VOLUM 29 NÚM. 3 SETEMBRE - DESEMBRE 2014

MEDICINA · BALEAR

PUBLICACIÓ DE LA REIAL ACADÈMIA DE MEDICINA DE LES ILLES BALEARS

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Consumo de alcohol y riesgo de accidentes de tráfico. Aspectos preventivos

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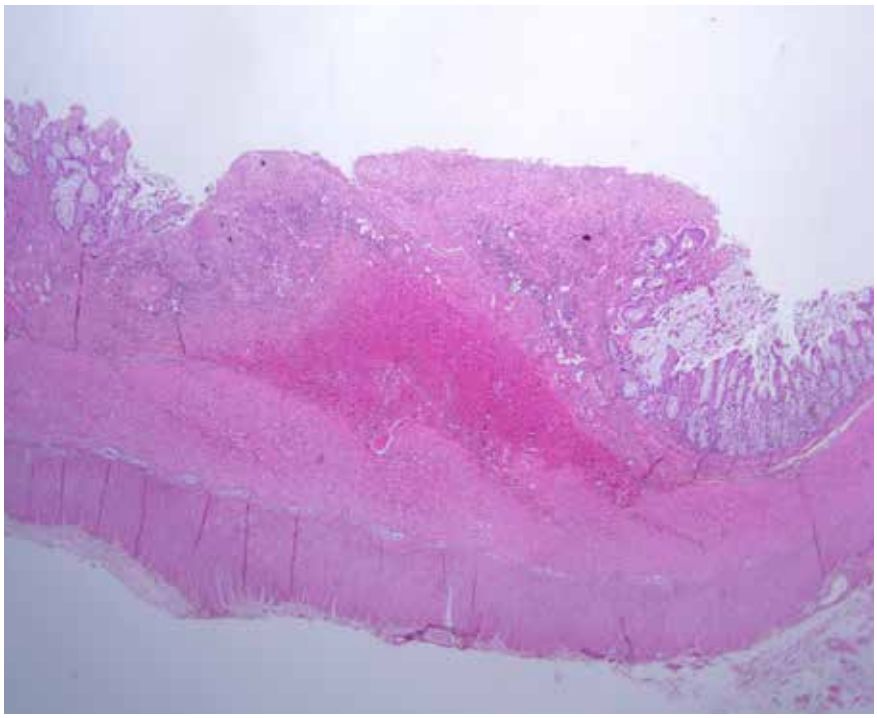

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EDITORIAL

Un bicentenari digne de commemoració: la "Toxicologie générale" de 1814

A bicentennial worthy to be commemorated: The 1814 edition of "Toxicologie générale"

Miquel Àngel Limon Pons

Doctor en periodisme. Acadèmic corresponent de la Reial Acadèmia de Medicina de les Illes Balears

Una efemèrides gens banal es commemora dins l'any 2014. Té el doble caràcter d'efemèrides de la història de la Medicina i, alhora, dels annals bibliogràfics de matèria científica que es relacionen amb les Illes Balears, i fins amb la vida de la nostra Reial Acadèmia de Medicina.

El 1814, un ambiciós i intel·ligent químic i metge instal·lat a París, en el melic de la ciència i la universitat mundials d'aleshores, presentava a les principals autoritats acadèmiques del país el manuscrit d'una obra que havia de ser cridada a reformar i refundar una branca científica que encara llavors es movia en la mera especulació i les contradiccions. Era la Toxicologia, una de les múltiples àrees de coneixement de les ciències de la salut que encara no havien conegut el salt a la investigació sistemàtica, a l'experimentació de laboratori i a la reformulació dels principis fonamentals de la mateixa.

Mateu Orfila, cap als 30 anys d'edat

Qui havia de ser autor d'una semblant capgirada a favor d'una especialitat científica nomia Mateu Orfila Rotger (1787-1853), segurament el primer menorquí en assolir una personalitat intel·lectual i científica moderna; d'altra banda, membre corresponent de la nostra docta corporació mèdica de les Balears.

Tot s'havia endegat aquells dies en què Orfila, de París estant, se sostenia impartint privadament cursos de química, de botànica, d'anatomia i de medicina legal. Ho feia en un petit laboratori privat, gairebé casolà, del carrer de Foin de Saint-Jacques. Amb major o menor dedicació, ho va mantenir durant tres o quatre anys, si més no fins l'1 de març de 1819 en què rebé el seu cobejat ingrés als cenacles universitaris, ara ja amb la condició de professor titular de la Sorbona.

Un dia d'abril de 1813 succeí que Orfila explicava al seu auditori una lliçó sobre les propietats de l'àcid arseniós. Com li agradava de fer, relacionava les propietats i descrivia les reaccions i precipitacions que una solució d'aquesta substància donava per l'acció de diferents reactius. Ell hi mantenia, però, les explicacions llibresques que la tradició anterior a ell oferia al respecte. Per casualitat, en aquells moments, durant una classe, Orfila hi disposava d'una escudelleta de cafè. I així, se li va ocórrer d'afegir-hi una mica de la solució arsenical al beuratge. Aleshores, ell esperava que les reaccions fossin les mateixes que es donaven quan es feia amb solucions aquoses. Però no. En les barreges de cafè i dissolució arsenical, cap de les reaccions tòpiques no es complien com en aigua. En paraules del mateix Orfila a la seva autobiografia, «em vaig procurar brou, llet, vi, infusions diverses…; en un mot, molts dels líquids que s'empren sovint en l'economia domèstica. El nombre d'experiments que vaig fer amb aquestes substàncies

fou molt gros; i tots em demostraren que els verins, si no tots, en la seva major part, no podien ésser reconeguts seguint els mètodes usuals quan es troben barrejats amb líquids d'origen animal o vegetal […]».

Regirant, de seguida, a les principals biblioteques científiques de París, i llegint i rellegint tot el que d'important s'havia escrit fins llavors sobre toxicologia, portaren Orfila a concloure així: «Idò, la toxicologia no existeix». En efecte, amb base i experimentació científica moderna i sistemàtica no existia encara. Tot era per fer. Acte seguit, el jove científic es lliurà a la investigació sobre un semblant cúmul d'interrogants, de dubtes i d'ardor investigadora. Reclòs a una casa de camp a Villeneuve-le-Roi, endegaria una febril experimentació al llarg de tot l'estiu de 1813. Un a un, feia proves i més proves amb verins i líquids de tota mena de procedència. En els quaderns de notes, hi anotava els processos i hi registrava els resultats. El rigor i la sistemàtica ho presidí tot amb absoluta escrupolositat metòdica. Fou així que durant l'hivern de 1813 i la primavera de 1814 ja es va considerar en òptimes condicions d'oferir a l'editor de la Facultat de Medicina de París, M. Crochard, un primer volum de l'obra que anomenà *Traité des poisons tirés des regnes minéral, vegetal et animal ou toxicologie générale*. L'any 1815, li feia a mans el segon i darrer tom del treball que havia de marcar fita en els annals de la ciència europea internacional. Orfila, amb ella, acabava d'establir els fonaments de la toxicologia científica moderna. Hi havia rebut, a més, la sanció elogiosa de l'Institut de França, de manera que el treball va assolir un èxit fenomenal i fulgurant en tots els principals nuclis acadèmics i científics d'Europa. En vida d'Orfila, se'n ferien cinc edicions en llengua francesa; i les traduccions a l'anglès i l'alemany són del mateix 1814. L'any 1821, finalment, el traduí al castellà el Dr. Larra, l'insigne i poc recorregut intel·lectual espanyol afrancesat, pare del periodista romàntic Mariano José de Larra, *Fígaro*.


TRAITÉ
DES POISONS
TIRÉS
DES RÈGNES MINÉRAL, VÉGÉTAL ET ANIMAL
OU
TOXICOLOGIE GÉNÉRALE
Considérée sous les rapports de la Physiologie, de la Pathologie et de la Médecine légale;
PAR M. P. ORFILA,
Naturaliste pensionnaire d'Espagne, Docteur en Médecine de la Faculté de Paris, Professeur de Chimie et de Physique;
TOME PREMIER — Ire PARTIE.
A PARIS,
Chez CROCHARD, Libraire, rue de l'École-de-Médecine, n°. 3.
1814.

Portada de la primera edició de la "Toxicologie générale"

Les novetats científiques que la recerca d'Orfila aportava eren múltiples. Direm, tanmateix, que, abans de la publicació de l'obra, els verins eren cercats en els conductes digestius de la persona que n'havia ingerit alguna dosi. Orfila, però, lluny de limitar-se a aquesta localització, investigà la presència dels tòxics en altres òrgans, com ara el fetge o el cervell. Hi aplicava procediments nous per a descobrir-los, i el seu ús metòdic havia de permetre de revelar-ne mínimes quantitats. A París, es féu proverbial que la investigació essencial del Dr. Orfila li havia comportat el sacrifici de més de 4000 cans, als quals havia aplicat els tòxics i les dosis per després analitzar els òrgans interns de l'animal. En definitiva, aquella era una nova toxicologia: una toxicologia científica i moderna, arrels bàsiques de la toxicologia forense actual. Com ell mateix curà d'escriure en el pròleg de la primera edició, «un gran nombre de fets que han de servir de fonament a la toxicologia eren abans desconeguts o mal estudiats».

En paraules de Josep Sureda i Blanes, va ser així que Orfila entrà en el camí que el portaria «a la glòria científica del seu temps». I a guanyar-se per a si —afegim— un grau d'immortalitat permanent en la història de la ciències modernes amb evident abast internacional, orgull avui de les Illes Balears.

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ORIGINAL

Usefulness of Bayesian networks in epidemiological studies

Utilidad de la redes bayesianas en los estudios epidemiológicos

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Abstract

Introduction: Bayesian networks are a form of statistical modelling, which has been widely used in fields like clinical decision, systems biology, human immunodeficiency virus (HIV) and influenza research, analyses of complex disease systems, interactions between multiple diseases and, also, in diagnostic diseases. The present study aimed to show the usefulness of Bayesian networks (BNs) in epidemiological studies.
Material and Methods: 3,993 subjects (men 1,758, women 2,235) belonging to the public productive sector from the Balearic Islands (Spain), which were active workers, constitute the data set.
Results: A BN was built from a dataset composed of twelve relevant features in cardiovascular disease epidemiology. Furthermore, the structure and parameters were learnt with GeNIe 2.0 tool. Taking into account the main topological properties some features were optimized, obtaining a hypothesized scenario where the likelihoods of the different features were updated and the adequate conclusions were established.
Conclusions: Bayesian networks allow us to obtain a hypothetical scenario where the probabilities of the different features are updated according to the evidence that is introduced. This fact makes Bayesian networks a very attractive tool.

Keywords: Bayesian networks, model averaging, cardiovascular lost years, cardiovascular risk score

Resumen

Introducción: Las redes Bayesianas son una forma de modelización estadística, las cuales han sido ampliamente utilizadas en campos como la decisión clínica, biología de sistemas, virus de inmunodeficiencia humana (VIH) e investigación en influenza, análisis de sistemas de enfermedades complejos, interacciones entre múltiples enfermedades y, también, en enfermedades de diagnóstico. Este estudio tiene como objetivo mostrar la utilidad de las redes Bayesianas en estudios epidemiológicos.
Material y Métodos: 3,993 individuos (hombres 1,758, mujeres 2,235) pertenecientes al sector productivo público de las Islas Baleares (España), los cuales eran trabajadores activos, constituyen la base de datos.
Resultados: Una red Bayesiana se ha obtenido a partir de una base de datos compuesta de doce características relevantes de la epidemiología de la enfermedad cardiovascular. Por otra parte, la estructura y los parámetros se han obtenido con la herramienta Genie 2.0. Teniendo en cuenta las principales propiedades topológicas algunas características fueron optimizadas.
Conclusiones: Las redes Bayesianas permiten obtener un escenario hipotético donde las probabilidades de las diferentes características se van actualizando de acuerdo con la evidencia introducida. Este hecho hace de las redes Bayesianas una herramienta muy atractiva, además permite establecer diversas conclusiones.

Palabras clave: Redes bayesianas, modelo promediado, años cardiovasculares perdidos, escala de riesgo cardiovascular

Introduction

Bayesian networks (BNs)[16, 25] also referred to as causal networks or beliefs networks, are a form of statistical modelling which allow us to obtain a graphical network describing the dependencies and conditional independencies from empirical data. They have proven to be a promising tool for discovering relationships[9], they capture the way an expert understands the relationships among all the features [6] and, even, they have been used in data analysis [8]. The origins of BN modelling lie within the data mining and machine learning literature[5, 13]. BNs are a kind of probabilistic graphical model (PGM)[18], which combine graph theory (to help in the representation and resolution of complex problems) and probability theory (as a way of representing uncertainty). A PGM is defined as a graph where nodes represent random variables[4, 12] and arcs represent dependencies between such variables[11, 24]. A PGM is called a BN when the graph connecting its variables is a directed acyclic graph (DAG). The graphical representation of BNs captures the compositional structure of the relations and the general aspects of all probability distributions factorized according to that structure[12].

BN modelling is widely used in fields like clinical decision[23], systems biology[7, 13], human immunodeficiency virus (HIV) and influenza research[21, 26], analyses of complex disease systems[14, 19, 20], interactions between multiple diseases[17] and, also, in diagnostic diseases[1, 2, 3, 22, 27].

The aim of the present study was to show the usefulness of Bayesian networks (BNs) in epidemiological studies focused in cardiovascular risk factors.

Theoretical Background

Let us consider a probabilistic model **M**, consisting of a set **V** of discrete random variables (features) and a joint probability distribution **P**. Let **D** (it is the graphical structure of the causal network) be a directed acyclic graph (DAG), whose set of vertices has a one to one correspondence with the variables of **M**. Two random variables X and Y in a causal network are *d-separated* if for all the paths between X and Y, there is an intermediate variable Z such that either i) the connection is serial (X→Z→Y or X←Z←Y) or diverging (X←Z→Y) and Z is instantiated or ii) the connection is converging (X→Z←Y), and neither Z nor any of Z's descendants have received evidence[15]. **D** is said to be an I-map of **M** if every d-separation condition in **D** corresponds to a conditional independence relationship in **M**. **D** is a minimal I-map of **M** if none of its arrows can be remove without destroying its –I-mapness. A BN of the probabilistic model is defined as a DAG **D** that is a minimal I-map of **M**. The joint probability distribution factorized as a product of several conditional distributions and denotes the dependency/independency structure by a DAG, which is called the *chain rule for BNs*:

$$P(X_1,\ldots,X_n)=\prod_{I=1}^{n} P(X_i \mid Pa(X_i))$$

The independencies from the graph are easily translated into the probabilistic model.

The *local Markov condition* and the global *Markov property* are important characteristics of the network topology when the BN is used to make inferences (that is to predict new scenarios when new information is introduced). The *local Markov condition* establishes that each feature is conditionally independent of the set of all its non-descendants given the set of all its parents. The *global Markov property* states that any node is conditionally independent of any other node given its *Markov blanket* (which includes its parents, its children, and the other children's parents (spouses). Any node in the BN would be *d-separated* from the nodes belonging to the *non-Markov blanket* given its *Markov blanket*.

Learning Bayesian networks

Learning BNs from a dataset has become an increasingly active area of research. Although, sometimes experts can create good BNs from their own experience, it can be a very tedious task for domains with large knowledge bases. Many methods (learning algorithms) from machine learning community have been developed to automate the creation of BNs using cases collected from past experience.

To obtain a BN, it is necessary to determine a structure (defined by a DAG) and the conditional probabilities assigned to each node of the DAG. Therefore, to learn a BN involves two tasks: I) structural learning, that is, the identification of the topology of the BN, and II) parametric learning, that is the estimation of numerical parameters (conditional probabilities) for a network topology.

Bayesian network structure learning

Basically, there are two approaches to structure learning: I) *search-and-score* structure learning, and *constraint-based* structure learning. Search and score search algorithms assigns a number (score) to each Bayesian network structure, and we look for the model structure with the highest score. Constraint based search algorithms establish a set of conditional independence analysis on the data. Based on this analysis an undirected graph is generated. Using additional independence test, the network is converted into a BN.

Bayesian network parameter learning

In a BN the conditional probability distributions are called the parameters, obtaining a conditional probability distribution for each node of the network topology.

Materials and Methods

Participants

Participants were active workers belonging to the public productive sector from the Balearic Islands (Spain). Subjects were invited to participate in the study during their annual work health assessment. Any worker attending the work health assessment could be included in the study. 4,300 workers were invited to participate. Among them, 3,993 subjects (men 1,758, women 2,235) agreed to participate. Participants signed informed consent prior to enrolment in the study. After acceptance, a complete family and personal medical history was recorded. The study design was in accordance with the Declaration of Helsinki and received approval from the Balearic Islands Clinical Research Ethical Committee.

Epidemiological model

From the dataset, and using GeNIe 2.0 tool [10], a BN structure was inferred. A Bayesian search algorithm was selected to obtain a DAG, which is a search-and-score algorithm. **Figure 1** shows the obtained structure.

Once the structure is obtained the parameters could be calculated. The EM (expectation-maximization) algorithm, which is an iterative method for finding maximum likelihood or maximum a posteriori (MAP) estimates of parameters in statistical models, was used to determine the parameters. A distribution probability was obtained for each node (feature) in the DAG. The resulting BN is shown in **Figure 2**.

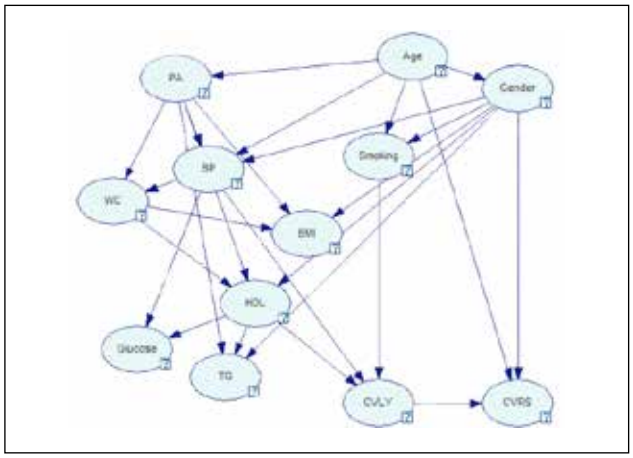


Figure 1: Structure of a BN obtained performing a Bayesian search algorithm. From the DAG it can be observed how the different features are connected.

Results and Discussion

BNs are used to make inferences [4], that is, to obtain new likelihoods of features when new information is introduced. To show it, two patterns of reasoning were selected: *causal reasoning* (from top to bottom), and *intercausal* reasoning which is close to human reasoning. In this last case the concept of *Markov blanket* was considered.

BN Inference: Causal reasoning pattern

We use this pattern when we reason from top to bottom. To illustrate this sort of reasoning we have selected four examples comparing the likelihood variations in men and women groups.

In **Figure 3** Physical Activity feature is instantiated to the "no practice" value (PA = no practice), Smoking feature is instantiated to the "yes value" (Smoking = yes), and Gender feature is instantiated to the "men value". Then, it can be observed how the likelihoods of the different features change. Likelihood of Blood Pressure (BP) feature in optimal state decreased from 0.47 to 0.18; and increased states such as HTA severe, mild and moderate, from 0.01, 0.16, and 0.05 to 0.03, 0.28, and 0.11 respectively. BMI feature in Obesity TI and Overweight GII states increased its likelihoods from 0.13 and 0.19 to 0.29 and 0.32 respectively.

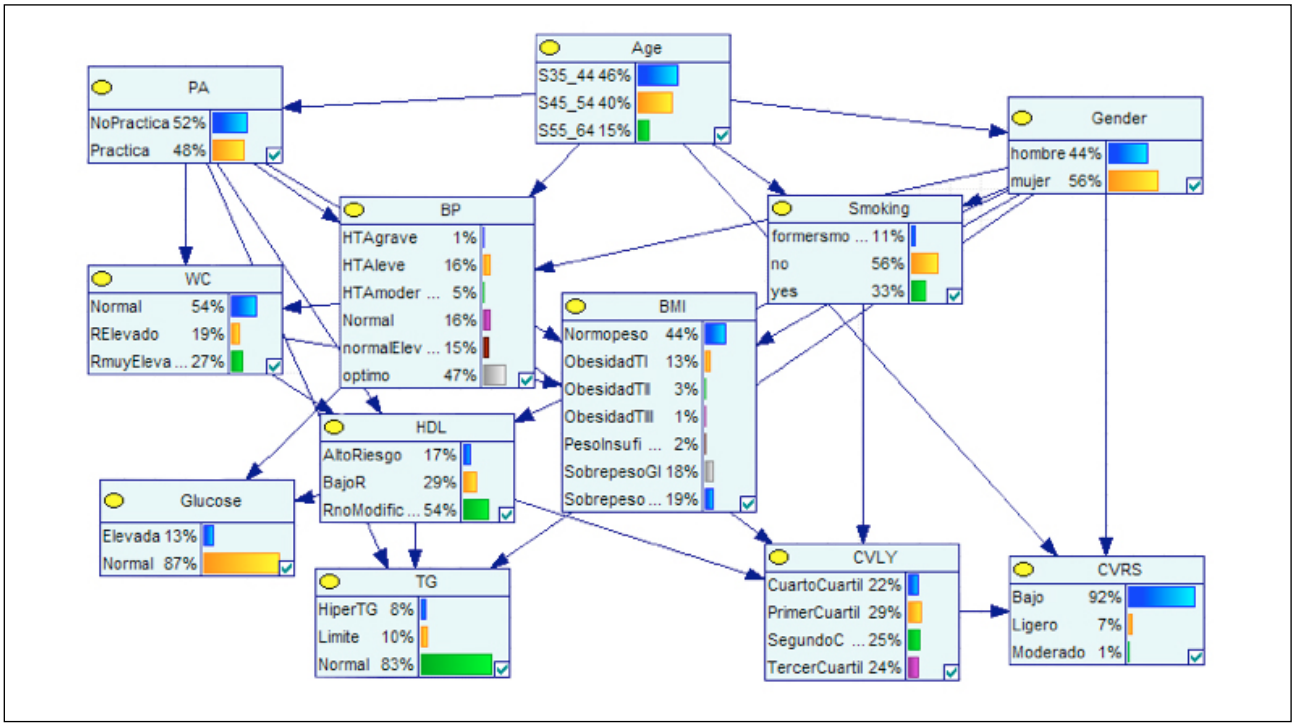


Figure 2: BN model obtained for cardiovascular disease risk factors. From the BN likelihoods this sample shows normal triglycerides (TG), normal glucose, normal cardiovascular risk score (CVRS) and normal waist circumference (WC).

