avoid its further disintegration

To select one family member to be the first option to provide support to the child to avoid sending the child to foster care

Care algorithm used in CAINM (Figure 3)

To develop secondary and tertiary prevention strategies against child abuse

To provide group therapy for mothers who generate violence against their children

Professional functions

The medical team:

- a) should solve the medical and surgical problems of the patient
- b) will investigate and diagnose the evidence of violence against the child or adolescent
- c) will notify the authorities about injuries suffered by a child or adolescent after the interdisciplinary assessment concludes the patient has suffered child abuse or neglect
- d) will closely oversee the evolution of any physical changes as a consequence of child abuse in the short and medium term
- e) will implement primary, secondary and tertiary prevention strategies
- f) will provide guidance to mothers and female adolescents about current family planning methods.

2. The mental health team (psychiatry and/or

psychology):

- a) will establish the psychoemotional status of the child, the likely aggressor (if any) and the family.
- b) will support or discard the existence of any psychiatric disorder in the adult that favors the abuse against the child
- c) will implement psychoemotional care strategies for the child and family
- d) will closely oversee the victim's evolution in the short and medium term
- e) will develop a group therapy plan for mothers who generate violence against their children
- f) will participate in primary, secondary and tertiary prevention campaigns against child/juvenile abuse and neglect

3. The social work team:

- a) will develop the clinicosocial history (CSH) that allows to support or discard any form of child abuse or neglect
- b) will assess strengths and weaknesses of the child's family and social environment through the CSH and a home visit
- c) will define a support network for the child (with relatives, the government or civilians) and propose it to the office of the attorney general
- d) will provide an essential link between the medical and legal areas
- e) will closely oversee the victim's appropriate evolution

in the short and medium term.

f) will participate in primary, secondary and tertiary campaigns against child/juvenile abuse and neglect

4. Infirmary

a) will analyze the health conditions of the victim and family

b) will aid the physician to watch the appropriate evolution of victim's injuries

c) will assess the patient's physical condition by checking and following-up vital signs

d) will review the patient's vaccine program follow-up

e) will implement strategies to prevent accidents

f) will guide the mother about family planning methods

g) will evaluate the appropriate evolution of the victim in the short and medium term.

h) will participate in primary, secondary and tertiary campaigns against child abuse and neglect

5. Nutrition

a) establishes the nutritional status of the abused child

b) supports the medical team with the solution of nutritional changes

c) guides the family about basic nutrition and hygiene concepts of food and cooking

6. The legal team

a) will verify that injuries are correctly reported to the appropriate authorities

b) will verify that all team members report the child abuse to the appropriate authorities

c) will provide guidance to the family about the result of the notification and whether they are able to retain guardianship of the child and parental authority (*patrias potestas*)

d) will watch the appropriate legal status of the victim in the short and medium term

e) will participate in primary, secondary and tertiary campaigns against child abuse and neglect

Teaching activity

The personnel at CAINM teach health care professionals and allied health personnel so that they acquire the ability to suspect, diagnose, care and follow-up children who have suffered any form of child abuse and neglect.

Purposes

Recognition by family doctors, pediatricians, and other specialists of the basic elements of child abuse and neglect through the development of congresses, symposia, workshops and clinical case discussions in different forums

Encourage the interest of pediatricians and other specialists regarding the subject so that they develop their abilities through the "Postgraduate Course for Specialist Doctors on Child Abuse and Neglect" by the CAINM

Encourage other interested specialists to participate in the Masters' Program in Public Mental