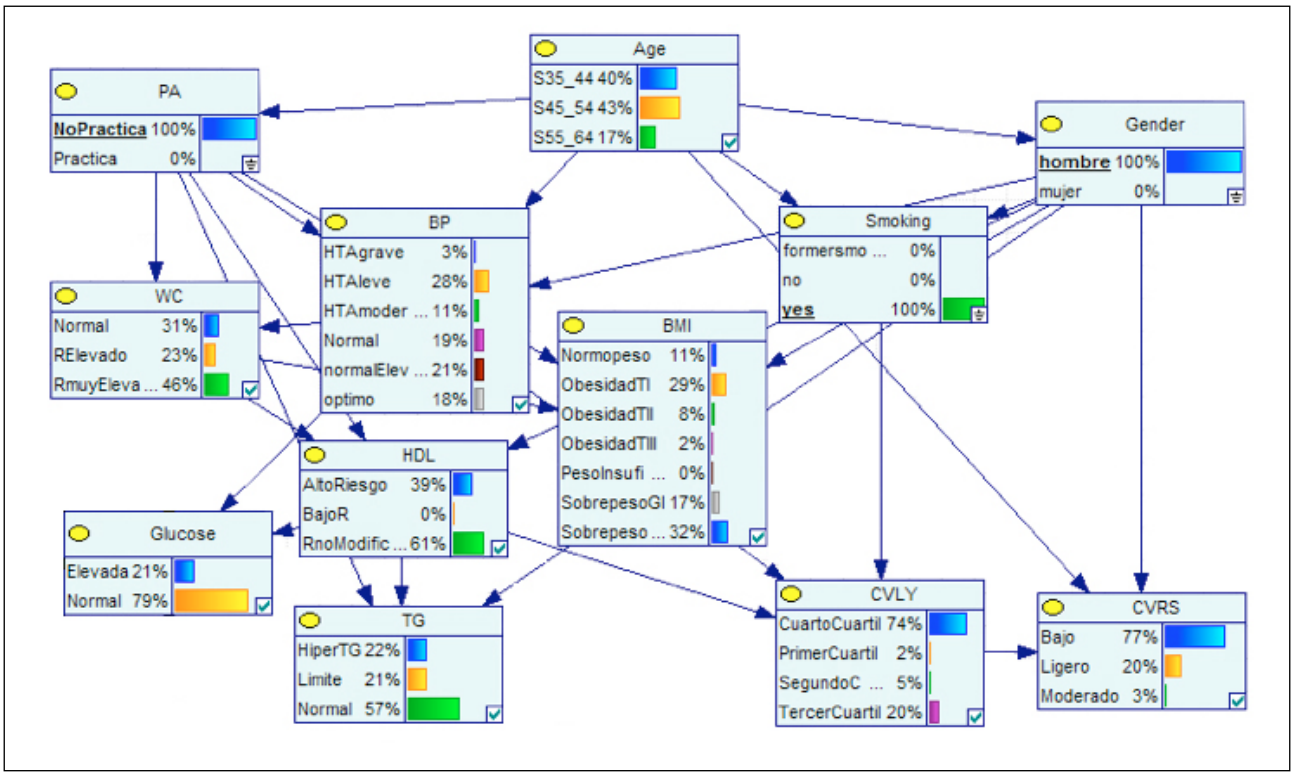


Figure 3: BN where the following evidence is introduced: physical activity (PA) = no practice, Smoking = yes, and Gender = men.

Triglycerides (TG) in normal state decreased its likelihood from 0.83 to 0.57. Glucose in normal state decreased its likelihood from 0.87 to 0.79. Cardiovascular lost years feature (CVLY) increased its fourth quartile from 0.22 to 0.74.

To compare the likelihoods variations within the group of women, we selected women state in the Gender feature. The likelihood variations are shown in **Figure 4**.

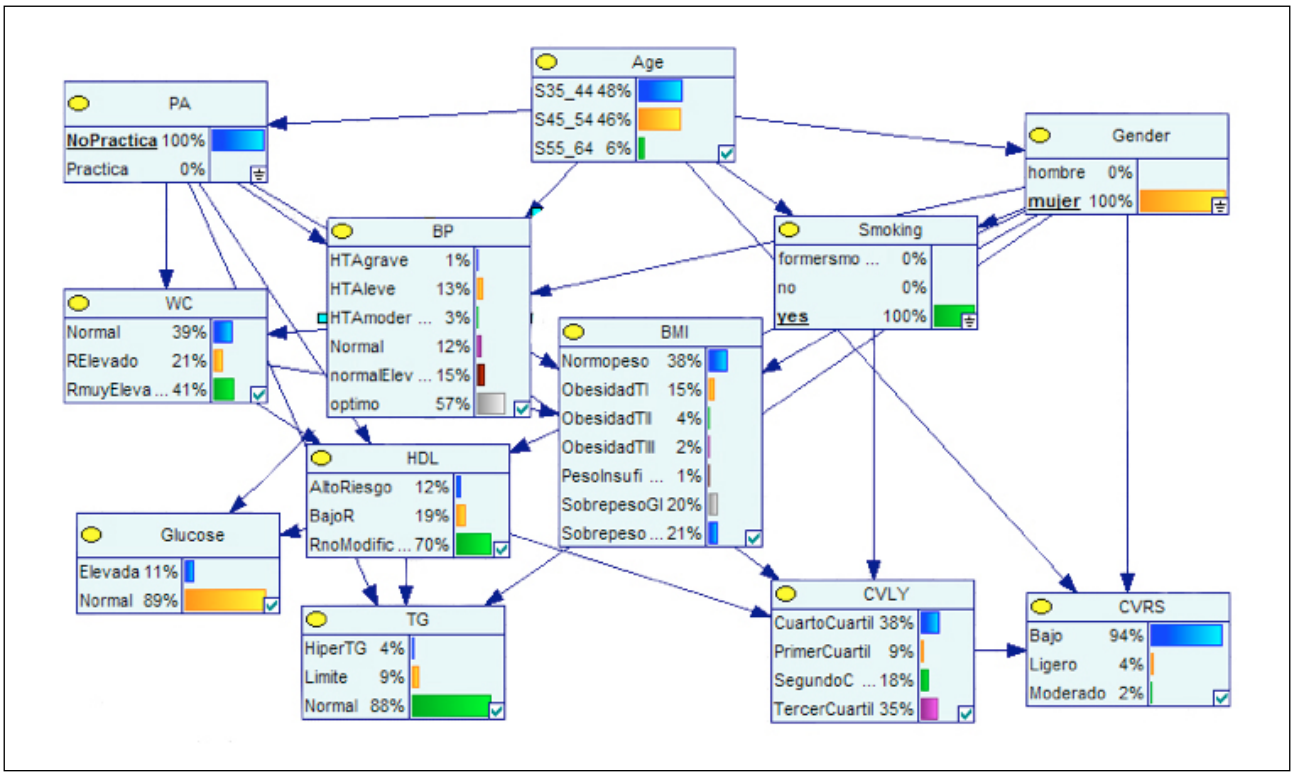


Figure 4: BN considering the following evidence is introduced: physical activity PA = no practice, Smoking = yes, and Gender =women.

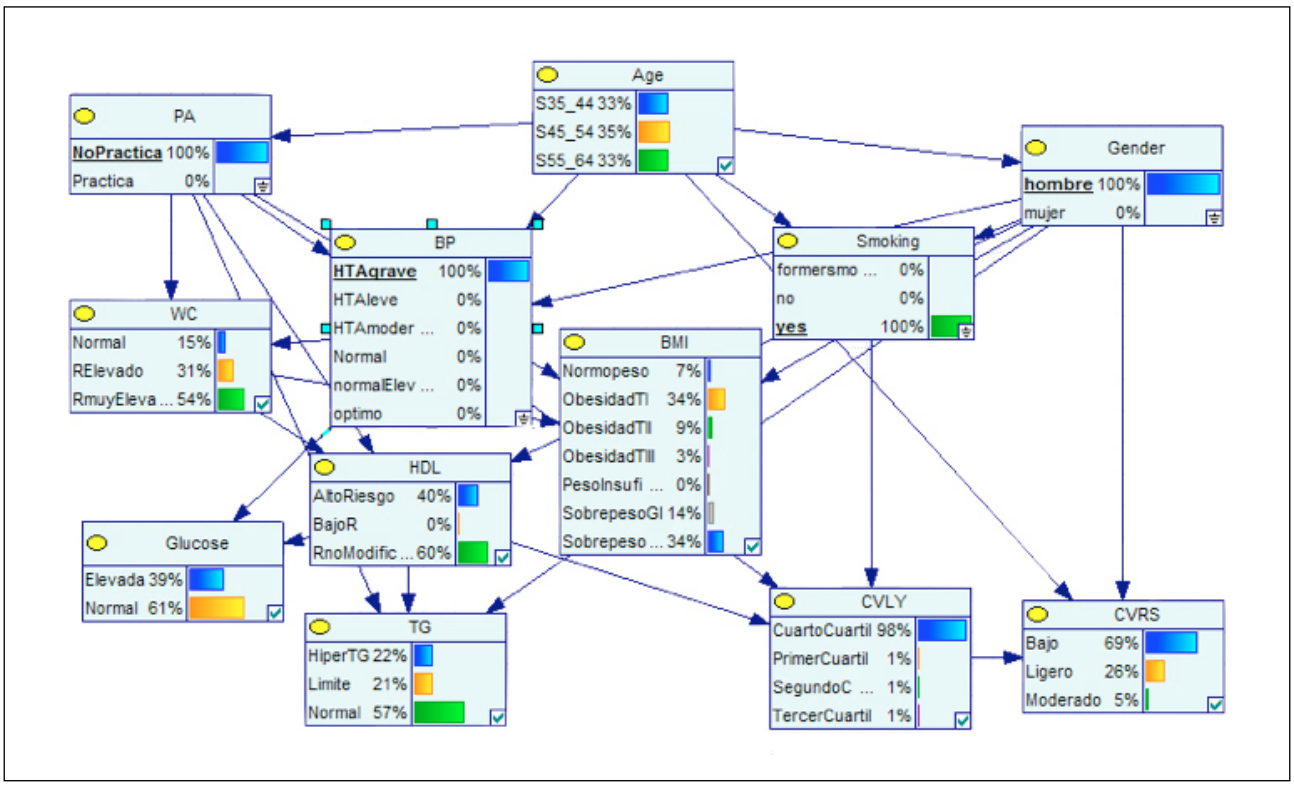


Figure 5: BN considering the following evidence: physical activity PA = no practice, Smoking = yes, Gender = men, and BP = severe.

Likelihood of Blood Pressure (BP) feature in optimal state increased from 0.47 to 0.57; and decreased states such as HTA mild and moderate, from 0.16 and 0.05 to 0.13 and 0.03 respectively; but also normal state decreased from 0.16 to 0.12. BMI feature in Obesity TI and Overweight GII states increased its likelihoods from 0.13 and 0.19 to 0.15 and 0.21 respectively, being higher in men than in women.

Triglycerides (TG) in normal state increased its likelihood from 0.83 to 0.88. Glucose in normal state decreased its likelihood from 0.87 to 0.89. Cardiovascular lost years feature (CVLY) increased its fourth quartile from 0.22 to 0.36; and its third quartile from 0.24 to 0.35. Results indicated that men were at increased cardiovascular disease risk compared to women under conditions of smoking and no practice of physical activity.
We also considered another hypothetical situation characterized by a severe hypertension (BP). The likelihood changes are shown in **Figure 5**.

Cardiovascular lost years feature (CVLY) increased its likelihood in fourth quartile from 0.22 to 0.96 and Cardiovascular risk score (CVRS) decreased its low state from 0.92 to 0.69. On the other hand, results obtained in women when blood pressure was instantiated to the highest value are shown in **Figure 6**.

In this last situation, Cardiovascular lost years feature (CVLY) increased its likelihood in fourth quartile from 0.22 to 0.83. And Cardiovascular risk score (CVRS) preserved its low state in 0.92. Taking into account these results, men were revealed again as the gender with higher cardiovascular disease risk.

BN Inference: Intercausal reasoning pattern

We refer to intercausal reasoning, which constitutes a very common pattern in human reasoning, when different causes of the same effect can interact. Using this reasoning pattern, the following two examples were considered: maximizing CVLY in first quartile state and maximizing CVLY in fourth quartile state.

To illustrate this way of reasoning the following features from the Markov blanket of CVLY were considered: CVRS, BP, HDL and Smoking. **Figure 7** shows the likelihood variation when Smoking feature is instantiated to non-smoker, Cardiovascular risk score (CVRS) is instantiated to low value, Blood pressure (BP) is instantiated to optimal value and HDL is instantiated to low value.

Under these instantiations the following changes can be observed: Gender in women state increases from 0.56 to 0.90, showing that under this situation the likelihood of being a woman is higher. Age in 35-44 state increased its likelihood from 0.46 to 0.59. The likelihood of practising physical activity increased from 0.48 to 0.83. BMI in normal weight state increased from 0.44 to 0.68.

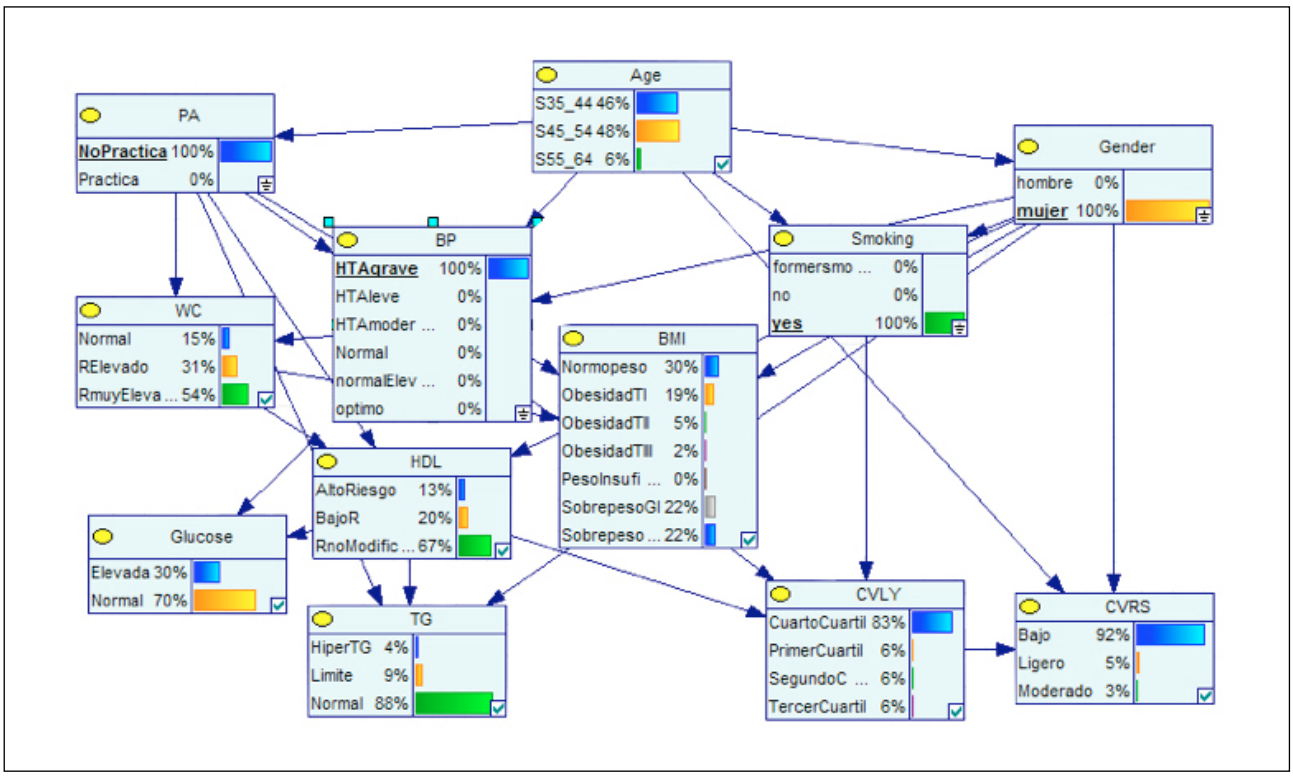
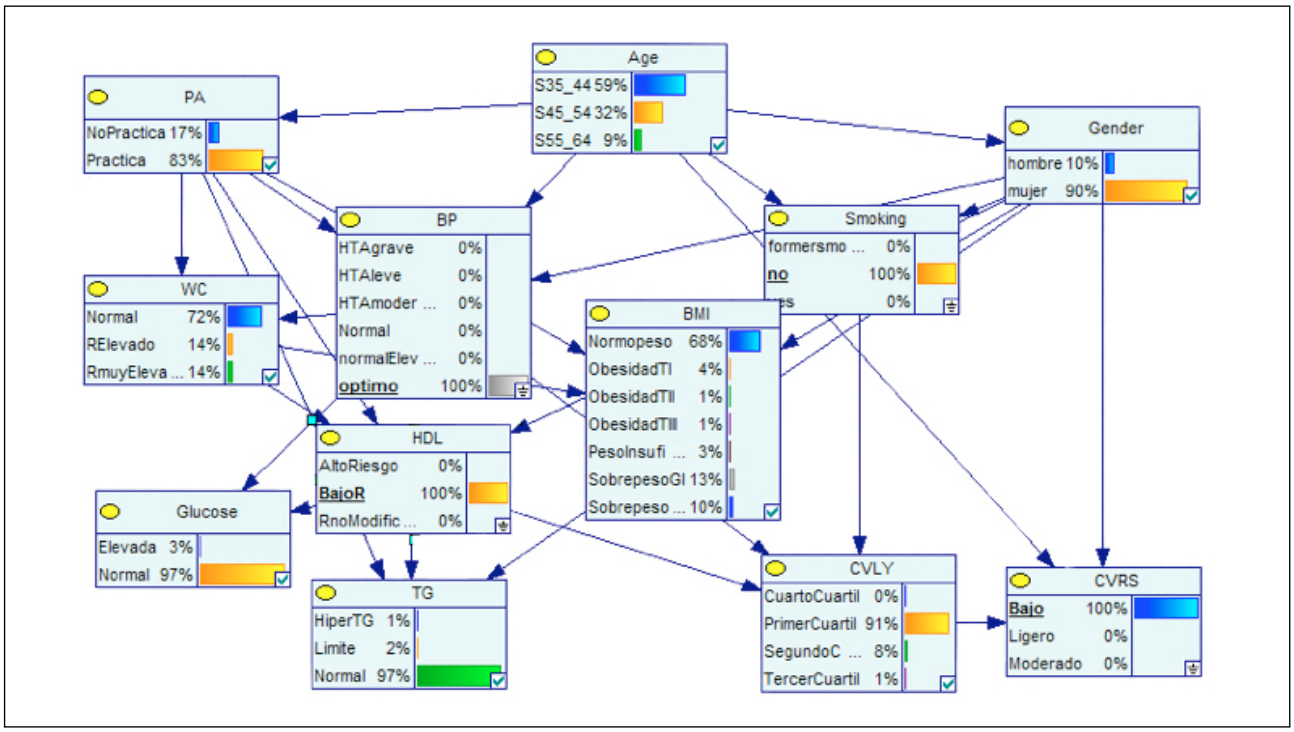


Figure 6: BN where the following evidence is introduced: physical activity PA = no practice, Smoking = yes, Gender =women, and BP = severe.



Triglycerides in normal value increased its likelihood from 0.83 to 0.97. Glucose in normal value increased its likelihood from 0.87 to 0.97. Waist circumference in normal value increased its likelihood from 0.54 to 0.72, and Cardiovascular lost years in first quartile value increased its likelihood from 0.29 to 0.91.

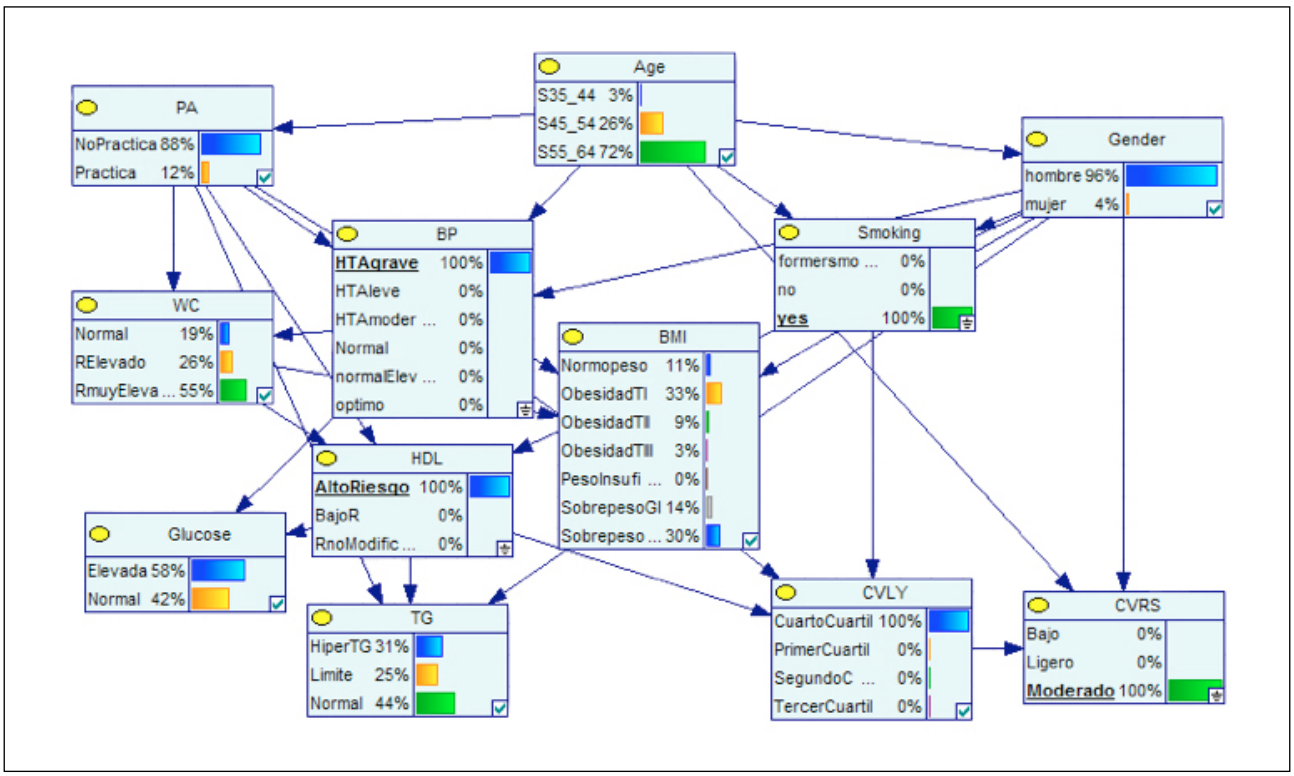


Figure 8: BN with the following evidences: Smoking = yes, CVRS = Moderate, BP = Severe, and HDL = High.

Then, to compare with this last example, Smoking feature was instantiated to the yes value, Cardiovascular risk score (CVRS) was instantiated to moderate value, Blood pressure (BP) was instantiated to severe value and HDL was instantiated to high value. The likelihood variations are shown in **Figure 8**.

Under these instantiations the likelihoods changes are as follows: Gender in men state increased from 0.44 to 0.96, showing that under this situation the likelihood of being a man is higher. Age in 56-64 state increased its likelihood from 0.15 to 0.72. Physical activity in no practice state increased its likelihood from 0.44 to 0.96. BMI in obesity TI state increased its value from 0.13 to 0.33; and in overweight GII increased its likelihood from 0.19 to 0.30. Triglycerides in normal value decreased its likelihood from 0.83 to 0.44. Glucose in high value increased its likelihood from 0.13 to 0.58. Waist circumference in very high value increased its likelihood from 0.27 to 0.55, and Cardiovascular lost years in fourth quartile value increased its likelihood from 0.22 to 1.00.

Conclusions

Using a BN model the relationships between features can be determined in a graphical and appealing way. The BN structure allows us to differentiate between direct and indirect relationships. Furthermore, the BN was used to make inferences, i.e., to predict new scenarios when hypothetically new information was introduced. Two reasoning patterns were considered: causal and inter-causal reasoning to show the likelihood variations. Because cardiovascular diseases are multi-factorial, application of this Bayesian networks could be of special interest.

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ORIGINAL

Consumo de alcohol y riesgo de accidentes de tráfico en España. Aspectos preventivos

Alcohol and traffic accidents risk in Spain. Preventive aspects

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Resumen

Introducción: Las bebidas alcohólicas se consumen ampliamente en todo el mundo y también en España. Aunque la mayoría de la población adulta tiene un patrón de consumo de bajo riesgo, existen personas que presentan patrones lesivos de consumo que van desde el bebedor diario de gran cantidad, al consumo de riesgo ocasional/social. Esta situación genera problemas de seguridad vial en casi todos los países asociados a cambios en el rendimiento psicomotor del consumidor con posterior repercusión en riesgo de accidentes.
Método: Para realizar esta revisión se han consultado la base de datos de la Organización Mundial de la Salud: *World Health Organization. Global Information System on Alcohol and Health (GISAH) y los resultados del estudio EDADES*. Se ha hecho una búsqueda bibliográfica en PubMed y otras bases de datos de referencia (Latindex, Scopus, Índice Bibliográfico Español en Ciencias de la Salud –IBECS sobre los términos de búsqueda: alcohol consumption and road traffic injuries, seleccionándose a criterio de los autores aquellos trabajos considerados más significativos).
Conclusiones: Se trata de un complejo problema con repercusión individual en los afectados y trascendencia socioeconómica y en la que destaca la especial implicación en sus efectos de las personas más jóvenes, lo que requiere de un esfuerzo preventivo conjunto sanitario, social y de las Administraciones Públicas para obtener resultados en plazos lo más breves posible y reducir la mortalidad, morbilidad y limitaciones resultantes ocasionadas por la conducción bajo los efectos de las bebidas alcohólicas, con frecuencia asociados al consumo de otro tipo de drogas y aceptado cada vez más por la sociedad en actividades de ocio.

Palabras clave: Consumo de alcohol, accidentes de tráfico, prevención de accidentes, políticas de salud, factores de riesgo.

Abstract

Introduction: Alcoholic beverages are widely consumed around the world and also in Spain. Although most of the adult population has a pattern of low-risk drinking, there are people with harmful drinking patterns ranging from daily drinker wealth, consumption casual / social risk. This creates traffic problems in almost all countries associated with changes in psychomotor performance consumer with subsequent impact on accident risk.
Methods: To perform this review we have consulted the database of the World Health Organization: World Health Organization. Global Information System on Alcohol and Health (GISAH) and the results of the EDADES study. It has become a literature search in PubMed and other databases of reference (Latindex Scopus Spanish Bibliographic Index of Health Sciences -IBECS about search terms: Alcohol Consumption and road traffic injuries, and have been selected by the authors tose works considered more relevants.
Conclusions: This is a complex issue with individual impact on those affected and socio-economic importance and which highlights the special involvement in the effects of younger people, which requires a preventive effort overall health, social and government for results in shorter periods and may reduce mortality, morbidity and resulting limitations caused by driving under the influence of alcoholic beverages, often associated with the consumption of other drugs and increasingly accepted by society in leisure activities.

Keywords: Alcohol drinking, traffic accidents, accident prevention, health policy, risk factors

Introducción

El consumo de alcohol tiene una elevada prevalencia en la sociedad en general y su consumo crónico se ha convertido en uno de los principales factores relacionados con el estado de salud de los individuos y de los principales determinantes de la salud, desde una perspectiva epidemiológica en cuanto a la relación salud-enfermedad, habiendo sido objeto tradicional de estudio desde perspectivas diferentes y en colectivos poblacionales diversos[1,2].

Las bebidas alcohólicas se consumen ampliamente en todo el mundo y, aunque la mayoría de la población adulta tiene un patrón de consumo de bajo riesgo, ya que habitualmente o se abstiene por completo, o consume de forma esporádica, existen personas que presentan patrones lesivos de consumo de alcohol que van desde el bebedor diario de gran cantidad, al consumo de riesgo ocasional/social. Esta situación genera tanto problemas de salud pública, como de seguridad en casi todos los países según el informe de la OMS de 2014[3].

Para manejar datos fiables de prevalencia de consumo de alcohol, la principal fuente de información a nivel mundial es el Global Information System on Alcohol and Health (GISAH)[4], que recoge más de 200 indicadores distribuidos en siete categorías: producción de alcohol y disponibilidad; niveles de consumo; patrones de consumo; consecuencias y daños; aspectos económicos; políticas de control; y recursos para prevención y tratamiento. Revisando los datos referidos a 2010 se observa que el consumo mundial *per cápita* de bebidas alcohólicas en dicho año equivalía a 6,2 litros de alcohol puro consumido por cada persona de 15 años o mayor. Una gran parte de este consumo (un 24,8 % o 1,54 litros por persona) se realiza en forma de alcohol de producción casera, con un mayor riesgo de daño debido a impurezas o contaminantes desconocidos y potencialmente peligrosos en estas bebidas.

En España, para valorar de una forma aproximada la situación del consumo de alcohol, se toman como base los resultados de la Encuesta Domiciliaria sobre Alcohol y Drogas (EDADES)[5]. Esta encuesta utiliza un cuestionario y una metodología similares a los que usan en otros países de la Unión Europea y Estados Unidos, lo que permite realizar comparaciones internacionales.

El EDADES se comenzó a realizar en el año 1995 y, desde entonces, se ha realizado en España bianualmente. Esta encuesta es promovida por las delegaciones del Gobierno para el Plan Nacional sobre Drogas y el objetivo general es obtener un instrumento con el que diseñar y evaluar las políticas dirigidas a prevenir el consumo y los problemas relacionados con las drogas. La que sirve de base a este trabajo es la publicada en 2011, con datos procedentes de 2009.

Los resultados muestran que la evolución en la prevalencia del consumo de alcohol ha ido disminuyendo desde 1997 hasta 2011, si bien la extensión del consumo de esta sustancia en la sociedad española es prácticamente universal. En 2011 el 90,9% de la población encuestada de 15 a 64 años lo había consumido alguna vez en su vida, el 76,6% lo había consumido durante el año anterior a ser encuestado y el 62,3% lo hizo alguna vez durante el mes previo a la encuesta. Más del 10% de la población encuestada reconoció un consumo diario durante el mes previo. El porcentaje de abstemios era en los datos publicados en 2011, de un 8% en hombres, 17,1% en mujeres. En total un 12,6%.

Uno de los aspectos más importantes a la hora de considerar el consumo abusivo de alcohol es el daño que puede causar al propio consumidor y a las personas del entorno, destacando en este sentido los accidentes de tráfico entre los más frecuentes[6].

Los datos publicados por la OMS en 2014 y procedentes de 2012, estiman los años de vida perdidos por accidentes de tráfico en 7,6% para hombres y 1,8% para mujeres de los que son atribuibles al alcohol el 17% y el 6.7% respectivamente. La puntuación en la escala de años perdidos según la OMS es de 4 siendo 5 el máximo.

El consumo de alcohol y el riesgo para la conducción en España

El alcohol produce cambios en el rendimiento psicomotor del consumidor con posterior repercusión en riesgo de accidentes: aumenta el tiempo de reacción, afecta la coordinación bimanual, la atención (concentrada y dividida) y la resistencia a la monotonía. Además altera la capacidad para juzgar la velocidad, la distancia y la situación relativa del vehículo, así como la habilidad para seguir una trayectoria o hacer frente a lo inesperado. Todo ello provoca una grave alteración en la capacidad de conducir con seguridad e incrementa el riesgo de accidente de tráfico[7,8,9].

Aunque el alcohol produce un marcado deterioro de las funciones cognitivas y psicofísicas, el consumidor de bebidas alcohólicas no es consciente de estos cambios; ya que la intoxicación provoca una sensación subjetiva de mayor seguridad en sí mismo. Bajo los efectos del alcohol son frecuentes las reacciones de euforia, agresividad, conductas temerarias y violentas[10].

Sin embargo el 22% de los conductores hace un consumo de riesgo, el 3'2% hace un abuso y se calcula que un 0'26% tiene una dependencia al alcohol. La mayoría de los conductores españoles, según el EDADES (75% de los varones y 50% de las mujeres) son bebedores habituales, es decir han consumido más de 7 días en los últimos 30.

Este deterioro causado por el alcohol en la capacidad de conducir vehículos es directamente proporcional a su concentración en sangre. La conducción con 0,5 g/l de etanol en sangre supone casi el doble de probabilidad de sufrir un accidente de circulación, respecto a la conducción sin ingestión de alcohol, aumentando dicha probabilidad progresivamente a partir de esta concentración; así con 0,8 g/l el riesgo es casi cinco veces mayor que el que presentan los que no han bebido alcohol. La probabilidad de fallecimiento es cinco veces mayor entre

los conductores y peatones que presentan una alcoholemia superior a 0,5 g/l[11]. Se estima que el riesgo relativo de sufrir un accidente mortal con alcoholemias de 0,8 g/l es máximo entre la población de 16-17 años (165 veces) y entre la de 18-19 años (70 veces)[12,13].

La causa de muerte más frecuente entre los 16 y 24 años son los accidentes de tráfico con intoxicación alcohólica del conductor y a veces también de los acompañantes[14].

Según publicación de la dirección General de Tráfico en el año 2010, el 40% de los fallecidos en accidente de tráfico conducían bajo el efecto de una droga, y el alcohol estaba presente en prácticamente la totalidad de ellos, a veces solo y en ocasiones con otras sustancias. El alcohol se encuentra implicado en el 30-50% de los accidentes mortales, en el 20-40% de los accidentes con víctimas no mortales y en el 10-30% de los accidentes con daños materiales exclusivamente[15].

La situación es similar en Europa, donde se calculan unas 17.000 muertes anuales debidas a accidentes de tráfico en relación con el consumo de alcohol, 1 de cada 3 fallecimientos del tráfico rodado, así como más de 10.000 muertes estimadas de tráfico en personas distintas al conductor intoxicado[16].

Las tasas de alcoholemia actualmente en vigor en España, por encima de las cuales no se permite la circulación dependiendo del tipo de vehículo son las siguientes:

- Como norma general se establece en 0,5 gramos de alcohol por litro de sangre (o 0,25 mg de alcohol por litro de aire espirado) para personas que conducen vehículos y bicicletas.
- Para los vehículos destinados a transporte de mercancías de más de 3.500 kg, para los vehículos destinados al transporte de viajeros, servicio público, transporte de menores y escolar, de mercancías peligrosas o de servicios de urgencia o transportes especiales, los conductores no podrán superar la tasa de alcohol en sangre de 0,3 gramos por litro de sangre (o de 0,15 mg por litro de alcohol en aire espirado).
- Los conductores de cualquier vehículo, durante los dos años siguientes a la obtención del permiso o licencia que les habilita para conducir, no podrán superar la tasa de alcohol en sangre de 0,3 gramos por litro de sangre (o de 0,15 mg por litro de alcohol en aire espirado).

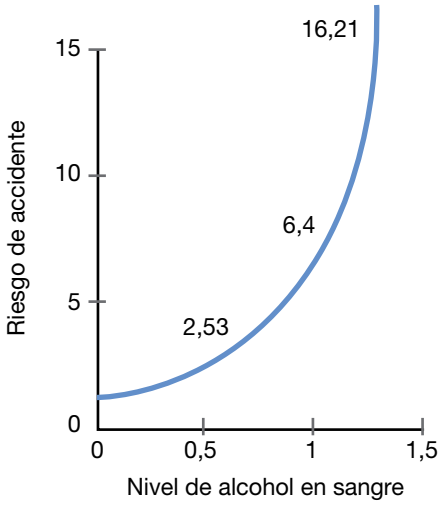
Los accidentes de tráfico causados por el alcohol son lo bastante importantes para que sean una de las cinco prioridades de la Comisión de la UE para reducir el daño causado por el consumo de alcohol[18]. Destaca especialmente el inicio temprano en el uso del alcohol (antes de los 14 años) como factor predictivo de riesgo de accidentes de tráfico[19].

El riesgo de que ocurra un accidente y su relación con las cifras de alcoholemia viene representado por la curva de Freudenberg que se muestra en la **Figura 1**.

En España, el Instituto Nacional de Toxicología y ciencias Forenses publica una memoria periodica sobre las víctimas analizadas en los centros de toxicología con datos correspondientes al Departamento de Barcelona (de donde provienen los datos de las Comunidades Autónomas de Cataluña, Aragón, Navarra, Baleares y la Comunidad Valenciana), el Departamento de Madrid (Galicia, Asturias, Cantabria, País Vasco, La Rioja, Castilla y León, Madrid, Castilla La Mancha y Murcia); el Departamento de Sevilla (Andalucía, Extremadura, Ceuta y Melilla) y los datos correspondientes a la Delegación de La Laguna (Comunidad Autónoma de Canarias). La **Figura 2** muestra los resultados de los test realizados a los conductores y las diversas sustancias examinadas[20].

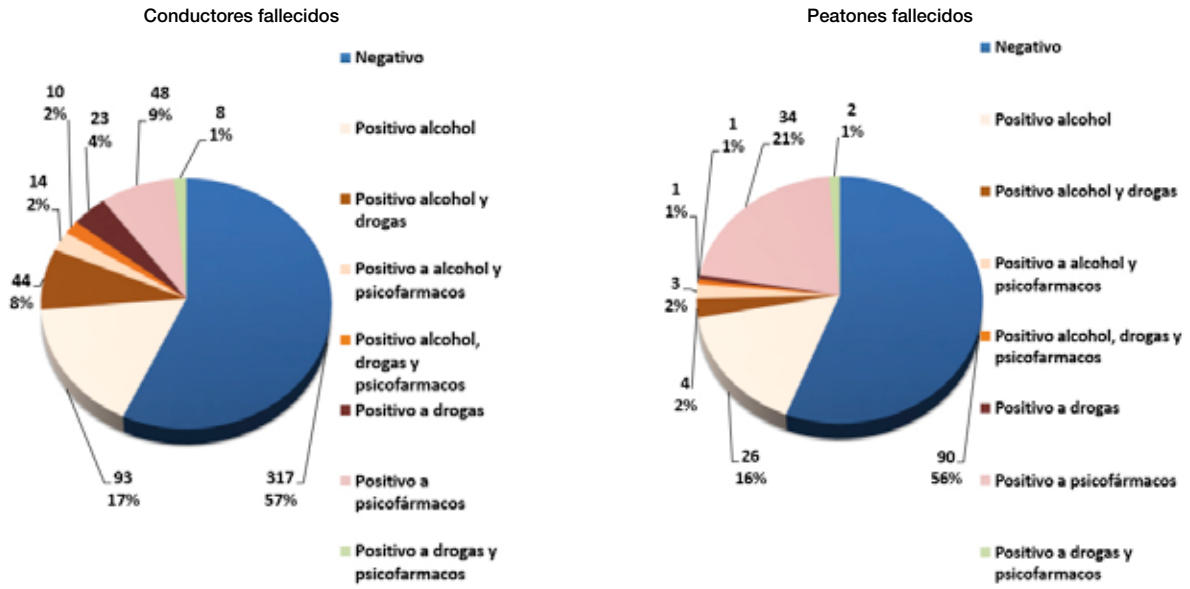
Según datos del Instituto Nacional de Toxicología y ciencias Forenses, el 43,09% (240) de los conductores fallecidos presentaron resultados positivos en sangre a drogas y/o psicofármacos y/o alcohol. De ellos en 161 (67,08% de los conductores que dieron resultados positivos y 28,90% del total de conductores) se detectó solo alcohol o alcohol y drogas/psicofármacos. En 93 conductores (38,75% de los conductores que dieron resultado positivos y 16,69% del total de conductores) solo apareció resultado positivo para el alcohol. Un 15% del total no habían consumido alcohol pero se encontraban bajo los efectos de otras sustancias psicoactivas. La distribución según el total de la tasa de alcoholemia se expone en la **Figura 3**.

Figura 1: Curva de Freudenberg



Fuente: DGPNSD Informe alcohol 2007 http://www.pnsd.msc.es/Categoria2/publica/pdf/InformeAlcohol.pdf

Figura 2: Distribución según la tasa de alcoholemia y otras sustancias de los conductores y peatones fallecidos en España en 2013



Fuente: Modificado de Víctimas mortales en Accidentes de Tráfico año 2013. INTCF. https://**www.administracionde justicia.gob.es/paj/PA_WebApp_SGNTJ_NPAJ/descarga/Memoria%20INTCF%20INTCF%202013.pdf?idFile=d9eecb8d-1e61-4a56-aad8-5131679085e1**

Hay un aumento considerable de fallecidos con la tasa por encima de 2,01 g/l. La división de las alcoholemias no es igual en todos los tramos y llama la atención el alto número de fallecidos con alcoholemias bajas. Es frecuente que el consumo de alcohol en conductores se asocie al de otras drogas, tal y como se puede ver en la **Tabla I**.

Tabla I: Conductores positivos a alcohol y otras drogas en España en 2013.

Sustancias consumidas	Número de positivos
Alcohol + cocaína	22
Alcohol+ cannabis	12
Alcohol +benzodiacepina	8
Alcohol + antiepiléptico	2
Alcohol + antidepresivo	3
Alcohol+ cocaína+ cannabis	4
Alcohol+ cocaína+ anfetamina	1
Alcohol + cocaína + benzodiacepina	2
Alcohol+ cocaína + opiáceos	3
Alcohol +cannabis + anfetamina	1
Alcohol + cannabis + benzodiacepina	3
Alcohol +benzodiacepina+ antidepresivo + antiepiléptico	1
Alcohol +cocaína + MDMA +benzodiacepina	1
Alcohol+ cocaína+ cannabis + anfetamina	1
Alcohol + cannabis + benzodiacepina + antiinflamatorios	1
Alcohol + cocaína + benzodiacepina + analgésico	2
Alcohol + cannabis + benzodiacepina + antidepresivo	1
Total	**68**

Fuente: Víctimas mortales en Accidentes de Tráfico año 2013. INTCF https://www.administracionde justicia.gob.es/paj/PA_WebApp_SGNTJ_NPAJ/descarga/Memoria%20INTCF%202013.pdf?idFile=d9eecb8d-1e61-4a56-aad8-5131679085e1

Los resultados de los test realizados a los peatones que fallecieron en accidentes de tráfico en 2013 a las diversas sustancias examinadas se expone en la figura 2 y muestra que el 44,10% de los peatones presentaron resultados positivos para sustancias de abuso y/o psicofármacos. De ellos, en el 47,89% de los peatones que dieron resultados positivos y en 21,73% del total, se detectó solo alcohol o alcohol y drogas/psicofármacos. En el 36,61% de los peatones que dieron resultados positivos y en el 16,14% del total de conductores, solo apareció resultado positivo para el alcohol.

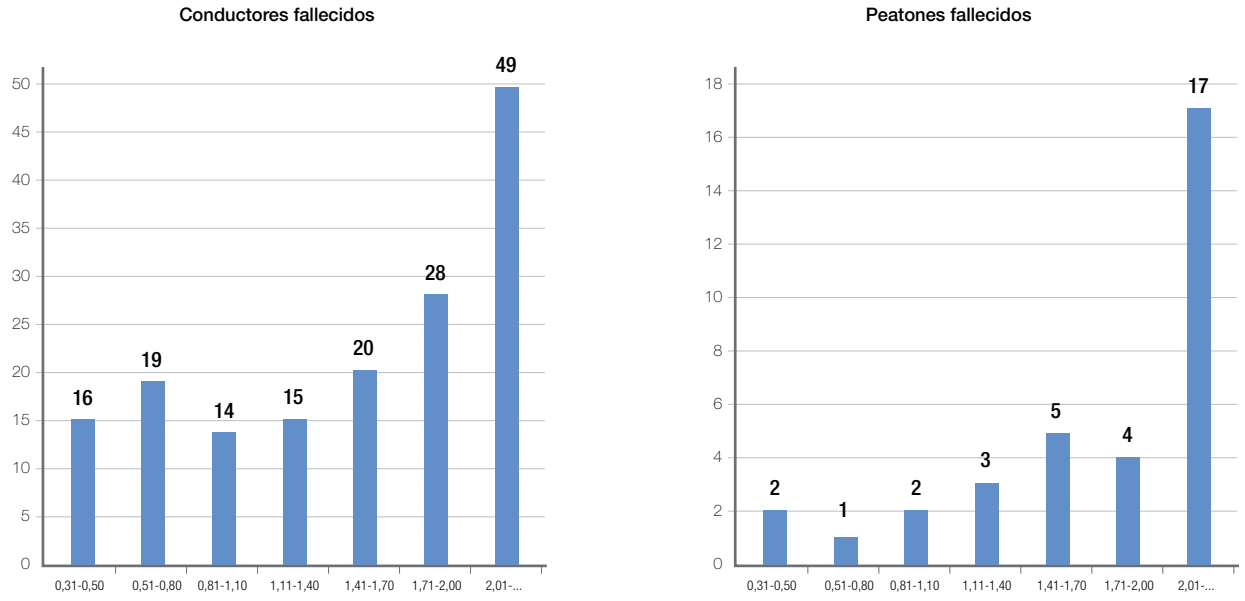
En la **Figura 3** se muestra la distribución de las tasas de alcoholemia de los peatones fallecidos.