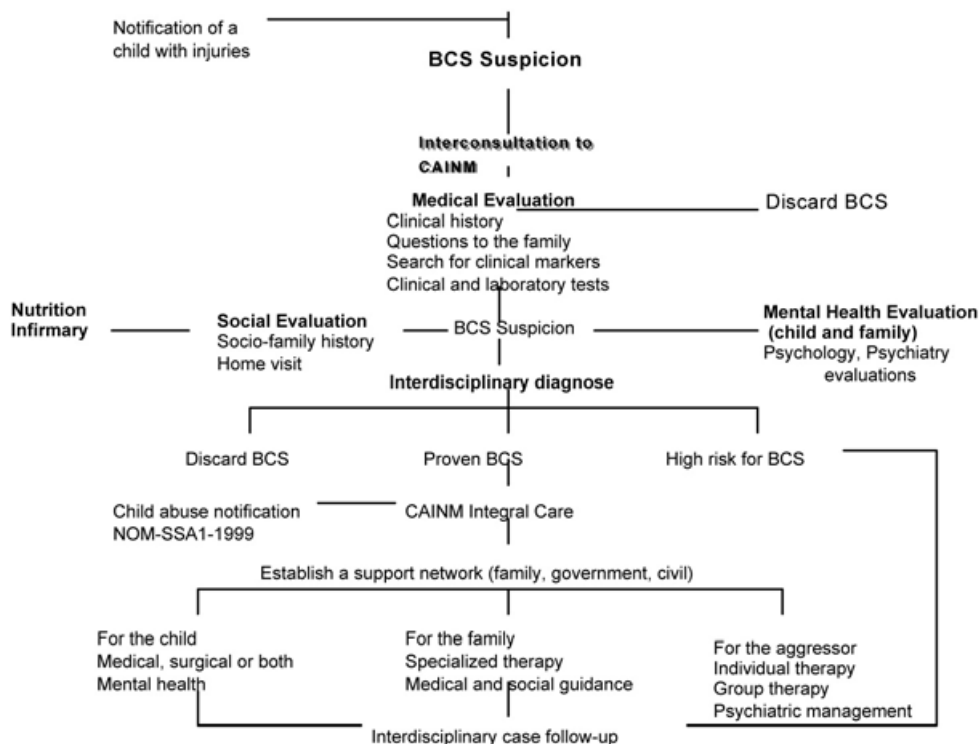


Figure 3. CAINM's algorithm for integral care of abused and neglected children and adolescents.

Health through courses available at the National Institute of Psychiatry and CAINM.

Study the Masters' Program in Behavioral Medicine developed by the UNAM Faculty of Psychology at the CAINM

Develop a distance learning program about child abuse and neglect in order to reach several states and other Spanish-speaking countries

Research activities

Because the subject of child abuse and neglect subject has several aspects and different expressions in urban, suburban and rural environments, different research programs should be developed and implemented so that their results are suitable for each scenario.

Purposes

The interested professional should learn the basic concepts about Research Methodology.

There should be implementation of concept-standardization projects.

There should be development of clinical research projects.

There should be development of projects in epidemiological research.

There should be development of basic science research projects.

Research results can be published in specialized medical and pediatric journals and books in order to inform the medical and allied health communities as well as society about this community problem.

Human resources

Ideally, this team should be comprised of pediatricians, mental health specialists (psychiatrist or psychologist), social workers and attorneys with a professional profile about the subject.

If the team cannot include those elements, its work will be constrained by the available resources and its actions will be limited.

Physical resources

Considering the importance of this team, it is necessary to plan and design a specific area with the extension, privacy and equipment required to develop this function.

- a) Care area with physician's offices, somatometry, a Gessel chamber
- b) Teaching area with meeting rooms, classrooms for

teaching and conferences

c) Private area for personal and group offices

d) Communications including internet, telephone, fax

e) Necessary materials to administer psychological tests

Financial resources

It is currently necessary to have economic resources in order to carry out various academic activities.

Purpose

Every professional participating in the team must receive a salary.

External financial support must be obtained to carry out research projects, assist at congresses and coordinate academic events.

The Ministry of Health or other governmental organization should provide scholarships to medical residents enrolled in the masters' and doctoral programs.

Agreements

Several agreements are necessary with the following agencies in order to reach a greater diffusion of the aforementioned actions.

- a) Ministries of Health, Education, Social Development, etc.
- b) State Governments
- c) National Institutes of Health
- d) State Pediatric Hospitals
- e) Community Health Centers
- f) Legal Institutions
- g) Foreign Institutions
- h) Others

In conclusion, the experience gained regarding child abuse and neglect during the last 10 years at the Mexican National Institute of Pediatrics and through the Clinic of Integral Care for the Abused and Neglected Child and the UNAM's Medicine Faculty (CAINM-INP-UNAM) allows us to highlight the development of actions in the medical, psychoemotional, social and legal environments for urban, suburban and rural areas in Mexico.

This experience has produced the following results:

- a) publication of 60 subject-related articles in pediatric and other specialty magazines
- b) four books
- c) postgraduate course for Specialist Physicians on Child

Abuse and Neglect (currently in its 9th generation)

d) collaboration in the Masters' Program in Health Care Sciences in the Public Mental Health area

e) clinical experience available for residents of Behavioral Medicine in the Masters' program in Psychology (Faculty of Psychology, UNAM)

f) coordination of academic events (congresses, symposia, workshops, conferences)

g) research beginning with child abuse and neglect and continuing to include clinical, epidemiological, social, psychological, legal and medical aspects (genetics and genomics)

h) care consisting of 120 internal medicine consultations per year, 40 confirmed cases during the same period and follow-up of 250 children and adolescents

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VITAL STATISTICS

Recent evolution of the behavior of diabetes mellitus in Mexico during childhood and adolescence (1990-2007)

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Analysis of the behavior of diabetes mellitus in childhood and adolescence is currently most important due to the extent that this condition represents a chronic degenerative disease that has increased over the last decade.