La evolución de los casos analizados con resultados positivos en consumo de alcohol tanto en peatones, como en conductores durante los últimos cinco años se muestra en la **Figura 4** y permite apreciar cómo van aumentando hasta llegar a 2013, año en el que existe un importante descenso hasta los niveles menores del último lustro, tanto en peatones como en conductores. Hasta el descenso del 2013 la cifra de fallecidos en los peatones del 2009 es la única más alta que la del año posterior.

Discusión

La preocupación por los efectos del alcohol en salud pública y, de forma concreta en el riesgo de accidentes de tráfico, constituye un problema que afecta a todos los países del mundo y también en España. Una revisión de

Figura 3: Distribución según la tasa de alcoholemia de los conductores y peatones fallecidos en España en 2013



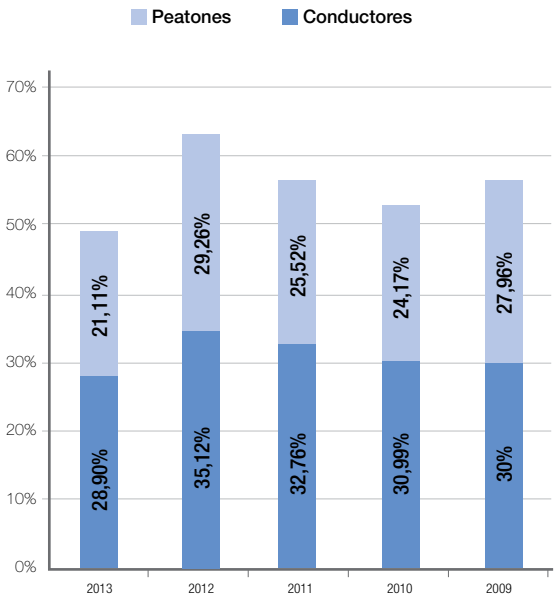
Fuente: Modificado de Víctimas mortales en Accidentes de Tráfico año 2013. INTCF. https://**www.administracionde justicia.gob.es/paj/PA_WebApp_SGNTJ_NPAJ/descarga/Memoria%20INTCF%20INTCF%202013.pdf?idFile=d9eecb8d-1e61-4a56-aad8-5131679085e1**

publicaciones científicas e institucionales llevada a cabo desde 1990 a 2011 en nuestro país ha puesto de manifiesto el elevado consumo en jóvenes, de predominio en los hombres sobre las mujeres. En 2011 se atribuyó al alcohol el 10% de la mortalidad de la población comprendida entre los 15-64 años. Cerca del 30% de esas muertes fueron debidas al consumo abusivo de alcohol. En este grupo de población, al menos el 0,8% tenía problemas por abuso de alcohol, un 5% de ellos había requerido de intervención clínica por ello y cerca de un 20% habían tenido alguna intoxicación aguda por alcohol en el último año.

Por todo ello, en España se considera un problema de salud pública con un coste social que representa aproximadamente el 1% del producto interior bruto[21].

Si bien es idea compartida por todos los investigadores que el alcohol tiene un efecto adverso en el rendimiento de la conducción, los efectos de dosis moderadas son inconsistentes y difieren a lo largo de la curva de intoxicación. Por ello algunos autores han centrado sus investigaciones en valorar las asimetrías de rendimiento cognitivo que acompañan a la aparición y la recuperación tras el consumo moderado de alcohol. Los resultados obtenidos en un estudio con participación directa de los afectados muestran que el nivel de intoxicación de los participantes en el estudio estaba mal relacionado con sus niveles reales de alcoholemia y por tanto con grado de deterioro, y diversos aspectos de la conducción y el

Figura 4: Evolución de alcoholemias positivas de los peatones y conductores fallecidos del 2009 al 2013 en España



Fuente: Modificado de Víctimas mortales en Accidentes de Tráfico año 2013. INTCF. https://**www.administracionde justicia.gob.es/paj/PA_WebApp_SGNTJ_NPAJ/descarga/Memoria%20INTCF%20INTCF%202013.pdf?idFile=d9eecb8d-1e61-4a56-aad8-5131679085e1**

rendimiento cognitivo empeoraron durante el descenso de las cifras de alcohol en sangre. Esto indica que los conductores no son buenos para juzgarse a sí mismos en cuanto su aptitud para conducir después de beber, aun solo cantidades moderadas de alcohol y se sugiere un enfoque prioritario en educación pública respecto al consumo de alcohol y sus efectos en la conducción[22].

El hecho de consumir alcohol y conducir se asocia con tasas elevadas de accidentes y muertes en accidentes. El alcohol afecta la percepción de peligro y potencia las conductas de riesgo; sin embargo, el cómo el alcohol afecta a todo ello es un hecho menos claro, ya que se han demostrado diferencias individuales en las curvas de concentración de alcohol en sangre conocidas como tolerancia aguda. En estudios realizados a doble ciego se pone de manifiesto que, tanto la percepción de peligro, como la voluntad para conducir mostraron tolerancia aguda en el grupo de consumidores de alcohol. Los participantes con curvas ascendentes de alcohol mostraron ser significativamente más peligrosos y más dispuestos a conducir y con menor sensación de peligro, que los que se encontraban en las curvas descendentes de consumo[23].

La percepción en estado de embriaguez se asocia con conductas de riesgo, por ello, los esfuerzos preventivos se centran en aumentar la conciencia sobre el peligro de conducir después de beber y son notablemente mejorables mediante la educación de los conductores sobre cómo la intoxicación alcohólica puede alterar esta percepción y en potenciar las intervenciones para beneficiar al conductor acerca de orientación sobre percepción de peligrosidad en estas situaciones frente a cuando están sobrios[24].

Especial atención merece la población joven, como población diana en prevención, en los que destaca el exceso de confianza en sus propias habilidades de conducción para hacerlo bajo los efectos del alcohol y el control del comportamiento percibido. Este sesgo de optimismo resulta más llamativo en los hombres frente a las mujeres Se trata por ello de diseñar intervenciones efectivas para prevenir los riesgos asociados con el alcohol al volante en la población joven, si bien esta efectividad es un punto de discusión y parece orientar hacia intervenciones centradas en la percepción del riesgo y en el cumplimiento de las normas en el grupo de conductores jóvenes y en la promoción de opciones de manejo preventivas y alternativas al consumo del alcohol[25].

Otro de los puntos de debate en el momento actual es determinar el costo-efectividad de las intervenciones para reducir los accidentes de tránsito causados por la conducción bajo los efectos del alcohol. Los resultados difieren según países y según las intervenciones realizadas. En un estudio llevado a cabo en Tailandia se recomienda una mayor intensidad de la realización de controles de alcoholemia para complementar la inversión en campañas de comunicación masiva. En conjunto, estas intervenciones estiman una potencial reducción del coste por lesiones debidas a accidentes de tráfico relacionados con el alcohol de un 24%[26].

En un estudio también de coste efectividad llevado a cabo en jóvenes y en un servicio de urgencias hospitalario se tomó como base una entrevista motivacional y consejo breve para el abandono de conductas de riesgo relacionadas con el alcohol ajustando el costo que supone de incremento la entrevista motivacional respecto a la calidad de vida ganada. Esta breve intervención representa según los autores una buena inversión social en comparación con otras intervenciones médicas comúnmente adoptadas[27].

Finalmente una información de interés en coste efectividad mediante intervenciones preventivas en alcohol y conducción de vehículos, parte de una revisión sistemática realizada para determinar la eficacia y la eficiencia económica de los programas multicomponentes, con participación comunitaria, para reducir el riesgo de accidentes por el alcohol. Esta revisión se realizó bajo la coordinación de los Servicios Preventivos de la Comunidad y concluye apoyando los programas multicomponentes que generalmente incluyen una combinación de esfuerzos para limitar el acceso al alcohol (especialmente entre los jóvenes), junto con responsabilidad en la dispensación de bebidas alcohólicas, controles de alcoholemia, educación pública, y la promoción de medios diseñados para obtener el apoyo de legisladores y público en general para reducir La conducción bajo el efecto del alcohol[28].

Vemos pues que nos hallamos ante un complejo problema con repercusión individual en los afectados y trascendencia socioeconómica y en la que destaca la especial implicación en sus efectos de las personas más jóvenes, lo que requiere de un esfuerzo preventivo conjunto sanitario, social y de las Administraciones Públicas para obtener resultados en plazos lo más breves posible y reducir la mortalidad , morbilidad y limitaciones resultantes ocasionadas por la conducción bajo los efectos de las bebidas alcohólicas, con frecuencia asociados al consumo de otro tipo de drogas y aceptado cada vez más por la sociedad en actividades de ocio.

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ORIGINAL

The influence of organochlorine compound exposure on the physiological development of children

Influències de les exposicions a composts organoclorats en el desenvolupament fisiològic dels infants

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Abstract

The present study summarizes the advances on the knowledge of the health disturbances associated to fetal exposure to organochlorine compounds in a cohort of children from Menorca. Higher incidence of diverse deleterious health effects at 4 years of age have been observed, e.g. hexachlorobenzene (HCB) and poor social behavior and attention-deficit hyperactivity disorder, 4,4'-DDE and asthma, wheeze, lower respiratory tract infections and alteration of urinary coproporphyrins, HCB, ß-hexachlorocyclohexane and 4,4'-DDE and alteration of thyroid hormones, HCB, 4,4'-DDE and polychlorobiphenyls (PCBs) and overweight, 4,4'-DDT and PCBs and lower neurodevelopment. A protective effect of breastfeeding against decreases of cognitive skills in children due to 4,4'-DDT exposure has also been documented. This protective effect shows that other factors besides pollutant exposure and genetic variability influence on the health effects of environmental pollutants into human populations. These results are important for the understanding of the health implications of exposome studies.

Keywords: Organochlorine compounds, fetal exposures, childhood exposures, DDT, polychlorobiphenyls, neurodevelopment, asthma, obesity, attention-deficit hyperactivity disorder

Resum

Aquest estudi resumeix els avenços en el coneixement dels trastorns de salut associats a l'exposició fetal a compostos organoclorats en una cohort de nens de Menorca. S'ha observat una incidència major de diversos efectes perjudicials per la salut als 4 anys d'edat, per exemple, hexaclorobenzè (HCB) i comportament social pobre i trastorn per dèficit d'atenció amb hiperactivitat, 4,4'-DDE i asma, xiulets pulmonars, infeccions de les vies respiratòries baixes i alteració de coproporfirines urinàries, HCB, ß-hexaclorociclohexà i 4,4'-DDE i alteració de les hormones tiroïdals, HCB, 4,4'-DDE i policlorobifenils (PCBs) i sobrepès, 4,4'-DDT i PCBs i menor desenvolupament neurològic. També s'ha documentat un efecte protector de la lactància materna contra la disminució de les habilitats cognitives dels nens a causa de l'exposició a 4,4'-DDT. Aquest efecte protector mostra que altres factors, a més de l'exposició a contaminants i genètica personal, influeixen en els efectes de salut dels contaminants ambientals en les poblacions humanes. Aquests resultats són importants per comprendre les implicacions per la salut dels estudis d'exposomes.

Palabras clave: Composts organoclorats, exposicions fetals, exposició a la infància, DDT, policlorobifenils, neurodesenvolupament, asma, obesitat, trastorn per dèficit d'atenció amb hiperactivitat

Introduction

The life expectancy of the individuals from western countries has more doubled that of their ancestors two centuries ago. This than great success results from the strong technologic and scientific development generated by the industrial revolution. However, some changes introduced during this period have also generated new risks for human health.

The synthesis, use and environmental spill of organochlorine compounds (OCs) constitute one of these risks. These compounds encompass a series of molecules that are responsible for a large number of deleterious health effects related to chronic exposure to organic chemicals. The most abundant in the environment and human tissues involve pentachlorobenzene (PeCB), hexachlorobenzene (HCB), hexachlorocyclohexanes (α-, β- and γ-HCH isomers), polychlorobiphenyls (PCBs; the main congeners: PCB28, PCB52, PCB101, PCB118, PCB138, PCB153 and PCB180) and DDT and metabolites.

The history of the past use of these compounds is contradictory. Several of them were considered to be very beneficial at the initial application period but they had to be banned later in view of the observed deleterious health effects in humans and organisms. The most striking example is 4,4'-DDT. In 1948 Paul Hermann Muller was awarded the Nobel Prize in Physiology and Medicine for "its discovery of the high efficiency of DDT as a contact poison against several arthropods". However, in 1962 Rachel Carlson wrote "Silent Spring" describing that this insecticide had also several major effects on the health of warm blood species. Finally, this compound and its metabolites were included in the list of compounds of the Stockholm Convention on Persistent Organic Pollutants for the restriction of its production and use except in the case of disease vector control. In 2005, the World Health Organization recommended the continued use of DDT in limited quantities for public health purposes in situations where potential loss of human life associated with unstable malaria transmission and epidemics is greatest and alternatives were not available[1, 2].

A parallel story could be described for hexachlorobenzene. At the beginning this compound was used as fungicide for the preservation of wheat sowing, which avoided the use of organomercurial compounds for preservation against fungal degradation. However, a major intoxication episode occurred in the Turkish Kurdistan with development of porphyria cutanea tarda as consequence of human consumption of bread manufactured from hexachlorobenzene-treated wheat. This compound was therefore banned after this intoxication episode and now it occurs in the environment because it is generated as by-product in the synthesis of organochlorine solvents.

OCs are very stable from chemical and environmental standpoints. Once released into the environment they remain in organisms, sediments, soils, air and other environmental compartments for decades. After the implementation of the regulations of the Stockholm Convention their concentrations have decreased in some cases but this is not yet a general rule. Furthermore, they have a lipophilic character which enhances their accumulation in organisms, including humans, instead of water dilution.

The strong stability of these compounds is due to the high abundance of chlorine substituents in their molecules. Because of this unique chemical composition, they are unknown to the metabolism of humans and other organisms. No exposure to these compounds occurred in the past. From an evolutionary viewpoint it is now the first time of human OC exposure and bioaccumulation and our metabolism does not know how to treat them. Thus, they accumulate in tissues and fat as consequence of their physical-chemical properties without significant metabolic interaction/degradation and without that membrane barriers may stop their distribution between organs. For instance, they accumulate in maternal tissues, placenta and fetus during pregnancy[3] and children receive an important dose of these compounds during breastfeeding[4]. In consequence, children are exposed at present to these compounds since the earliest stages of their development when their tissues and organs are still in formation. This situation is new in relation to the environmental chemical structures to which humans were exposed earlier than the fifties when these compounds were not in the environment neither in food items.

Now, humans receive inputs of these compounds throughout their life, including the fetal, breastfeeding and toddler periods, infancy, adolescence, maturity and aging. This raises up a new toxicity concept which is not related with the dose but the time of exposure: What are the effects of being exposed to low amounts of one toxicant for very long time periods such as the whole life, including the earliest stages of development?

This question is even more relevant for children. They are not small adults. They have specific needs and problems because their metabolism and organs are in formation. They have to face development at the physical, cognitive and psychosocial levels. Thus, chemical insults may be more significant in some critical formation time windows than in others. Furthermore, exposure to chemical pollutants in these development stages may lead to clinical deleterious effects later in life[5].

Among the common non-communicable diseases whose incidence may be related, at least in part, to environmental exposure to toxicants, obesity/cardiovascular diseases, diabetes, respiratory disease (including chronic obstructive lung diseases and asthma), cancer and neurological disorders must be considered[6]. Non-com-

municable diseases have long been the major causes of mortality and morbidity in high income countries but low and middle income countries are now also beginning to experience epidemics[6]. The development of these diseases is mostly related to life-time exposures. For example, lung cancer is mainly caused by exposures to tobacco, asbestos and air pollution. However, evidences indicating that an important part of its origin lies in fetal and early life chemical assimilations are increasing. There is a clear need to ascertain what exposures, which individual characteristics, e.g. genetics, life style, and what clinical or non-clinical health disturbances can be related to environmental pollutants at older age.

In order to get progress into this topic, a collaborative network of research focused on children exposure to environmental pollutants was established in Spain[7]. This network involved the study of cohorts of newborns from Menorca, Ribera d'Ebre, Valencia, Sabadell, Granada, Gipuzkoa and Asturias. Among other aspects, the network promoted the measurement of the above mentioned OCs in cord blood serum for assessment of the exposures of newborns during the fetal period. Depending on the cohort, these compounds were also measured in maternal venous cord blood, in breastmilk or in venous cord blood of children at 4 years old.

Among the INMA cohorts, the one from Menorca is the oldest and the one who provided more insight into the consequences of in utero exposure to environmental pollutants and health disturbances in infants during the first years of age. These results have been widely quoted in the international literature. Menorca does not have factories producing OCs but DDT was used for agriculture in the past. The individuals participating in the cohort were therefore exposed to baseline POP levels and can be taken as examples of the regular exposure to POPs in western countries.

In the present paper the advances on the knowledge of the health disturbances resulting from OC exposures in the fetal period is summarized. Impacts on overweight, thryroid function, neurodevelopment, lower respiratory tract infections and asthma are considered. Besides their intrinsic value for the understanding of the etiology of some of the non-communicable diseases, the reported findings illustrate that other aspects besides those related with direct OC exposures or genetic factors are also relevant for the final health outcomes related to OC bioaccumulation.

Methods

The cohort recruited all women presenting for antenatal care over 12 months starting in mid 1997[7]. 482 children were enrolled and 470 (97.5%) provided complete outcome data up to the fourth year visit (**Table I**). Among these, 410 (85%) had OCs measured in cord blood and 285 (59%) in sera collected at four years.

Table I: Characteristics of the study population.

	Number of individuals	%
Participants		
At birth (at four years)[a]	410 (285)[a]	
Sex		
Male	202 (136)[a]	49 (48)[a]
Female	208 (148)	51 (52)
Feeding mode		
Maternal milk	339 (235)[a]	83 (83)[a]
Formula milk	71 (49)	17 (17)
Time of lactation (weeks)		
0.3-10 (0.3-12)[a]	85 (59)[a]	25 (25)[a]
10-20 (12-21.5)	85 (59)	25 (25)
20-28 (21.5-28)	85 (59)	25 (25)
28-100 (28-96)	84 (59)	25 (25)
Time of gestation (weeks)		
27-39	106 (72)[a]	26 (25)[a]
39-40	208 (161)	51 (57)
40-44	96 (50)	23 (18)
Maternal body mass index		
15.3-20.6 (15.3-20.4)[a]	102 (71)[a]	25 (25)[a]
20.6-22.0 (20.4-22.0)	103 (72)	25 (25)
22.0-24.3 (22.0-24.2)	103 (71)	25 (25)
24.3-48.5 (24.2-48.5)	102 (71)	25 (25)
Maternal age		
17-26 (17-26)[a]	102 (71)[a]	25 (25)[a]
26-29 (26-29)	103 (72)	25 (25)
29-32 (29-32)	103 (71)	25 (25)
32-42 (32-41)	102 (71)	25 (25)

[a]*Subset of the same individuals participating in the study at four years old*

OCs were analysed in serum of cord blood and venous blood collected at four years of age. The analytical methods used for these measurements have been described elsewhere[8, 9]

Results

The ages of the participant mothers at delivery represented nearly the whole range of reproductive activity (**Table 1**). Body mass index (BMI) encompassed a large spectrum of cases from underweight (15.3) to obesity (48.5) (**Table 1**). Some cases involved short gestation periods (**Table 1**). 83% of children were breastfed. Time of lactation ranged from very short (2 months or less) to very long (more than one year intervals). No significant biases between the group of participants at birth (n = 410) and 4 years later (n = 285) were observed.

Concentrations of organochlorine compounds

The median concentrations of HCB, HCH, DDTs and PCBs in the cord blood and venous serum collected at 4 years from the Menorca cohort are shown in **Table II**. 4,4'-DDE was the most abundant OCs. Pentachloroben-

zene was generally found above the limit of detection in fewer than 10% of the samples. The median HCB value, 0.68 ng/ml (**Table II**), was high in comparison with those found in studies from other areas except Chukotka (Russia). The high value in Menorca was consistent with the HCB levels of the Spanish general population (not newborns) described in previous studies that are higher than in other European countries[10].

The distributions of HCH were highly dominated by ß-HCH as it is the usual case in human samples from other populations. The α-, γ- and δ-HCH isomers were only found above quantification limit in less than 5% of the total samples (**Table II**). These compounds were therefore not included in the studies. The median ß-HCH in Menorca was lower than those found in Chukotka (Russia[11]), Veracruz (Mexico[12]), Rio de Janeiro (Brazil[13]), New Delhi (India[14]) and Arctic Canada[15].

The median values of 4,4'-DDE and 4,4'-DDT were 1.0 ng/ml and 0.08 ng/ml, respectively (**Table II**). The dominance of 4,4'-DDE over 4,4'-DDT is consistent with the old origin of this mixture of pollutants because the latter is the one used as pesticide and the former is a transformation compound. The concentrations of 4,4'-DDE observed in Menorca were lower than those found in areas that have recently used this compound for malaria control such as Veracruz (Mexico[12]), Chukotka (Russia[11]) and New Delhi (India[14]) but higher than those found in other areas such as the Faroe Islands (Denmark[16]), Arctic Canada[15] and Rio de Janeiro (Brazil[13]) (**Table II**).

The distributions of PCBs were dominated by PCB138, PCB153 and PCB180 which corresponds to the congeners with more hydrophobic properties from this group of pollutants. The median of total PCB concentrations for the seven congeners analyzed was 0.51 ng/ml. These concentrations were lower than those reported in Michalovce[17], the Faroe Islands[16] and Chukotka[11] and higher than those found in the newborn populations of Rotterdam[18] and the Canadian Arctic[15].

Maternal determinants of OC concentrations in children.

Cord blood OC concentrations showed significant correlations with the age of the mother at delivery for HCB, ß-HCH, 4,4'-DDE, 4,4'-DDT, PCB118, PCB153, PCB138 and total PCBs[4]. According to these results, older mothers transferred higher OC concentrations into newborns. The compounds exhibiting these correlations were those found in higher concentration in cord blood. These results are in agreement with maternal age dependences of the concentrations of PCBs and HCB in newborns from Germany[19], 4,4'-DDE in newborns from Ribera d'Ebre[20] and 4,4'-DDE, PCBs and HCB in newborns from Quebec[19]. The concentrations in sera collected at four years only showed significant correlation with age of the mother for HCB ($p < 0.01$) and 4,4'-DDT ($p < 0.05$)[4]. The incorporation of new OC inputs through diet (e.g. breastfeeding) probably decreased significantly the relevance of the initial *in utero* intake, except in the case of the two aforementioned compounds.

OC concentrations in cord blood showed significant correlations with the BMI of the mother at delivery for HCB, 4,4'-DDE and 4,4'-DDT[4]. Higher BMI corresponded to higher OC concentrations in cord blood. No significant association between the concentrations of these compounds and cord blood lipids was observed. For HCB and 4,4'-DDE the degree of significance was very high ($p < 0.0001$ and $p < 0.001$, respectively). These two compounds were those present in the highest average concentration in the newborns (**Table II**). The concentrations in sera of four year old children only showed significant correlation with maternal BMI for HCB ($p < 0.05$). These data from the cohort of Menorca showed for the first time a direct relationship between maternal BMI and the concentration of some OCs in children at birth and at four years old.

Table II: Comparison of the median concentrations of organochlorine compounds in cord serum between Menorca and other world areas.

Area of study	N	Period of delivery	∑PCBs[a,b] ng/ml	HCB[a] ng/ml	β-HCH[a] ng/ml	4,4'- DDE[a] ng/ml	4,4´-DDT[a] ng/ml	Reference
Menorca (cord blood)	410	1997-1998	0.51[c] 0.64[d]	0.68[c] 0.76[d]	0[c] 0.22[d]	1.0[c] 1.6[d]	0.08[c] 0.18[d]	(4)
Menorca (four years of age)			0.73[c] 1.0[d]	0.31[c] 0.42[d]	0.21[c] 0.29[d]	0.81[c] 1.6[d]	0[c] 0.081[d]	(4)
Rotterdam (Netherlands)	382	1990-1992	0.45	NA	NA	NA	NA	(18)
Michalovce (Slovakia)	92	2002-2004	1.21	NA	NA	NA	NA	(17)
Faroe Islands	316	1986-1987	1.8	NA	NA	1.3	NA	(16)
Chukotka (Russia)	48	2001-2002	6.6[c]	4.0[c]	5.6[c]	6.4[c]	0.66[c]	(11)
Arctic Canada	400	1994-1999	0.23[c]	0.07[c]	0.03[c]	0.34[c]	0.03[c]	(15)
Veracruz (Mexico)	60	1997-1998	NA	0.8	0.7	6.0	0.8	(12)
Rio de Janeiro (Brazil)	10	1997-1998	NA	0.13	0.54	0.76	ND	(13)
New Delhi (India)	23	2006-2008	NA	NA	3.59	1.98	0.93	(14)

[a]The concentrations are reported in the same units as given in the referenced studies. [b]The concentrations are reported according to the number of congeners analyzed by the authors. [c]Median. [d]Mean. [e]Geometric mean. NA: Not analyzed; ND: Not detected.

Influence of milk feeding

The average concentrations of HCB, 4,4'-DDE, 4,4'-DDT, PCB153, PCB138 and PCB180 and total PCBs in sera collected at four years exhibited significantly higher values in breastfed than artificially fed children[4]. The degree of significance of the differences was very high ($p < 0.0001$) for most of these compounds. Accordingly, breastfeeding was very significant for the concentrations of OC in four year old children despite they stopped breastfeeding 2.3-3.5 years before being tested. The period of lactation was also correlated with the concentrations of HCB, ß-HCH, 4,4'-DDE, PCB118, PCB153, 4,4'-DDT, PCB138, PCB180 and total PCBs accumulated in four year old breastfed children.

In all cases, longer lactation corresponded to higher concentrations in serum. These results were consistent with studies on ß-HCH, HCB, 4,4'-DDE and PCBs in newborns from Germany (7 years[21]) and PCBs and 4,4'-DDT in Michigan (4 years[22]) and in Groningen (18 months[23]). In the Menorca cohort, the nursing period encompassed a very wide time range (0.3-100 weeks) and nearly all OCs examined showed significant correlation with this determinant.

The magnitudes of change varied between compounds, breastfed children showed concentration increases of 0.5 ng/ml of total PCBs in the blood serum content at 4 years when compared to birth. 4,4'-DDE increases were of about 0.2 ng/ml and ß-HCH increased by 0.1 ng/ml. Conversely, volatile compounds such as PeCB and HCB decreased, 0.1 ng/ml and 0.22 ng/ml, respectively. In the case of children fed with formula only concentration decreases in the blood serum collected at four years with respect to birth were observed, involving decreases of 0.3 ng/ml for total PCBs, 1.4 ng/ml for 4,4'-DDE, 0.6 ng/ml for ß-HCH and between 0.1 and 0.2 ng/ml for 4,4'-DDT, ß-HCH and PeCB[4].

As expected, dilution resulting from children growth tended to reinforce the decreases and counterbalance the increases. In the Menorca cohort the average growth involved changes from ca. 3.2 kg at birth to ca. 16.2 kg at four years of age corresponding to approximate blood volumes of 0.24 L and 1.2 L, respectively. Accordingly, the observed changes involved increases of total POPs in all cases but these were much higher in breastfed children than in formula fed children. Total concentrations of 4,4'-DDE, PCBs, HCB, ß-HCH and 4,4'-DDT in the venous system increased by 1.9, 1.3, 0.4, 0.3 and 0.1 µg in the former and by 0.1, 0.6, 0.05, 0.25 and 0.1 µg in the latter.

Methods

Overweight

Overweight at 6.5 years was defined as a BMI z-score ≥85th percentile of the World Health Organization reference. The OC concentrations in cord blood were measured and treated as categorical variables (tertiles). Children's diet was assessed by a food frequency questionnaire. No statistically significant associations between OC and height were found.

Children in the highest cord blood HCB group (> 1.0 ng/ml) had higher weight and BMI at age 6.5, ß = 1.92 kg (0.64) and 0.95 kg/m^2 (0.31), respectively[24]. The highest prevalence of overweight (20%) and obesity (17%) was also found in this group. Increased relative risks of overweight in the highest group of prenatal exposure to PCBs (> 0.9 ng/mL) was also found, 1.7 (95% confidence interval 1.9-2.64) (**Table III**[25]). Significant results were observed for the second tertiles of 4,4'-DDE exposure (0.7-1.5 ng/ml) showing a Relative Risk of 1.67 with a confidence interval of 1.10-2.55[25]. These associations were stronger in girls than in boys. Adjustment for birth

Table III: Crude and adjusted estimated effects (RR, 95%CI) of prenatal PCBs, DDE and DDT concentrations on overweight at 6.5 y in the cohort of Menorca (n = 344; Valvi et al., 2012).

	OC concentrations (ng/ml)	N	Crude model	Multivariable adjusted model[a]	Multi-pollutant adjusted model[a,b]
PCBs					
RR (95% CI)	<0.6	110	Ref.	Ref.	Ref.
	0.6-0.9	117	0.82 (0.51,1.32)	0.97 (0.58,1.62)	0.92 (0.54,1.56)
	>0.9	117	1.30 (0.86,1.96)	1.70 (1.09,2.64)	1.54 (0.95,2.49)
DDE					
RR (95% CI)	<0.7	113	Ref.	Ref.	Ref.
	0.7-1.5	116	1.52 (0.97,2.40)	1.67 (1.10,2.55)	1.45 (0.93,2.24)
	>1.5	115	1.41 (0.88,2.25)	1.28 (0.81,2.03)	0.94 (0.58,1.54)
RR per each ng /mL lnDDE increase		344	1.19 (0.99,1.43)	1.15 (0.95,1.39)	1.13 (0.91,1.42)
DDT					
RR (95% CI)	<0.06	108	Ref.	Ref.	Ref.
	0.06-0.18	124	1.32 (0.84,2.10)	1.19 (0.76,1.87)	1.12 (0.73,1.71)
	>0.18	112	1.42 (0.90,2.26)	1.17 (0.73,1.88)	1.11 (0.68,1.81)
RR per each ng/mL lnDDT increase		344	1.09 (0.95,1.25)	1.04 (0.91,1.19)	1.01 (0.87,1.15)

[a]Adjusted for birth weight, previous parity, maternal pre-pregnancy BMI, maternal education and social class at pregnancy, maternal smoking in pregnancy, maternal age at delivery and breastfeeding. [b]Additionally adjusted for HCB and the other OCs shown in this table (all OCs in tertiles).

weight, other OCs and diet did not modify the model. Prenatal exposure to HCB, PCBs and DDE was therefore likely associated with an increase in BMI and weight at age 6.5 years.

Thyroid function

Thyroid hormones are essential for normal brain development. At birth, examination of associations between levels of thyrotropin (TSH, thyroid-stimulating hormone) and OCs showed a positive association with cord blood serum concentrations of ß-HCH in the cohort of Menorca[26]. High ß-HCH levels were paralleled with high TSH concentrations. Studies of four-year-old children in the cohort of Menorca[26, 27] have shown that higher prenatal levels of 4,4'-DDT, ß-HCH and PCB congeners PCB138, PCB180, PCB153 and PCB118 were related to lower total triiodothyronine (T_3) levels (**Table IV**). In addition, free thyroxine (T_4) was found to be inversely related with PCB118 concentrations (**Table IV**), while no association was observed between TSH and any of the OCs measured.

Asthma, wheeze and risk of lower respiratory tract infections

Early life exposure to OCs is also suspected to increa-

Table IV: Unadjusted association (coefficient and standard error) between thyroid hormones and TSH concentrations and quartiles of organochlorine compounds. (n=259)[27].

	lnTSH Coefficient	p	Free T4 Coefficient	p	Total T3 Coefficient	p
HCB (ng/ml)						
0.00 - 0.193 (reference)	0.46 mU/l		1.06 ng/dl		155 ng/dl	
0.194- 0.304	-0.02 (0.08)		0.00 (0.02)		-6.1 (3.8)	
0.305 - 0.506	0.02 (0.08)		0.00 (0.02)		-8.8 (3.8)*	
0.507 - 4.52	0.13 (0.08)	0.079	-0.02 (0.02)	0.602	-5.3 (3.8)	0.120
p,p'-DDE (ng/ml)						
0.00 - 0.435 (reference)	0.50 mU/l		1.05 ng/dl		151 ng/dl	
0.436 - 0.807	-0.05 (0.08)		0.00 (0.02)		0.1 (3.8)	
0.808 - 1.75	-0.06 (0.08)		0.01 (0.02)		-1.4 (3.8)	
1.76 - 43.9	0.09 (0.08)	0.280	-0.02 (0.02)	0.379	-5.0 (3.8)	0.166
p,p'-DDT (ng/ml)						
10.00 - 0.025 (reference)	0.42 mU/l		1.06 ng/dl		156 ng/dl	
0.026 - 0.049	0.04 (0.08)		0.00 (0.02)		-7.5 (3.8)*	
0.050 - 0.103	0.11 (0.08)		0.00 (0.02)		-9.0 (3.8)*	
0.104 - 0.657	0.12 (0.08)	0.101	-0.03 (0.03)	0.360	-7.9 (3.8)*	0.40
β-HCH (ng/ml)						
0.00 - 0.107 (reference)	0.57 mU/l		1.08 ng/dl		155 ng/dl	
0.108 - 0.190	-0.15 (0.08)		-0.03 (0.02)		-5.0 (3.8)	
0.191 - 0.304	-0.16 (0.08)*		-0.04 (0.02)		-7.1 (3.8)	
0.305 - 5.65	-0.01 (0.08)	0.833	-0.05 (0.02)	0.070	-9.0 (3.8)*	0.015
PCB-138 (ng/ml)						
0.00 - 0.104 (reference)	0.50 mU/l		1.06 ng/dl		153 ng/dl	
0.105 - 0.174	-0.09 (0.08)		0.00 (0.02)		-0.8 (3.8)	
0.175 - 0.276	0.05 (0.08)		0.00 (0.02)		-4.8 (3.8)	
0.277 - 8.71	0.02 (0.08)	0.382	-0.01 (0.02)	0.674	-6.2 (3.8)	0.061
PCB-180 (ng/ml)						
0.010 - 0.063 (reference)	0.44 mU/l		1.07 ng/dl		151 ng/dl	
0.064 - 0.115	-0.01 (0.08)		-0.04 (0.02)		2.6 (3.8)	
0.116 - 0.211	0.14 (0.08)		-0.01 (0.02)		-4.4 (3.8)	
0.212 - 7.20	0.09 (0.08)	0.097	-0.02 (0.02)	0.694	-4.3 (3.8)	0.097
PCB-153 (ng/ml)						
0.014 - 0.140 (reference)	0.49 mU/l		1.06 ng/dl		152 ng/dl	
0.141 - 0.250	-0.07 (0.08)		0.00 (0.02)		2.0 (3.8)	
0.251 - 0.410	0.03 (0.08)		0.01 (0.02)		-4.9 (3.8)	
0.411 - 10.88	0.07 (0.08)	0.208	-0.02 (0.02)	0.482	-6.3 (3.8)	0.032
PCB-118 (ng/ml)						
0 - 0.069 (reference)	0.39 mU/l		1.09 ng/dl		155 ng/dl	
0.069 - 0.098	0.17 (0.08)*		-0.03 (0.02)		-3.2 (3.8)	
0.099 - 0.128	0.09 (0.08)		-0.06 (0.02)*		-4.8 (3.8)	
0.129 - 1.824	0.12 (0.08)	0.247	-0.07 (0.02)**	0.003	-11.5 (3.8)**	0.003
sum of PCBs (ng/ml)						
0.148-0.546	0.41 mU/l		-0.04 ng/dl		155 ng/dl	
0.547-0.775	0.08 (0.08)		-0.01 (0.02)		-4.7 (3.8)	
0.776 - 1.171	0.09 (0.08)		-0.05 (0.02)		-7.4 (3.8)	
1.172 - 41.17	0.16 (0.08)	0.046	1.08 (0.02)	0.193	-8.3 (3.8)*	0.021

** p- value <0.05 ** p-value <0.01 (in comparison to the reference category)*

se the risk of lower respiratory tract infections (LRTIs) and wheeze in infants. The effects of these pollutant exposures have been documented at 14 months, 4 and 6.5 years.

Children in the ages of 4 and 6.5 years were examined for increased risk of asthma and atopy upon exposure to 4,4'-DDE[28, 29]. Asthma was defined on the basis of wheezing at 4 and 6.5 years of age, persistent wheezing or doctor-diagnosed asthma. Specific immunoglobulin-E (IgE) against house dust mite, cat, and grass in sera extracted at 4 years of age was measured.

Wheezing at 4 years of age was found to increase with 4,4'-DDE concentration, particularly in the highest quartile (9% in the lowest quartile (<0.57 ng/ml) versus 19% in the highest quartile (1.90 ng/ml); relative risk = 2.63 (95% CI: 0.96–7.20), adjusting for maternal asthma, breast feeding, education, social class, or other OCs; **Table V**). The association was not modified by IgE sensitization and occurred with the same strength among non-atopic subjects and among those with persistent wheezing or diagnosed asthma. 4,4'-DDE was not associated with atopy alone. No association was found for 4,4'-DDE concentrations in these infants at 4 years and the pulmonary or atopy indicators. The results were consistent with contributions of prenatal exposure to 4,4'-DDE residues to asthma development.

The relevance of epigenetic changes in the association between 4,4'-DDE and asthma was investigated in 122 children of the cohort of Menorca[30]. DNA methylation of the CpG site in the arachidonate 12-lipoxygenase (ALOX12) gene was identified as a possible epigenetic biomarker for the risk of asthma-related phenotypes.

Wheezing phenotypes were defined between 4 and 6 years. Cytosine-guanine (CpG) dinucleotide site DNA methylation differences associated with wheezing phenotypes were screened using the Illumina GoldenGate Panel I. ALOX12 DNA methylation was strongly determined by underlying genetic polymorphisms. The findings were validated and replicated using pyrosequencing.

Information on maternal smoking and folate supplement use was obtained through questionnaires. The genotypes were extracted from genome-wide data. The screening identified lower DNA methylation at a CpG site in the ALOX12 gene in children having persistent wheezing compared with those who never wheezed (p = 0.003). DNA hypomethylation at ALOX12 loci was associated with higher risk of persistent wheezing (odds ratio per 1% methylation decrease, 1.13; 95% CI: 0.99–1.29; p = 0.077). Higher levels of prenatal 4,4'-DDE were associated with DNA ALOX12 hypomethylation (p = 0.033).

Table V: Adjusted associations between 4,4'-DDE in cord serum and wheezing at age 4 (risk ratio and 95% confidence interval)[28].

	All	Non-atopic
4,4'-DDE in quartile (ng/ml)*		
< 0.57	1	1
0.57 – 1.03	1.00 (0.41-2.43)	1.32 (0.37-4.70)
1.03 – 1.90	1.62 (0.70-3.74)	2.63 (0.96-7.20)
> 1.90	2.36 (1.19-4.69)	2.49 (1.00-6.19)

** adjusted for the socio-economic variables*

Poor social behavior and Attention-Deficit Hyperactivity Disorder

Poor social behavior and attention-deficit hyperactivity disorder (ADHD) was examined in infants as early indicator of developmental neurotoxicity. Positive associations of these disturbances in pre-schoolers of 4 years and prenatal exposure to HCB were identified in Menorca (**Table VI**[31]). The California Preschool Social Competence Scale and the ADHD were scored by each 4-year-old-child's teacher. Children's diet and parental sociodemographic information was obtained through a questionnaire. All prenatal HCB exposure categories were associated with an increase in the risk of having a poorer Social Competence and ADHD, but only those children with HCB concentrations above 1.5 ng/ml at birth had a statistically significant increased risk of having a poor Social Competence = 4.04 (1.76–9.58) and ADHD = 2.71 (1.05–6.96) (relative risk (standard error); **Table VI**). No association was found between prenatal HCB and the cognitive and psychomotor performance of these children. No association was found for HCB concentrations of these infants at 4 years and the test scores.

Cognitive skills

Early life exposure to OCs is suspected to have deleterious effects on neurodevelopment which may involve decreases in cognitive or psychomotor skills. Studies on 4-year-old children from the cohort of Menorca in which OCs were measured at delivery and at 4 years were used for further assessment of DDT impact of the critical exposure age of infant development. Examination on the neuropsychological development using the McCarthy Scales of Children's Abilities (MCSA) at 4 years of age showed that 4,4'-DDT cord serum concentration at birth was inversely associated with verbal, memory, quantitative, and perceptual-performance skills[32]. Children whose 4,4'-DDT concentrations in cord serum were >0.20 ng/ml had mean decreases of 7.86 points in the verbal scale (standard error, 3.21) and 10.86 points in the memory scale (standard error, 4.33) when compared with children whose concentrations were <0.05 ng/ml (**Table VII**). These associations were stronger among girls. Prenatal exposure to higher concentrations of 4,4'-DDT was associated with a decrease in preschoolers' cognitive skills. No association was found for 4,4'-DDT concentrations of these infants at 4 years.

Further examination of prenatal exposure to OCs and impaired neurodevelopment at 4 years of age showed no statistically significant effects of the sum of prenatal

PCBs on MCSA scores. Nevertheless, individual congener analyses yielded significant detrimental effects of prenatal PCB153 on the majority of MCSA scores, while no effects were observed for other PCB congeners. The levels of PCBs at 4 years of age were not associated with neurodevelopment. Thus, prenatal exposure to low-level concentrations of PCBs, particularly PCB153, was observed to be associated with an overall deleterious effect on neuropsychological development at 4 years of age, including negative effects on the executive and verbal functions and on visuo-spatial abilities, but not on motor development[33].