The evolution of such behavior should be reviewed from a double perspective: morbidity and mortality, which constitutes the purpose of this document. For the first case, data sources consulted were *The Annals of Morbidity of the General Directorate of Epidemiology*, which provides the figures on new cases registered. Number of deaths was obtained from national databases integrated by the National Institute of Statistics and Geography (INEGI). As a denominator for the construction of the corresponding rates, the Population Projections of CONAPO were used (version based on the 2005 census count). The period analyzed was from 1990 to 2007.

Morbidity

Available information closest to morbidity is the number of new cases recorded annually in Mexico for this disease. In general, according to the information system for epidemiological surveillance, cases recorded for the entire population between the years 1990 and 2007 have more than tripled, and this trend is particularly noteworthy among those >25 years of age.

Analysis within the age groups of children and teenagers shows some difficulties in interpretation for several reasons: 1) unequal management over time that has been given to these age groups and 2) problems of accuracy in the statistics of this disease due to its characteristics may imply significant levels of data underreporting (Table 1).

Despite the two previously stated issues, it is worth noting that throughout this period there has been relatively little increase for children <5 years of age, even though among children <1 year of age the figures have doubled. With respect to the group of children 5- to 14-years of age, a slow but gradual increase has been observed to the extent that in the year 2005 the figure almost doubled compared to what was recorded in 1990. In the group of adolescents 15- to 19-years of age, its evolution is significant, considering that only since the year 2000 the number of cases have multiplied nearly 5-fold in 2006, climbing from 411 to 1905 cases. The effects are shown in Figure 1.

With the goal of complementing the vision of the morbidity attributed to diabetes mellitus itself, we use the figures from the second-level medical care units regarding the frequency of hospitalizations that are generated within the National Health System (excluding the private sector due to lack of information).

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Vol. 66, May-June 2009

These figures are more solid and reliable than the case registry even when they relate to hospital events and not to number of patients. The trend shown between the years 2000 and 2007 evidences a growing figure that the population of those <20 years of age nearly doubled, increasing from 890 to 1652 discharges between those years. As expected, the number grows in proportion to the age group so that the cumulative total is just over 10,000, half corresponding to the group of adolescents between 15 and 19 years of age (Table 2).