Examination of the possible influence of genetic variability in the 4-year-old infants from this cohort showed a significant relation with GST genes (*GSTP1*, *GSTM1*, and *GSTT1*[34]). Genotyping was conducted for the coding variant Ile[105]Val from *GSTP1* and for null alleles from *GSTM1* and *GSTT1*. Linear regression models were used to measure the association between OCs and neurodevelopment scores by GST polymorphisms. In children having any *GSTP1* Val-105 allele DDT cord serum concentration was observed to be inversely associated with general cognitive, memory, quantitative, and verbal skills, executive function and working memory (**Table VIII**). *GSTP1* polymorphisms and prenatal DDT exposure showed a statistically significant interaction for general

Table VI: Crude and adjusted relative risk of having Poor social behaviour (< 80 points in the Social Competence Scale) and Attention-Deficit Hyperactivity Disorder at age 4 in relation to in utero exposure to HCB (95% CI)[31]

	Unadjusted n=377	Adjusted † n=377	Adjusted for other OCs ‡ n=377	Menorca cohort ‡ n=329
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
SOCIAL COMPETENCE				
HCB category				
Reference¶	1	1	1	1
0.5-0.99 ng/ml	1.16 (0.62-2.18)	1.40 (0.68-2.87)	1.77 (0.83-3.79)	1.84 (0.82-4.11)
1-1.49 ng/ml	1.04 (0.48-2.29)	1.47 (0.59-3.62)	1.83 (0.72-4.69)	1.51 (0.52-4.35)
≥ 1.5 ng/ml	2.88 (1.39-5.97)*	4.04 (1.76-9.58)*	5.63 (2.13-14.88)*	6.18 (2.06-18.50)*
HCB, ng/ml#	1.52 (1.05-2.22)*	1.79 (1.15-2.76)*	2.10 (1.30-3.40)*	2.18 (1.28-3.74)*
ATTENTION-DEFICIT HIPERACTIVITY DISORDER				
Reference¶	1	1	1	1
0.5-0.99 ng/ml	1.19 (0.58-2.42)	1.23 (0.54-2.78)	1.47 (0.63-3.46)	1.38 (0.57-3.32)
1-1.49 ng/ml	1.73 (0.77-3.91)	2.28 (0.88-5.96)	2.74 (1.01-7.45)*	2.17 (0.73-6.49)
≥ 1.5 ng/ml	2.05 (0.90-4.67)**	2.71 (1.05-6.96)*	3.43 (1.24-9.51)*	3.11 (1.01-9.55)*
HCB, ng/ml#	1.49 (0.99-2.24)**	1.63 (1.02-2.63)*	1.88 (1.13-3.14)*	1.77 (1.00-3.11)*

¶ Reference group: <0.5 ng/ml. # Natural logarithmic transformed HCB concentration. * p<0.05; ** p<0.10. † Adjusted for age, cohort, gender, maternal education, paternal education, tobacco and alcohol exposure, maternal age in years and type and duration of breastfeeding (see methods). ‡ Adjusted for same variables above and PCBs, 4,4'-DDE and 4,4'-DDT

Table VII: Adjusted¶ associations between DDT and the general cognitive, the verbal and memory McCarthy areas according to gender[32]

	Concentration of 4,4'-DDT 0.05-0.10 Reference † ng/ml β (SE)		0.10-0.20 ng/ml β (SE)	> 0.20 ng/ml β (SE)
All infants	*n=203*	*n=86*	*n=74*	*n=112*
General Cognitive	104.03	1.45 (2.72)	-2.01 (2.95)	-5.87 (2.60)*
Verbal	98.38	1.80 (3.36)	-4.02 (3.65)	-7.86 (3.21)*
Memory	88.93	1.64 (4.53)	-4.46 (4.92)	-10.86 (4.33)*
Girls	*n=101*	*n=48*	*n=33*	*n=55*
General Cognitive	104.67	-1.37 (3.95)	-0.44 (4.47)	-8.89 (3.89)*
Verbal	97.22	-2.26 (4.86)	-2.58 (5.51)	-12.79 (4.80)**
Memory	88.22	-2.46 (6.61)	-4.76 (7.47)	-17.19 (6.51)**
Boys	*n=102*	*n=38*	*n=41*	*n=57*
General Cognitive	102.64	3.39 (4.09)	-5.15 (4.06)	-3.74 (3.63)
Verbal	101.99	5.66 (5.05)	-6.65 (5.01)	-3.41 (4.47)
Memory	96.54	2.47 (6.82)	-6.30 (6.77)	-5.63 (6.04)

Each row is a different multivariate model. Adjusted for gender, scholar trimester at examination, psychologist, breastfeeding, maternal social class and maternal consumption of alcohol and tobacco during pregnancy. Neurodevelopmental scores are centered to the mean.
† Infants in the lowest quartile of DDT exposure (<0.05 ng/ml)

cognitive (p = 0.051) and quantitative (p = 0.018) skills, executive function (p = 0.009) and working memory (p = 0.017; **Table VIII**).

According to *GSTM1* and *GSTT1* polymorphisms, there were no significant associations between DDT and cognitive functioning at the age of 4 years. The results indicated that children with *GSTP1* Val-105 allele were at a higher risk of the adverse cognitive functioning effects of prenatal 4,4'-DDT exposure.

These studies on neurodevelopment were extended to 11 years by use of the continuous performance test-II (CPT-II) which was administered to 393 11-year-old children[35]. The results showed that a number of socio-environmental factors during prenatal life and early childhood, such as socio-demographic characteristics, breast feeding, maternal nutritional supplementation with folic acid and vitamins and OC exposure, e.g. 4,4'-DDE and PCB levels at 4 years, may influence inattentive and hyperactive/impulsive symptomatology during preadolescence[35]. This study was the first reporting some relationships between low neuropsychological development at 11 years and OC exposure at preschooler ages instead of *in utero*. Confirmation from other independent studies is needed.

Influence of breastfeeding on neurodevelopment

Breastfeeding was associated with increases of the preschoolers cognition performance in the McCarthy Scale while DDT was associated with lower performance[36]. Children who were breastfed for more than 20 weeks had a better cognitive performance regardless of their in utero DDT exposure. A linear dose response between breastfeeding and cognition was observed in all DDT groups (adjusted ß for high exposed to DDT (SE) = 0.30 (0.12) per week breastfed) (**Table IX**[36]).

As described in multiple studies[37-40], breastfeeding alone is beneficial for children's neurodevelopment which may be due to the occurrence of superior nutrients in breast milk than in formula milk[41, 42] or to the high frequency of physical and psychological contact between mothers and their infants during the breastfeeding process[43]. Children that are breastfed have a continuous exposure to OCs that in formula fed infants is much lower[4]. As a result, the concentrations of DDT and DDE at 4 years are higher among the longer-term breastfed children than in those with short or no breastfeeding (**Table IX**). However, the 4-year old children from the cohort of Menorca show that long term breastfeeding was beneficial for child development regardless the concentration of DDT in cord serum (**Table IX**). These results suggest that breastfeeding did not increase the neurotoxicological risk through higher potential DDT exposure. Maybe breast milk nutrients could counterbalance the negative effect of DDT but other possibilities should also be investigated.

Correspondences between OC exposures and health effects

The repeated analysis of OCs in the Menorcan children allows to discriminating between effects of environmental OC exposure in utero and at 4 years of age. As shown in **Table X**, in all cases the diverse health effects observed at 4 years were related to OC exposure in utero and not

Table VIII: Adjusted associations (ß(standard error)) between concentrations of DDT† in cord serum (ng/ml) and neurodevelopment at age 4 years by GSTP1 polymorphisms[34].

	GSTP1 genotype		
	Ile/Ile N=149	**Ile/Val or Val/Val N=177**	**p for interaction**
McCarthy areas			
General cognitive	7.125 (6.163) p = 0.250	-8.410 (4.208) p = 0.047	0.051
Perceptual-performance	4.670 (5.751) p = 0.418	-3.805 (4.147) p = 0.360	0.207
Memory	0.898 (6.389) p = 0.888	-6.748 (4.314) p = 0.120	0.350
Quantitative	8.959 (7.228) p = 0.217	-3.584 (1.457) p = 0.015	0.018
Verbal	0.619 (6.484) p = 0.924	-8.234 (4.298) p = 0.057	0.341
Motor	10.326 (5.621) p = 0.068	2.941 (4.084) p = 0.472	0.751
Executive function	10.166 (6.434) p = 0.117	-10.145 (4.243) p = 0.018	0.009
Working memory	7.360 (6.912) p = 0.289	-2.754 (1.162) p = 0.019	0.017

†p,p´-DDT.
‡ Each cell is a different multivariate model. Adjusted for sex, school trimester at examination, psychologist, breastfeeding, maternal social class, and maternal consumption of alcohol and use of tobacco during pregnancy.

to the concentrations of these pollutants at 4 years, the age in which health disturbances were measured. The effects of exposure to OCs are therefore more critical during the prenatal than the postnatal periods. Accordingly, the period of highest human formation and growth is also the most critical to chemical insults by environmental pollution. Studies devoted to assess health diseases related to environmental pollutants should take into account this temporal perspective since no associations between OC intake and deleterious effects at 4 years would be identified from the sole analyses of the concentrations of these compounds at this age. This observation is relevant for the use of new concepts such as the exposome, which is devoted to evaluate all accumulated exposures to environmental pollutants in humans to correlate this information with the health clinical history of the individuals and their genetic characteristics. Failure to correctly assess what were the contributions to the exposome in the growth periods may lead to trivial non-significant results.

This temporal perspective may also be relevant for exposure effects in the early stages of postnatal growth and health disturbances later on age. Thus, the use of the CPT-II test have shown that exposure to 4,4'-DDE and PCBs at 4 years may be associated to low neuropsychological development at 11 years[35]. These results are preliminary and should be confirmed with further research. However, in what concerns neurodevelopment they are consistent with the process of progressive brain development during childhood and adolescence that if not completed adequately may lead in some cases to diverse psychiatric disturbances[45, 46].

On the other hand, the positive effects of breastfeeding involve some interesting questions concerning the current modes of association between exposure to environmental pollutants and health diseases. Breastfeeding time is one of the life periods in which humans incorporate most OCs. In Menorca, we have observed very significant differences in serum OC composition among 4 year-old children who breastfed and who did not, des-

Table IX: Adjusted change¶ (coefficient and 95% confidence intervals) in the general cognitive, verbal and memory McCarthy areas scoring by breastfeeding according to exposure to DDT at birth[36]

	All population n=391	Low exposed < 0.05 ng/ml n=162	Mid exposed 0.05-0.20 ng/ml n=138	High exposed > 0.20 ng/ml n=91
General Cognitive				
Reference†	103.98	109.04	100.32	91.91
Short-term Breastfeeding	1.90 (2.57)	2.11 (4.21)	0.35 (4.74)	3.79 (5.09)
Long-term Breastfeeding	7.66 (2.66)*	5.69 (4.53)	6.90 (4.86)	13.04 (5.83)*
Verbal				
Reference†	48.26	50.97	46.74	38.61
Short-term Breastfeeding	0.28 (1.54)	0.48 (2.54)	-0.91 (2.80)	2.27 (3.07)
Long-term Breastfeeding	3.10 (1.60)	2.21 (2.74)	2.41 (2.70)	5.92 (3.53)
Memory				
Reference†	21.26	23.46	19.33	15.73
Short-term Breastfeeding	0.37 (1.01)	0.87 (1.63)	-0.24 (1.89)	1.15 (2.06)
Long-term Breastfeeding	2.03 (1.05)	0.85 (1.75)	2.22 (1.81)	3.13 (2.37)

* p-value < 0.05 ¶ Adjusted for gender, scholar trimester at examination, psychologist, maternal social class, maternal education and maternal consumption of alcohol and tobacco during pregnancy. † Scoring in infants who were formula fed

Table X: Observed effects of exposure to persistent organic pollutants in humans

	Exposure[a]	Effect	Reference
HCB	*In utero*	Poor social behavior	(31)
HCB	*In utero*	ADHD	(31)
HCB	*In utero*	Alteration of thyroid hormones	(26, 27)
HCB	*In utero*	Overweight	(24)
DDE	*In utero*	Asthma, wheeze and lower respiratory tract infections, including genetic variability	(28-30)
DDE	*In utero*	Alteration of thyroid hormones	(26, 27)
DDE	*In utero*	Alteration of urinary coproporphyrins	(44)
DDE	*In utero*	Overweight	(25)
DDE	4 years	Neuropsychological development	(33)
DDT	*In utero*	Decrease of cognitive skills and influence of genetic variability	(32, 34)
ß-HCH	In utero	Alteration of thyroid hormones	(26)
PCBs	In utero	Overweight	(25)
PCBs	In utero	Neuropsychological development	(35)
PCBs	4 years	Neuropsychological development	(33)

[a]Exposure refers to the time at which the pollutants were measured.

pite that breastfeeding only encompassed three months in most cases and six months at the most[4]. The OC input associated to breastfeeding is therefore very significant.

In this same cohort, children whose 4,4'-DDT concentrations in cord blood serum were above 0.2 ng/ml showed significant decreases in the verbal and memory scales at four years of age in comparison with those having 4,4'-DDT concentrations below 0.05 ng/ml (**Table VII**). An association between higher exposure to 4,4'-DDT and lower cognitive performance is observed. However, this association is not found when comparing the 4,4'-DDT concentration of the four-year-old children with their cognitive skills at this age. One main reason for this lack of association appears to be the beneficial effects of breastfeeding on neurodevelopment (**Table IX**). According to these results, an univocal association between exposure to OCs and deleterious effects on neurodevelopment cannot be established. Besides differences of the impact of these pollutants at different growing periods, activities such as breastfeeding have beneficial effects despite they involve an important increase of these pollutants in breast feeders. This observation must be considered in scientific approaches trying to establish direct associations between integrated life exposure to pollutants (the exposome), genetic variability and health disturbances, the models may not be univocal such as in the case of breastfeeding.

Conclusions

The analysis of OCs in cord and 4-year-old blood serum in children from the cohort of Menorca has shown higher incidence of several health disturbances at 4 years of age that are related to in utero exposure and not to concentrations at four years. Some of these health effects are associated to exposure to one specific pollutant, such as HCB and poor social behavior and ADHD or 4,4'-DDE and asthma, wheeze, lower respiratory tract infections and alteration of urinary coproporphyrins. In other cases, the associations are observed for more than one compound such as HCB, ß-HCH and 4,4'-DDE and alteration of thyroid hormones, HCB, 4,4'-DDE and PCBs and overweight, 4,4'-DDT and PCBs and lower neuropsychological development.

The present results show that chemical insults at some critical growth periods may generate health disturbances later in age. This time-delayed correspondence has also been observed for chemical exposure to 4,4'-DDE and PCBs at four years and higher incidence of delays in neuropsychological development in eleven-year-old children. This is the first case of identification of OC exposure at childhood and effects at 11 years. These results should be confirmed with further studies.

According to these results, full understanding of the possible health effects of this type of chemical insults in children requires a follow up of their health status along time. Crosssectional studies only considering pollutant body burden concentrations and health status at one specific time window may miss causal associations. A protective effect of breastfeeding against decreases of cognitive skills due to 4,4'-DDT exposure has also been documented. This result, besides its obvious nutritional interest, shows that other factors than pollutant exposure and genetic variability are relevant for the incidence of the deleterious health effects of environmental pollutants into human populations.

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ORIGINAL BREU

Respiratory tract infections caused by Human Coronavirus (HCoVs) in Balearic Islands, 2014

Infecciones del tracto respiratorio causadas por los Coronavirus Humanos (HCoVs) en las Islas Baleares, 2014

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Abstract

Introduction: The main human Coronavirus (HCoVs) involved in human respiratory tract infections are the 229E, NL63, and OC43. Due to the lack of information about these infections in our country, it seemed important to know its impact on acute respiratory disease.

Material and Methods: In the period February-April 2014, we have studied the presence of different respiratory viruses in 950 samples (throat swabs and/or nasopharyngeal aspirates) belonging to 674 (70.9%) children (<15 years) and 276 adults (29.1%). The detection of respiratory viruses was performed using commercial automatic real-time PCR system (Anyplex RV16), detecting 16 different viruses.

Results: The overall HCoV detected was 4.6% of all samples studied and 7.8% (44 cases) of the positive samples. The 44 HCoVs detected corresponded to 20 HCoV-OC43 (45.4%), 17 HCoV-NL63 (38.6%) and 7 HCoV-229E (15.9%). The HCoVs alone were detected in 25 cases (56.8%) and with other respiratory viruses in 19 (43.2%) cases (coinfections). In the mixed infections, rhinovirus was detected in 11 cases (57.8%), influenzavirus type B in 6 cases (31.5%), adenovirus in 1 case and RSV-A in 1 case. HCoVs were detected in the 26 children (59%) and 18 adults (41%). Of the 44 cases, 13 (29.5%) required hospital admission, No patients infected by HCoVs died as a direct result of respiratory tract infection.

Conclusions: This study demonstrates the importance of respiratory infections caused by HCoVs, especially in children

Keywords: Human Coronavirus (HCoVs), OC43, NL63, 229E, Epidemiology

Resumen

Introducción: Los principales coronavirus humanos (HCoVs) causantes de infección respiratoria son el 229E, NL63 y OC43. Debido a la falta de información sobre este tipo de infecciones en nuestra comunidad, nos ha parecido importante conocer su impacto en la enfermedad respiratoria aguda.

Material y método: En el período Febrero-Abril de 2014 se ha estudiado la presencia de los diferentes virus respiratorios en 950 muestras clínicas (aspirados nasofaríngeos o frotis faríngeos) peryenecientes a 674 niños (<15 años)(70.9%) y 276 adultos (29.1%). La detección viral se ha realizado mediante una RT-PCR comercial que detecta de forma simultánea y diferencial 16 virus distintos (Anyplex RV16).

Resultados: El porcentaje global de detección de los HCoVs fue del 4.6% en todas las muestras estudiadas y del 7.8% (44 casos) en las muestras positivas. Se detectaron 20 OC43 (45.4%), 17 NL63 (38.6%) y 7 229E (15.9%). En 25 casos sólo detectó un HCoV (56.8%) y 19 casos (43.2%) la infección fue mixta. En estas infecciones los virus detectados fueron: rinovirus 11 casos (57.8%), virus gripal tipo B en 6 casos (31.5%), y adenovirus y VRS-A un caso cada uno. Los HCoVs se detectaron en 26 niños (59%) y 18 adultos (41%). De los 44 casos, 13 (29.5%) precisaron de ingreso hospitalario. Ningún paciente falleció como consecuencia de la infección respiratorio por el HCoV.

Conclusiones: Este estudio demuestra la importancia de las infecciones respiratorias causadas por los coronavirus humanos, especialmente en niños.

Palabras clave: Coronavirus humanos (HCoVs), OC43, NL63, 229E, Epidemilología.

Introduction

Coronaviruses are among the enveloped RNA viruses that are transmitted through the respiratory tract and have been taxonomically classified into three antigenic groups. The main human Coronavirus (HCoVs) involved in respiratory tract infections are the 229E and NL63, belonging to antigenic group 1 (*Alphacoronavirinae*) and OC43 belonging to antigenic group 2 (*Betacoronavirinae*)[1]. The recent detection of a new HCoV (nHCoV-London) respiratory demonstrated the clinical significance of this group of viruses[2]. The incidence of respiratory infections by these viruses varies widely by geographic area. Due to the lack of information about these infections in our country, it seemed important to know its impact on respiratory disease.

The aim of this study is to determine the incidence and epidemiological characteristics of respiratory tract infections caused by HCoV (OC43, 229E and NL63). We investigated the presence of these viruses in respiratory samples in our region (Mallorca, Balearic Islands, Spain).

Material and methods

Sample Collection

In the period February-April 2014, we have studied the presence of different respiratory viruses in 950 samples (throat swabs and/or nasopharyngeal aspirates) belonging to 674 (70.9%) children (<15 years) and 276 adults (29.1%).

RNA and DNA extraction and real-time RT-PCR

The detection of respiratory viruses was performed using commercial automatic extraction system. Nucleic acids were extracted from 700 µl of specimens by easyMAG (Nimbus, Hamilton Robotics, USA). The Final elution volume of each sample was 50 µl. The cDNAs were synthesized from extracted RNAs with the cDNA Synthesis Premix (Seegene, South Korea). Respiratory virus detection kit-A and B were used to detect 14 types of RNA viruses and two types of DNA viruses, according to the manufacture's instructions. The amplification and detection process were realized with the CFX96 real-time PCR detection system (Bio-Rad, CA).

Results

In 557 (58.6%) of the 950 samples studied was detected some kind of respiratory virus. The overall HCoV detected was 4.6% of all samples studied and 7.8% (44 cases) of the positive samples. The 44 HCoVs detected corresponded to 20 HCoV-OC43 (45.4%), 17 HCoV-NL63 (38.6%) and 7 HCoV-229E (15.9%). The HCoVs alone were detected in 25 cases (56.8%) and with other respiratory viruses in 19 (43.2%) cases (coinfections). In the mixed infections, rhinovirus was detected in 11 cases (57.8%), influenzavirus type B in 6 cases (31.5%), adenovirus in 1 case and RSV-A in 1 case. The coinfections of the HCoV-OC43 were detected in 11 cases (55%), the HCoV-NL63 in 8 (47%) cases, and HCoV-229E in any case.

HCoVs were detected in the 26 children (59%) and 18 adults (41%), corresponding to 28 men (63.6%) and 16 women (36.4%). The 20 HCoV-OC43 were detected in 13 children (65%), having an age range of 2 months-7 years and a median age of 24.5 months; and in 7 adults with a range of 22-74 years (median age of 51.8 years). The 17 HCoV-NL63 were detected in 10 children (58.8%) with an age range of 19 days-15 years and a median age of 32.1 months; and in 7 adults (41.2%) with a range of 42-84 years and a median age of 67.4 years. The 7 HCoV-229E were detected in 3 children (42.8%), with a range of 1 month-14 years and a median age of 96.3 months; and in 4 adults (57.2%) with a range of 39-53 years and a median age of 45 years.

Of the 44 cases, 13 (29.5%) required hospital admission, 4 (30.7%) by HCoV-OC43 (20% of all cases), 5 (38.4%) for HCoV-NL63 (29.4% of all cases) 4 and HCoV-229E (57% of all cases). No patients infected by HCoVs died as a direct result of respiratory tract infection.

Discussion

The HCoVs are responsible for a variable percentage of respiratory tract infections in children and adults. Chinese studies have shown that these viruses can be detected in 4.4% of the children studied, of whom NL63 represented 2.6%, OC43 the 1.5% and 229E the 0.3%3. In our study, only in three months, we detected 7.8% of HCoVs, of which 3.5% were OC43, 3.1% NL63 and 1.2% 229E. In the study by Bastien et al.4, in Canada, the HCoV-NL63 was detected in 3.6% of the samples studied, this rate is similar to that detected in our study. The study by Gaunt et al.[1], in The Netherlands, shows a rate of HCoVs circulation between 3.17% and 2.96%, depending on the season of the year. We agree with this study, it seems that these infections occur preferentially in children (59%) and boys (63.6%). Our detection rate is higher, probably due to the winter season analyzed (highest incidence).

One of the problems of interpretation of the meaning of the HCoVs in respiratory disease is the high rate of coinfections. In our study we detected 43.2% of mixed infections, preferably by rhinovirus. Other studies have reported percentages varying between 11-42%, predominantly different respiratory viruses depending on the time of year when the analysis is performed[1,3-5]. We no detected clinical and epidemiological differences between single infections and coinfections with other respiratory viruses.

We are in agreement with Gaunt et al.[1] the infection of HCoVs with another respiratory virus does not affect the ability of these viruses to establish infection. So in mixed infections, detection of HCoVs should not be considered as an accidental infection that does not contribute to the pathogenesis of respiratory infection.

The HCoV-OC43 seems to be the most frequently detected[1,3]. In our study we also show that this virus, with 45.4%, is more frequently detected, especially in children. The 29.5% of our patients required hospital admission due to respiratory disease or underlying disease. It should be noted that 57.1% of all infections caused by HCoV-229E required hospital admission. In these cases all the admissions corresponding to the 4 adult patients, all of whom were immunocompromised, coinciding with the previous study of Gaunt et al.[1].

This study demonstrates the importance of respiratory infections caused by HCoVs, especially in children. They are one of the leading causes of respiratory urgent consultation and determine a near 30% hospital admission for these pathologies. The new multiplex genome amplification techniques allow a better understanding of the epidemiology of this new type of respiratory infections

Conflict of interest

We declare that we have no conflict of interest with respect to this study.

Funding

None declared.

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ARTICLE ESPECIAL

Bioethical analysis of transgenic animals and genetically modified organisms (GMO)

Análisis bioético de los animales transgénicos y de los organismos genéticamente modificados (OGM)

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Abstract

The important technological advance in genetic manipulation has led to the development of genetically modified animals. The resulting being is called a transgenic animal. This term refers to an animal, whose genome has been deliberately modified by transferring an exogenous DNA into all its cells, including the germinal ones. In 1981, GORDON and RUDDLE coined the term transgenic as an animal variant, result of the introduction of a gene, or genes, into its genome. More recently, there exists a tendency to use the term GMA (Genetically Modified Animal) to refer to transgenic animals.

Some arguments against the use of transgenic animals in research are related to the fact that during the creation of a transgenic animal its genetic integrity is not respected because of the recombination of genetic material from different species and even different kingdoms, as for example, animals and plants. Some people consider that this recombination of genetic material between species, or the creation of chimeras, which in occasions is a part of the technical strategy for the obtaining of a transgenic animal, alters the concept of *"species"*. In addition, they consider it as an unnatural intervention that might interfere in the conception of what makes that an animal is such. There is argued that the direct genetic modification is a mere extension of the traditional technologies of crossing. The genetic modifications of animals provide arguments for accusations as how to treat animals as things or merchandises.

Keywords: Transgenic animals, Biodiversity, Genetically modified organisms, Bioethics, Biotechnology, Recombinant DNA

Resumen

El gran avance en tecnología para la manipulación genética, ha conducido al desarrollo de modelos animales modificados genéticamente. Al ser resultante se le llama animal transgénico. Este término, se refiere a un animal cuyo genoma ha sido deliberadamente modificado, mediante transferencia de un DNA exógeno, en todas sus células, incluidas las germinales. En 1981, GORDON y RUDDLE acuñaron la palabra transgénico como una variante animal originada tras la introducción de un gen, o genes, en su genoma. Más recientemente se tiende a utilizar el término AMG (Animal Modificado Genéticamente) para referirse a los animales transgénicos.

Algunos argumentos en contra del uso de los animales transgénicos en investigación tienen que ver con una cuestión previa a su aplicación, como es que, en la creación de un animal transgénico, no se respeta la integridad genética de los animales ya que se produce la mezcla de material genético entre diferentes especies e incluso entre diferentes reinos, por ejemplo, entre animales y plantas. Algunas personas consideran que esta mezcla de material genético entre especies, o la creación de quimeras, que en ocasiones es parte de la estrategia técnica para la obtención de un animal transgénico, altera el concepto de *"especie"* y es una intervención antinatural que podría interferir en la concepción de lo que hace que un animal sea tal. Se argumenta que la modificación genética directa es meramente una extensión de las técnicas de cruzamiento tradicionales. Las modificaciones genéticas de animales proporcionan argumentos para acusaciones como tratar a los animales como cosas o mercancías.

Palabras clave: Animales Transgénicos, Biodiversidad, Organismos Genéticamente Modificados, Bioética, Biotecnología, DNA Recombinante

Introduction

German Fritz Jahr proposed in 1927 the first construction of the word bioethics as an equation *"Bio=Ethik"*, in addition to a *Bioethical Imperative*, which also should consider other living beings in their related natural frames, together with the contributions given by wisdom. There has to be included artistic perspectives and/or the lived religion - constructed and experienced by historical, or anonymous prominent figures - in order to have guidelines of conduct that were able to protect life (Bios) as a whole, not only of human beings. All of this with the reverential respect towards life, within natural functioning, as it was proposed by the Noble-Peace-Prize-Winner A. Schweitzer (ROA-CASTELLANOS; BAUER, 2009).

More recently, POTTER (1970) methodologically proposes in his article *Bioethics, Science of Survival* to include ancient knowledge from the fields of philosophy and science, as well as renowned knowledge, as for example empirical knowledge, exact sciences and books of the Holy Scriptures in order to establish guidelines of conduct that have allowed different human groups to survive. For POTTER, wisdom was a goal that would guarantee survival. But nowadays it can be perceived that the appreciation for each interlocutor has been more present in the real founders of bioethics, than in their legatees. This happens including with the so-called solver of moral medical problems, HELLEGERS (1971) that proposed the same neologism based on respect, even for the Georgetown school, though its proposal now has reduced for several years bioethics to its medical and legal problems. (CICCONE, 2006).

The term *transgenesis* developed in parallel designs the process of transferring genes in an organism. The transgenesis is used nowadays to create new plants and animals. Life as a meaning for some reason is not longer dignified or respected as an end by itself. There are different transgenic methods to modify cell reportoires or whole hosts, such as the use of pistols of genes or the use of bacteria or viruses as vectors to transfer the segments of genetic information (LACADENA, 1996).

Anyhow, the word *transgenic* refers to a plant or an animal into whose cells receive a fragment of exogenous DNA or DNA that cannot normally be found in the organism in question has been introduced. A transgenic mouse, for example, is one that has been injected with foreign DNA, through a fertilized-modified ovum that is implanted into an adoptive mother. The formed animal has not only its own DNA, but also the fragment of exogenous DNA that was reinjected in the stage of fertilization of the ovum.

In this fashion, it is possible to study what effect this gene has on the whole organism instead of only observing a single cell in a cell culture. This is important because many diseases do not affect one single type of cells, but the interactions between many different types of cells, even the so-called stromal cells. This type of technology allows exemplifying human diseases in other species, where it is possible to study the biology and possible therapies for the disease.

Transgenic animals

In the last decades, especially due to the huge advances in the knowledge of the molecular bases of diseases, there has appeared the need to have genetically defined models, that is, models in which the genetic mutations that predispose, or take part in the development of the disease, could be controlled. This fact, together with the significant advance in technologies for genetic manipulation, has led to the development of genetically modified animal models, which are then called *"transgenic animals"*[1]. This term refers to an animal whose genome has been deliberately modified by means transferring exogenous DNA into all its cells, including the germinal ones. In 1981, GORDON and RUDDLE coined the term transgenic as an animal variant, result of the introduction of a gene, or genes, into its genome.PALMITER and BRINSTER described in 1986 the introduction of genes into cells of the germinal line[2].

The simplest form to generate a transgenic animal is the one that involves the isolation of the gene that shall be introduced *(transgene)*, its cloning and manipulation, so that it can be expressed by target organism, as well as its insertion into the organism. To reach that all the cells of the organism express this new gene, it needs to be incorporated in an embryo, in a zygote stage or very early phases. Once the scientist is sure that the embryo incorporated the transgene, the new set of cells is implanted into a receptive animal, which acts as mother (in a procedure where is possible to use *in vitro fertilization techniques*).

If, on the other hand, one is not interested in an animal whose entire genome contains the transgene, but only certain type of its cells, a procedure similar to the previously described is being carried out, but instead of injecting the transgene into a zygote, it is injected, for example, into an already existing blastocyte. The result of this procedure is an organism with normal cells, as well as cells that contain the transgene.

1. More recently, there has been seen a tendency to use the term GMA (Genetically Modified Animals) to refer to transgenic animals.
2. The first transgenic laboratory mouse appeared in 1974 and was called *Brinster's Mouse*; nowadays there exist approximately 1.000 strains of knockout mice. A *knockout* is a mutant animal which lacks the specific expression of a gene, eliminated by genetic mutation. The so-called knockin has a new gene included.

An example of the use of this technology is the production of transgenic sheep or goats. These are created by injecting the gene that codifies the desired protein into a fertilized ovum, which is implanted into a mother sheep or goat. Then, the presence of the desired gene in the offspring and those goats that present it, are induced to produce milk with some special characteristics when producing proteins.

The creation of transgenic animals presents new opportunities, but also creates new challenges. Among the first ones there is a possibility of studying the function of certain proteins, including some causes of human diseases. One of the major problems is the randomized insertion of the desired genes and the epistasis phenomena.

Animal transgenesis includes the addition *(Knock in)*, substitution, elimination *(Knock out)* or inactivation of one, or multiple genes.Their applications include the area of basic investigation (creation of animal models for the analysis of animal and human pathologies, discovery of new therapies, etc.), the food supply (improvement of productive characters in livestock, resistance to diseases, etc.), the industry (synthesis of new textile compounds, therapeutic proteins, etc.) and the medicine (possibility of xenotransplants (PETROCELLI et al. 2003)[3], models for gene therapy, etc.) amongst others that can be summarized as follows:

- Genetic bases of diseases and therapy designs.
- Models for the investigation of infections and gene therapy.
- Models or bioreactors as basis for the testing of drugs and medicines.
- Biotechnological designs in agricultural industries.
- Animal models for the analysis of the effects of the modulation, activation or suppression of the gene expression.

The study of genetic syndromes, chronic metabolic diseases, generation of new medicines to treat diverse diseases and the transplant of organs, are possibilities in transgenesis that should be deepened with respect to biological and ethical principles. The most common animals for this type of transplant are pigs, which, because of the similarities with the humans are the animals that show proportional size and if managed lowest rejection rates.

In case of medicines, there are several advances from transgenic animals: insulin, growth hormone and anticoagulant medicines are some of them.

Through the insertion of certain genes into mice, diseases can be studied thoroughly, in order to know how they work.To test different treatments to find the best one, it is necessary to create transgenic mice that develop different types of cancer. Nowadays these experiments have been mainly carried out in mice, though it can be expected to be done further with bigger animals, whose similarities with the humans are remarkable.

Besides, transgenic animals improve quantitatively and qualitatively certain elements as those in milk in the case of the cow-derived products, for enhancing human growth and the protection against diseases.

In the case of milk it is to be said that transgenic cows are able to generate lactose-free milk as well as enriched milk that can provide a major nutrition to babies and elders[4]. There also exist transgenic hens that synthesize human proteins in the egg white of their eggs.

GMO - Derived food

The food products subjected to genetic engineering, also known as transgenic food, refers to products that were produced on the basis of a genetically modified organism by means of genetic engineering. In other words, it refers to food obtained from an organism to which genes derived from another organism have been added to the receptor in order to obtain desired characteristics. At present, there can be observed a major presence of food products coming from transgenic plants such as corn, barley or soybean.

The improvement of the species that would be used as food for mankind or domestic animals has been a common cause in the history of Humanity. Between 12.000 and 4.000 b. C. there already existed the procedure of improvement by an artificial selection of plants. After the discovery of the sexual reproduction in vegetables, the first intergeneric crossing was realized in 1876. In 1909 the first merger of protoplasts was carried out and in 1927 there were obtained plant mutants of major productivity by means of X-ray irradiation of seeds. In 1983 the first transgenic plant was produced. In those days, some biotechnologists manage to isolate a gene and to introduce it into a genome of the bacterium *Escherichia coli*.

Three years later, in 1986, Monsanto, a multinational biotechnological company created the first genetically modified plant. It was tobacco plant, whose genome received a gene of resistance to the antibiotic Kanamicyn. Finally,

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4. In Canada, some researchers did go further and used the genes of a spider in a goat, so that silk could be extracted from the milk of the latter.

in 1994 the commercialization of the first genetically modified food, tomatoes *FlavrSavr*, created by Calgene, a biotechnological Company, was approved. An antisense gene was opposed to the normal gene of the poligalacturonase, an enzyme that leads to the ripeness of the tomato, so that it would remain live longer.

Nonetheless, few years later, in 1996, this product had to be withdrawn from the market of fresh products because of unforeseeable consequences such as a soft peel, a strange flavor and some other changes in their composition. Even so, these tomatoes are used for the production of elaborated tomatoes in industry.

Worldwide, the damages produced by weeds destroy almost 10 % of the crops. To avoid this, the farmers use herbicides with the resulting economic expense and contamination of water and soil. Generating plants that are resistant to these crops would improve this situation. To achieve it, vectors that transport genes of resistance to herbicides are transferred. An example of the aforementioned, is the resistance to the herbicide gliphosate in the GMO soybean and corn. This substance is effective in low concentrations, but as chemical agent remains toxic for humans and the scavenging microorganisms of the soil.

The action of the glyphosate is on the *enzyme enolpyruvyl-shikimate-3-phosphate synthase (EPSP synthase),* important for biosynthesis of amino acids, and therefore, by inhibiting this enzyme, the plant dies. The use of those organisms turns out to be a great problem since it would mean the development of *"superundergrowths"*, due to the massive application of this herbicide, which with after some time generates resistance in undergrowths (weeds), in addition to possible crossings with similar non-transgenic plants. Many Latin-American populations are in a situation of fight, due to the loss of the native corn and varieties cultivated in remote times, that through policies are replaced by non replicative-GMO seeds, known as Terminator seeds. This type of technology try to prevent genetic mixture with wild types due to the high rate of crossing of this species since the way of dispersion of the pollen is the wind. However, this trait has been perversively used for economic purposes by attacking native-fitted varieties seen as competences for lab seeds. It is important to note this is not a scientific problem itself, but a problem of ethics in government agents and companies that allow such an unfair and anti-biodiversity use in times of environmental challange.

Nowadays, GMO corn and soybeans that are resistant to glyphosate compose the majority of raw material in markets of the USA and other countries (resistance observed for the first time in 1996). Since it introduction to the market, there has been a spectacular increase in the development of crops of the transgenic soybean. Sadly, they are harvest on regions of tropical forests where worldwide flora and fauna have their refugee. Consequences, besides that damage, are losses of soil and erosion, due to the cultivation and lack of a post-harvest-coverage. Similar things happened with the production of corn, cotton and rape (canoil) that also have had a high development rate at an almost equal level, but lower than the soybean. Of all these crops, the USA produces two-thirds of the worldwide production of GMO plant crops.

Nourishing along increasing qualities of crops

During the last 50-100 years, the genetic improvement of the plant cultures has resulted in an important improvement of the productivity and increase in the nourishing capacities, but in the last years there has been decreases and even stagnation in the productive levels, which might be due to a lack of policies for soil protection. An example of cultures where biotechnology has helped to correct a nutritional deficiency is the one of golden rice, which shows increased levels of beta-carotene, a predecessor of the vitamin A.The lack of this vitamin is a fact in many parts of Asia and Africa, where each year numerous children become permanently blind due to this deficiency. There has been detected a lack of nutrients in Latin America and the Caribbean. There are other studies that have been designed to increase the levels of fatty acids, of antioxidants and of other vitamins and minerals in the plant cultures (CAPÓ and DRANE, 2013).

Transgenic plants and edible vaccines

Vaccines need a manufacturing process under controlled condition. Nevertheless, in underdeveloped countries, there are problems regarding the production, transport or storage of the vaccines since the majority of them need refrigeration and all of them need to be under sterile conditions. It is because of this that there are inexpensive, synthesized vaccines that are being developed by synthesizing edible plants. GMO biotechnology may play a role for solving this situation. This way, the gene that codifies the antigenic subunit of the hepatitis B vaccine has been transferred to a tobacco plant and the same gene has been expressed in its leaves. In the same way, this technique is used to beat the cholera, as well as the use of other vegetables or fruit-plants as the potato or the banana that are being considered *edible plants*.

Nevertheless, considerations for the use of this tool it is understandable since what reaches our intestine is only the gene and not the complete virus or bacteria, there is no possibility that the person contracts the disease, but benefit is enough in order that our immune system reacts by protecting us against a possible infection.

Transgenic tobacco plants for the decontamination of soils

In this case, the transgenic plants are used for the biorremediation of soils. This study was carried out in a zone of a military training camp and firearm manufacturing site during the Second World War. The soil was poluted by residual TNT. To eliminate this problem, genetically modified tobacco plants have been planted. Those plants are capable of generating a major number of decomposing bacteria for this explosive without harmful elements.

Ethical aspects and processes

Scientists have admitted that science is not capable of predicting the whole set of risks and the impact obtained by the environmental release of genetically modified organisms. Therefore, transcendence of GMO release remains unknown and it is uncertain which effect they have on biodiversity, human and animal health, environment, producing systems and even on food safety.

Science can originate, under parameters of rationality, technology that is intended to be essentially productive. Such a pretension, on the other hand, legitimates the use of knowledge (PFEIFFER, 2001). Technology sets out the following issues within its area of duties subjected to the principilist frame of bioethics, as follows:

- Enhancement tool for human regulation of natural processes only through a moderate form and only if there is a need to do so - non- maleficence principle-.
- In a form that is reasonably useful for life, far away from conflicts of interest that can be detected due to private business - beneficence principle-.
- In conformity with desired rational and logical will of all the affected stakeholders - rational principle of autonomy - and in an impartial way for all living dependant creatures - principle of justice-

Any person who is employed at a laboratory of molecular biology or genetic biology will affirm that there is no ethical problem in the production of genetically modified bacteria or yeasts: they do not suppose any ethically relevant challenge beyond questions of biosafety. When these technologies came up, a moratorium regarding the use of these technologies took place. Back then, a series of experiments on DNA recombination was voluntarily postponed by the scientific community. This process ended with some ethical recommendations by Asilomar Conference regarding the issue in question.

The ethical challenges that arise due to genetically modified animals (GMA) are polyhedral since for the research and production of compounds for medical use, the use of the genetically modified animals is mainly being accepted, as long as few regulations for the manipulation and treatment of those are respected. But when these genetically modified organisms (GMO) are designed to produce tastier meat, the reticence grows and when GMOs of pets are created for capricious purposes, the ethical doubts increase.

For many researchers, the ethical problems of genetically irreversible modifications to invertebrate animals are nonexistent: the response is quite similar and the doubts are principally reduced to the problems of biosafety/biosecurity. The doubts appear when there are plans of modification in vertebrates and in the cases of animals close to the human phylogeny.

Concerns regarding the use of transgenics

The majority of the genetically modified products contain an introduced gene that codifies a protein that confers the desired character to the products (resistance to herbicide, to insects, etc.). Are there any environmental consequences for our health because of this?

In general, if the proteins are neither toxic nor allergic they do not have any negative physiological effect. In case of consuming the EPSP[5] gene of resistance to herbicide together with the plant, it will degenerate rapidly.

In Europe, unlike in the USA, it is obligatory to label transgenic food. As for the risks, a constant debate exists due to a great disagreement about whether there is or not any type of risk. Until now, there is not a solidly proven theory regarding that since there is no scientific proof to demonstrate that transgenic crops by themselves do possess direct risk. Everything lies under suspicion since veiled interests are mutual accusations on used data.

Intellectual Property

A frequently used argument against transgenic food is related to the management of the intellectual property rights and/or patents that force the farmers through market restrictions to pay royalties to the institutional improvement agent. In addition, some allude to the use of molecular

3. Petrocelli, A; Rodríguez, D., Spadafora, C., Tamino, G.; Zannini, P. (2003).- Cap. 1; In Ravarotto, L; Pegoraro, R. (ed). Transgenesi, Clonazione, Xenotrapianto. Ed. Piccini. Padova
4. In Canada, some researchers did go further and used the genes of a spider in a goat, so that silk could be extracted from the milk of the latter.
5. Enzyme enolpyruvyl-shikimate-3-phosphate synthase (EPSP synthase).

strategies that prevent the reutilization of the native tomato, that is, the employment of a part of the crop for cultivation in consecutive years. A known example of the latter aspect is the mentioned technology called Terminator, included in those restrictions of use (GURT)[6] , developed by the Department of Agriculture of the USA and the *Delta and Pine Company* during the decade of the 1990s. This technology has not been incorporated yet to commercial crops and its sale is not yet authorized. The patent restriction operates for example by inhibiting the germination of seeds.

In this point, it is necessary to emphasize the use of the hybrid vigor, one of the most frequent strategies in plant improvement used in the non-traditional varieties. This procedure is based on the crossing of two lineages that act like parental lines, giving place to an offspring with a mixed genotype that possesses advantages as for quality, fitness, and agricultural performance.

As for the possibility of patenting transgenic plants, these they cannot be a patent eligible subject in strict sense, but can be subject of rights of the breeder, managed by the *International Union for the Protection of new Varieties of Plants* (UPOV)[7]. From this perspective, transgenic plants are protected at a level that is equivalent to the one of the varieties generated by conventional procedures. This fact necessarily demands the possibility of using varieties that are protected for agriculture survival and scientific research. In 2003, the UPOV declared about the technologies of restriction of use such as the previously mentioned Terminator the following: in agreement to the existence of a legal frame of protection of the new varieties, is indicated that the application of these technologies is not necessary.

On the initial issue, since the creation of transgenic animals is one of the current applications of the technology of the recombinant DNA, the analysis of its safety and of the ethical implications of its use is a part of the social debate and penetrates the barriers of scientific analysis.At this moment, the use of transgenic animals, or genetically modified animals represents one of the most powerful and complete tools of research of the biological sciences. This is therefore the leading cause because of which the human being should treat animals humanly: for the respect that it owes to itself as another being. Humans cannot degrade its dignity with a conduct that does not bear in mind the animal suffering, and/or put in peril its own survival. Obviously, this conduct that respects the human dignity implies that the human being adequately understands the value of the living creatures that allow his/her own life and that of the nature. Furthermore, mankind should understand the need to pass on to future generations a world in good conditions, without excessive degradation produced by its own selfish desire, but, surprisingly, the key point because of which the human being should do all of this is the maintenance of its own dignity.

As happens with other applications of this technology, our societies are debating two visions that are *a priori* opposites. On the one hand, there had never before existed a major ethical sensibility regarding the respect towards the use of other creatures. On the other hand, the applications of this technology reach fields that are of an enormous social and economic interest and their use can be converted into considerable benefits for the humanity in times future survival is questioned.