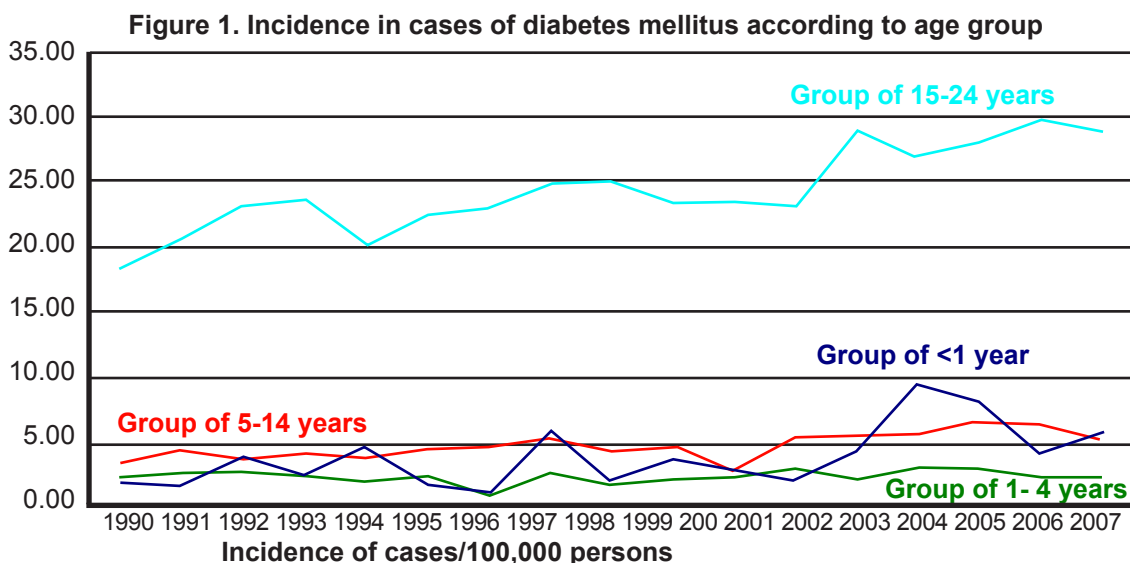
Mortality

As in many other diseases, advances in the field of health care have greatly benefited the population particularly in the early stages of life. The case for diabetes mellitus is no exception and the emergence of new medications has allowed for better disease control and, thus, a significant delay in the age at death. This is what may be inferred from the mortality figures included in Table 1 in which virtually all age groups (except the group of 15- to 19-year olds), the annual number of deaths dropped each year.

Table 1. New cases of diabetes mellitus reported according to age groups (Mexico: 1900-2007)

Year	Age groups						Total
	<1	1-4	5-9 10-14	15-19 20-24	25 and older		
1990	45	187	712	3317	129,195	133,456	
1991	41	222	911	3758	163,723	168,655	
1992	83	237	805	4320	176,058	181,503	
1993	61	220	860	4462	200,242	205,845	
1994	95	178	798	3860	179,199	184,130	
1995	42	206	950	4320	266,790	272,308	
1996	19	69	1000	4462	244,224	249,774	
1997	127	227	1114	4795	306,599	312,862	
1998	38	148	936	4839	331,006	336,967	
1999	82	198	1001	4562	278,968	284,811	
2000	64	182	192	421	411	4189	285,666
2001	49	237	374	750	998	3571	293,372
2003	88	193	353	807	1543	4166	386,694
2004	192	259	289	881	1372	4010	410,575
2005	166	231	417	976	1632	3943	403,386
2006	80	178	368	1008	1905	4089	401,952
2007	105	159	314	797	1770	4042	412,697

Source: Anuarios de Morbilidad, Dirección General de Epidemiología.
Data from 2008 unavailable. Between 1990 and 1999, breakdown was done by age group.



As can be seen, in relative terms the weight of mortality in the early stages of life with regard to the total deaths in the total population is low, although we do not minimize these unfortunate deaths. To present an idea of the magnitude, it is sufficient to mention that deaths attributed to diabetes mellitus (810,473) throughout the analyzed period and corresponding to persons <20 years of age (2294) represent 0.28% of the total deaths registered due to diabetes mellitus by age group (Table 3) (1990-2007).

Table 2. Number of hospital admissions* for diabetes mellitus in patients <20 years old (2000-2007)

Age groups	2000	2001	2002	2003	2004	2005	2006	2007
<1 year	6	3	7	10	13	17	21	14
1-4 years	45	54	69	75	82	87	70	113
5-9 years	108	136	154	167	173	214	210	233
10-14 years	255	299	387	421	411	461	463	537
15-19 years	476	540	609	629	658	607	728	755
Total general	890	1,032	1,226	1,302	1,337	1,386	1,492	1,652

Source: SSA/DGIS (National System of Statistics in Health).

*Admissions reported for all public health institutions in Mexico.

Table 3. Deaths reported for diabetes mellitus according to age groups (1990-2007)

Year	Age groups							Total
	<1 year	1-4	5-9	10-14	15-19	<20 years	20 years and older	
1990	9	28	20	27	63	147	25,586	25,733
1991	11	23	28	29	57	148	26,945	27,093
1992	5	6	17	33	79	140	28,103	28,243
1993	8	18	12	27	73	138	29,366	29,504
1994	6	8	13	23	63	113	30,136	30,249
1995	4	14	18	22	77	135	33,094	33,229
1996	3	21	16	28	68	136	34,643	34,779
1997	2	11	9	23	71	116	35,814	35,930
1998	3	9	11	27	58	108	41,636	41,744
1999	5	12	10	20	60	107	45,440	45,547
2000	5	10	13	31	77	136	46,389	46,525
2001	4	12	10	31	70	127	49,728	49,855
2002	5	13	15	27	71	131	54,697	54,828
2003	4	9	12	29	67	121	58,998	59,119
2004	1	8	15	22	77	123	62,078	62,201
2005	2	10	13	33	71	129	66,961	67,090
2006	4	7	13	24	74	122	68,231	68,353
2007	4	9	5	19	80	117	70,334	70,451
	85	228	250	475	1,256	2,294	808,179	810,473

Source: Death statistics (INEGI/SSA).