This double way is responsible for the presence of different sensibilities as for the use of the animals (transgenic or not). In this way, some defend the abolition of the use of animals on the basis of the rights of these organisms, whereas others defend that society is legitimized to use the animals, regardless of whether animals are considered to have rights or not. Survival acts as a bottom line in both cases. This debate, which is not exclusive for transgenic animals, serves nevertheless as frame for some arguments against its use, especially regarding its application to experimentation and lab animals.

There are arguments against the use of the transgenic animals in research related to an issue prior to its application. For example, during the creation of transgenic animals the genetic integrity of the animals is not respected since takes place a recombination of genetic material of different species and even different kingdoms (between animals and plants for example). Some consider that this recombination of genetic material between species, or the creation of chimeras, which in occasions is a part of the method, alters the concept of *"species"* and is an unnatural intervention that might interfere in the conception of what makes that animal. By thinking this way, questions arise, such as: What is the pig that possesses human genes for avoid transplant rejection[8]?

6. Genetic Use Restriction Technologies.

7. The International Union for the Protection of new Varieties of Plants (UPOV) is an intergovernmental organization with headquarters in Geneva (Switzerland); it was created by the International Convention for the Protection of New Varieties of Plants. The Agreement was adopted in Paris in 1961. Its mission is to provide and to promote an effective system for the protection of new varieties of plants, with respect to the development of new plant varieties for the benefit of the society. Brazil, Spain, Bolivia or Chile are in this union that counts with a total of 66 members in December of 2008.

8. Evidently, in order to be able to observe this difference between human beings and other animals and to affirm the superiority of the human being, it is necessary to depart from a series of observations that show the similarities and differences between the human being and other animals; in this respect, a reasonable description offers the chapter 2 of Fox MA. The Case for Animal Experimentation. An Evolutionary and Ethical Perspective. Berkeley and Los Angeles: University of California Press, 1986; 262.

In response to these moral issues, it has been argued that in genetic engineering there is no recombination of genomes, but that there only are transferred one or two genes, a small fraction of the genome of the majority of the receiving species. That is why it is not possible to speak about "humanization" of the pig, when human genes are transferred to obtain a transgenic pig. "Humanized strains", however, is a word used in laboratories for those cases and individuals. In addition, it should not be ignored that many genes are preserved between different species, for what the presence of certain sequences does not seem to be determinant at the moment of defining the essence of a species.

As for the transgression of the barrier of species, and probable vulnerabilities towards infection agents, the discussion is complex from a scientific point of view since the barrier of species is sometimes neither clear nor immutable.

One of the central criteria has always been the one of cost and benefit. That is one of the the basis for utilitarian ethics analysis. Not only in the economic sense, but in term of knowledge, this means, what kind of knowledge has been obtained at the cost of the sufferings inflicted to the laboratory animals. With this, the ethical balance should be set out - this unstable equilibrium between benefit and sacrifice - and there should be a constant search for alternative methods.

The well known three *R's*, (RUSSELL AND BURCH, 1959) correspond to the initial letters of three basic principles that identify alternative methods[9]:

- *Remplacement* of the procedures that use animals by others that do not require them.
- *Reduction* of the number of animals used.
- *Refinement* of the methods used.

We as scientists consider that there should add a fourth *"R"*, which would be, at a personal level, the one of the scientist's *Responsibility*[10]. According to Jonas *"The human being is the only being known for having a sense of responsibility. Only human beings can choose consciously and deliberately between different alternatives of actions and this choice has its consequences."* (SIQUEIRA, 2001).

In addition, from another perspective, doing research with animals does generate high economic costs[11]; in many cases, this cost is provided by public funds. For that reason, the insistence on futile experiments will find an additional criticism if it is done without enough racionality.

Thus, *"It is perverse that the principal aim of certain activists of animal rights is science, precisely the area in which there is major moral justification for the death of animals."* (BALLESTEROS et al., 2004). Professional knowledge and suitability, therefore, is indispensable to think in the most appropiate and convenient use of these alternatives for society.

Apart from the individual valuation with regard to the use of animals for food supply or for other uses related to research or to industrial production, and independently of the moral consideration that one has on the manipulation of the animal genomes, it is important, from a global point of view, to indicate that the use of genetically modified animals, which is under a constant control[12], is generating important scientific and sanitary benefits that in the future can produce significant applications of industrial interest.

It is necessary to indicate as well that, from a technical point of view, the current procedures of genetic modifications in animals as well as biotechnological procedures are supervised[13].

At the moment, the use of transgenic animals, or GMO represents one of the most powerful and complete research tools for the biological and medical sciences.

The numerous possibilities of use of transgenic animals in very diverse fields of economic and scientific interest lead some researchers to think that the research with this type of animal is incompatible with the principle of reduction previously mentioned. To underline the fact that transgenic animals do not contribute to the reduction in the use of laboratory animals, here is some information: it is estimated that in the number of animals used for studies related to the creation and use of transgenics increased by 73 % between 1997 and 1998 in Canada, by 29% in Great Britain and by 20% in the USA (GRIFFIN et al., 2009). Knock out organisms are also daily used in laboratories all around the world.

9. In 1986, by means of the Directive 86/609/EEC, the European Community urges its member states to promote the legislation concerning the "three R's", which is being done since then, however, with different diligences. Finally, the CE has created the European Centre for the Validation of Alternative Methods (ECVAM), located in Ispra, Italy.
10. The moral progress, which is the only progress to which we might aspire, relies on responsibility. Today, there is neither a person nor an institution that could take responsibility for the results of all this experimentation 20 years from now.
11. To start a research project, it is necessary to process a whole series of permissions and train all the staff involved in the project (animal carers, graduate staff and specially trained personnel).
12. Cartagena Protocol on Biosafety to the Convention on Biological Diversity. 29th of January of 2000.
13. Nagoya-Kuala Lumpur Protocol on Liability and Redress, supplement to the Cartagena Protocol. 2010.

Studies which consider the evolution of the use of animals in different countries detect a similar situation: since 1996, there has been taken place a gradual decrease of the experiments that generate severe pain in non- anesthetized animals in Great Britain, Canada and the USA. Techniques have been refined. Currently, the quota of reporting this type of procedure are at a scarce level (GRIFFIN, 2002) and society counts on Research and Ethics Comittees to make sure animal experiments are rightly perfomed. Nevertheless, though the use of mice was decreasing gradually from 1991 to 1997, from then on, a progressive increase is being detected, coinciding with the increase in the use of the transgenic animals. The relevancy of this increase detected in mice turns out to be clear if one bears in mind that the rodents (mice and rats) constitute the group most extensively used as laboratory animals: in 1999, for example, rodents counted for85 % of the total of laboratory animals used in Europe.

Therefore, the information on the use of animals seems to indicate that until the mid 1990s, the effort to reduce the number of animals used for research made by the governments was turning out to be really effective, but from this date, and coinciding with the development of the genetic modification in animals, there has taken place an important change in this reductionist trend. A different necessity created a different demanding for lab animals.

The increase in the use of animals for research that include procedures of genetic modification are linked to the fact that they constitute models to study the detailed molecular mechanism of pathologies, and on the other hand, to the fact that in order to obtain transgenic mutants, a great number of animals that are rejected for not presenting the appropriate geno or phenotype (they do not show the specific characteristics that are required), or because they are not allowed to live. In many occasions a large part of transgenic animals do not survive over a long period of time from their birth, since the physiological and anatomical defects are directly derived from the introduction of the new gene are too significant. Also, these animals by law have to be destroyed once used.

Moreover, transgenetic technologies show a low-level of efficiency in many experiments and many of the animals used for the process die early during the embryonic development or due to anatomical, physiological or behavioral defects. In some occasions the transgenetic process leads to the appearance of unexpected phenotypes, due to a limited control of the technology of insertion of genes or due to unexpected interactions of the introduced DNA with other genes of the animal used (*background* or genetic pool). As an example, depending of the methodology used, the creation of a strain of transgenic mice in the year 2000 required an average of between 365 and 900 mice (HUGHES, 2001). Certainly, technologies have slightly improved since then, but the obtaining of a transgenic animal does still cause the "loss" of a high number of animals.

Once *"founded"* a strain of a transgenic animal, the subsequent animals are created by means of conventional crossing methods, in order to obtain animals that are going to be used for future experiments.

Moreover, in relation to the second *"R"*, **refinement**, the situation gets complex. Technologies of genetic modification, as will be shown, are increasingly precise in means of the insertion of genes. This is why the unwanted effects of the process of insertion, at least in some species, are getting easier to avoid. But random insertion is a persistent deleterious effect stilla for many transgenic techniques. Those animals are prone to have additional health vulnerabilities.

The use of the genetic modification is associated with the search for phenotypical effects that are easily detectable by the researcher, effects that usually are being associated with the presence of important anatomical, histological and physiological alterations, etc. In this respect, one of the most frequent and interesting applications, from the scientific point of view, is the creation of the previously mentioned transgenic *knock-outs*, those are, animals in which a functional gene is replaced with a non-functional version by means of homologeous recombination. This type of *site-directed mutagenesis* by deletion produces the absence of a certain functional gene product. This technology has been especially developed and applied to mice with the aim of creating models of human and animal neoplasic diseases. In these situations in which the disease is *"created"*, the animals undoubtedly suffer to some degree (MEMPHAM et al., 1999).

It is questionable whether it is appropriate to apply the technology of genetic modification to specifically generate animals that experience a disease that in many cases usually would not break out in this species under natural conditions.

Certainly, there might be discussed if the suffering generated by a "created" pathology in an animal model is unnecessary or not, or if it is necessary to be relieved of a iatrogenic process, but what is clear is that for health personnel it is a "must" to cure, if possible,, unless one previously decides not to "generate" the above-mentioned animal model. Sadly, slaughter is the most frequent end for paradoxically avoiding transgenic genes spread.

As for the importance of the genetically modified animals, there are two aspects that must be considered in the third "r" of **reemplacement**. On the one hand, the possibility of creating animal models in species as the mouse, gives the opportunity to reduce the use of non-human primates in some types of clinical trials, for example, the clinical trial of the polio vaccine (GORDON, 1997), in research on neurodegenerative diseases (CHAN, 2004), on viral infections such as hepatitis B, HIV, etc. On the other hand, the development of new technologies for the gene inactivation, as the interference RNA (RNAi), enables to think about alternative methods that in the near future could replace some experi-

ments that nowadays are carried out in mammalian *knock-outs*, such as clinical trials of gene silencing in cultures of stem cells or differentiated cells (HASUWA, 2002), or clinical trials carried out in non-mammalian animals for which the methodology of homologous recombination has not been developed up to the moment (ROIGNANT et al., 2003).

It is possible that the numerous scientific and biotechnological possibilities of the genetic modifications (studies on gene regulation, physiological research, production of proteins or specific hormones, clinical trials on toxicity of medicines, improvement of growth and of quality in agriculture, etc.) lead to an *explosion*, maybe temporarily, in its use. It is important to indicate that the justification for this explosion in the use of transgenic animals on the basis of the potential benefits that derive from their use, is a point of view that belongs to the area of the so-called "utilitarian ethics", which, nevertheless, is not shared by the whole society.

The characters introduced by means of genetic engineering in species destined to the production of edible products contribute to an increased productivity (for example by means of a major resistance to plagues) as well as the introduction of new characteristics of quality. Due to the major development of the genetic manipulation in plant species, all GMO food products correspond to derivatives of plants. A frequently used characteristic is, for example, the resistance to herbicides, as it is possible to use them in a way that they only affect the flora alien to the crop. It is to be emphasized that the employment of modified varieties that are resistant to herbicides has diminished the pollution due to the presence of these products in aquiferous and soils, though it is true that there would be no need for the use of these herbicides, which are very harmful because of their content of glyphosate (GLY) and ammonium glyphosinate (GLU) if these varieties were not planted, which are exclusively designed to resist to the above-mentioned compounds.

Insect pests are one of the most devastating elements in agriculture. For this reason, the introduction of genes that provoke the development of plants that are resistant to one or more insect orders has been a common element of many of the patented varieties. The advantages of this method leads to a minor use of insecticides in the fields sowed with these varieties, which results in a minor impact to the ecosystem that harbors the crops and to the health of the workers that manipulate the phytosanitaries.
Ultimately, the first transgenic animals are being developed. The first transgenic animal that has been approved for human consumption in the USA was a salmon called Aqua Bounty (2010)[14], which was capable of growing twice as fast and also during the winter, thanks to the growth hormone of another species of salmon and the "antifreeze" gene of another species of fish.

In several countries of the world there have appeared groups opposed[15] to the creation of transgenic organisms, principally made up of ecologists, associations that promote consumer rights, as well as some scientists and politicians. Those demand the labeling of genetically modified organisms since they worry about *food safety*, environmental impact, cultural changes and economic dependences that could arise from the use of these products. They invoke to avoid this type of food, whose production would involve damages to health, as well as environmental, economic, social damages and legal and ethical problems due to patent restrictions. Thus, the advantages and disadvantages of the process need to be taken into account. That is to say: the beneficial impact as for economy, environmental status of the near-crops ecosystem and on the health of the farmer should be taken into account, as previously described, as well as doubts with regard to the possible appearance of allergies, changes in the nutritional profile, dilution of the genetic array and the diffusion of resistances to antibiotics.

The Food and Agriculture Association (FAO) indicated the following with regard to the transgenics whose purpose is to serve as food supply: The countries in which transgenic crops have been introduced to fields have not observed notable damages to health or environment. In addition, the farmers use fewer pesticides or less toxic pesticides, reducing in this way the pollution of the water supplies and the damages to the health of the workers, allowing also the return to the fields of beneficial insects. Some of the concerns related to the flow of genes and the resistance to plagues have been approached thanks to new technologies of genetic engineering.

Nevertheless, that there have not been observed negative effects until now, does not mean that could not exist in the future. Many scientists request a careful case-by- case evaluation, before the product or process can be spread, in order to face the legitimate safety concerns.

The elimination of living autochthonous varieties due to the use of genetically improved populations, diminish the genetic range and the biodiversity for other characteristics that can be brought together with the selected characteristics. If one considers, in addition, the induced reproduction impossibility of certain populations or the lack of observation of other biological characteristics beyond the aim of the study, the damage is profound at an ecological level.

The World Health Organization indicates in this regard that the different genetically modified organisms (GMO) include different genes inserted in different ways. This means that

14. Aqua Bounty is a biotechnological company dedicated to research, the development and the commercialization of products that are intended to increase the productivity of the fish farming.
15. There was a protest by Spanish agrarian organizations against the use of transgenics in the ecological agriculture (Puerta del Sol of Madrid, on the 30th of August of 2008).

each genetically modified food (GM) and its innocuousness need to be evaluated individually and that is not possible to make generalized statements on the innocuousness of all genetically modified food. The genetically modified food that is nowadays available on the international market passed the risk assessments and it is not probable that they present risks to human health. In addition, there have not been demonstrated effects on the human health as a result of the consumption of the above-mentioned food by the general population, in the countries where they were approved. The constant use of risk assessments according to the principles of the codex and, where applicable, including the post-commercialization monitoring, need to be the base to evaluate the innocuousness of the genetically modified food.

This way, some arguments against the use of transgenic animals in research are related to an issue prior to its application, such as during the creation of a transgenic animal, the genetic integrity of the animals is not respected since there takes place a recombination of genetic material of different species and even different kingdoms (between animals and plants for example). Some consider that this recombination of genetic material between species, or the creation of chimeras, which in occasions is a part of the technical strategy for the obtaining of a transgenic animal, alters the concept of "species" and is an unnatural intervention that might interfere in the conception of what makes that an animal is such. By thinking this way, questions arise such as what makes that a pig is such in the case that it possesses human genes.

To conclude, there is argued that the direct genetic modification is merely a tool. It can be harmful or benefical; It is a mere extension of the traditional and biological technologies of crossing, so that if genetic modifications of animals provide arguments for accusations such as *"playing God"*, *"unnatural"* or *"to treat to the animals as goods"*, the same arguments would be applicable to the selective crossings that are used in a routine way (BOYD GROUP, 1999)[16].

16. Boyd Group is a forum for the exchange of points of view on questions of interest related to the use of laboratory animals.

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ARTICLE ESPECIAL

La prevención primaria del cáncer de cervix: las vacunas frente al virus del papiloma humano

Primary prevention of cervical cancer: vaccines against human papillomavirus

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Resumen

En la actualidad se encuentran disponibles dos excelentes vacunas frente al VPH: la tetravalente (VT), tipos 6-11-16-18, cuyo nombre comercial es Gardasil®, y la bivalente (VB), tipos 16-18, comercializada como Cervarix®.

Ambas vacunas han actualizado sus fichas técnicas en 2014. Son aspectos a destacar que la edad de administración es a partir de los 9 años, sin límite superior; que no hay alusión a que la actividad sexual de la mujer o su contacto previo con el VPH constituya barrera a la vacunación; que la protección se amplía a las neoplasias intraepiteliales de cérvix, vagina y vulva; que hay un cierto grado de protección cruzada, especialmente para la VB; que la VT protege - hombres (9-26 años) y mujeres - frente a la neoplasia anal y frente a verrugas genitales.

Asimismo cabe destacar tres novedades muy importantes: 1) Administradas cuando se va a tratar una neoplasia intraepitelial de cérvix (ambas vacunas) o de verrugas genitales (VT), las vacunas confieren una reducción importantísima (60% de media) del riesgo de recidiva o segunda lesión; 2) Dos dosis (meses 0 y 6) son suficientes en niños y niñas de 9 a 13 años (VT) y en niñas hasta 14 años (VB); 3) datos muy satisfactorios de inmunogenicidad, seguridad y eficacia de la vacuna nonavalente (V503, Merck), tipo 6/11/16/18/31/33/45/52/58, comparables en todo a los datos de la VT.

La seguridad de ambas vacunas está fuera de duda. La OMS y el Centro para el Control de Enfermedades de Estados Unidos (CDC) la han re-confirmado recientemente.

Palabras clave: Vacunas,VPH, efectos secundarios, prevención, cáncer de cervix

Abstract

Currently two excellent vaccines against HPV are available: the quadrivalent vaccine (VT) 6-11-16-18 types, marketed as *Gardasil*, and the bivalent one (BV), types 16-18, marketed as *Cervarix*.

Both vaccines have updated their sheets in 2014. There are several aspects to emphasize: the administration's age is from 9 years with no upper limit; sexual activity of the woman or her previous contact with the virus doesn't represent a barrier for HPV vaccination; protection conferred is extended to intraepithelial neoplasia of cervix, vagina and vulva; there is some degree of cross protection, especially for VB; VT protects -males (9-26 years) and women- against anal neoplasia and genital warts.

We also note three other important contributions: 1) If used to treat cervical intraepithelial neoplasia (both vaccines) or genital warts (VT), vaccines confer a dramatic reduction (60% on average) of risk of recurrence/ second injury; 2) Two doses (months 0 and 6) are enough in children aged 9 to 13 years (VT) and girls up to 14 years (VB); 3) very encouraging evidence of immunogenicity, safety and efficacy are reported about the nine-valent vaccine (V503, Merck), type 6/11/16/18/31/33/45/52/58, comparable to VT data .

Finally, safety of both vaccines is beyond doubt. WHO and the Center for Disease Control of the United States (CDC) have recently re-confirmed it.

Keywords: Vaccines , HPV, secundary effects, prevention, cervical cancer

El punto de partida

El grupo de Friburgo dirigido por Harald zur Hausen describió en 1977 la asociación causal del VPH con el cáncer de cérvix (CC). Recibió por ello el Premio Nobel en 2008. Un grupo multinacional – con los españoles del Institut Català d'Oncologia entre ellos – confirmo en 1999 que desde el punto epidemiológico esta vinculación del VPH con el CC era necesaria - no se espera que una mujer VPH negativa desarrolle un CC -, y que esto era cierto a nivel global, en cualquier circunstancia o escenario. El CC pasó a ser considerado un final infrecuente – la mayoría de las mujeres infectadas no lo desarrollan – de una infección frecuente – la infección VPH es muy prevalente a nivel mundial –. En 1992, un equipo dirigido en Queensland, Australia, por Ian Frazer había puesto a punto las partículas semejantes a los virus, "VLPs" en su acrónimo inglés, partículas inmunogénicamente iguales a los viriones nativos pero desprovistas de carga infectiva. Esta innovación hizo posible el desarrollo experimental de vacunas frente al VPH, trabajo que fue liderado por Doug Lowy y John Schiller en el Laboratorio que aún dirigen en el National Cancer Institute de Bethesda, USA. La posibilidad de fabricar una vacuna frente al VPH estaba servida y dos Compañías Farmacéuticas – GSK y Merck/SPMSD - se interesaron por la idea y trabajaron en su ensayo clínico.

La Organización Mundial de la Salud (OMS) tuteló el proceso[1] y marcó los niveles de control más altos nunca exigidos para una vacuna en el desarrollo de las vacunas frente al VPH. La OMS estableció que la neoplasia intraepitelial de cérvix (CIN) de alto grado podía ser la variable subrogada de eficacia a tener cuenta para cubrir el end-point principal de la validación clínica de las vacunas frente al VPH, la protección frente al cáncer invasor: el CIN2+ es paso necesario en la historia natural del CC, proteger frente a CIN2+ equivale a proteger frente a CC. Cabe recordar aquí una solicitud de la OMS, frecuentemente olvidada: los resultados de los ensayos clínicos de las dos vacunas – excelentes - no deben ser comparados, dado que el diseño de estos ensayos fue diferente, las poblaciones reclutadas para su desarrollo no fueron similares y la composición de y los criterios seguidos por los paneles de expertos que revisaron los resultados eran también desiguales.

La OMS ha certificado que disponemos de dos vacunas muy buenas frente al VPH y ha recomendado su aplicación universal[2]:

• Gardasil® (Merck / SPMSD), vacuna tetravalente con VLPs de los tipos 6 (20 microgramos (µg)), 11 (40 µg), 16 (40 µg) y 18 (20 µg). Producida por tecnología recombinante DNA usando un sistema de expresión en esporas celulares de Saccharomyces cerevisiae CANADE 3C-5. Adyuvante: Sulfato amorfo de hidrofosfato de aluminio (0.225 miligramos (mg) de Al).

• Cervarix® (GSK) vacuna bivalente con VLPs de los tipos 16 (20 µg) y 18 (20 µg). Producida por tecnología recombinante DNA usando un sistema de expresión de Baculovirus en células Hi-5 Rix4446 derivadas de la Trichoplusia ni. Adyuvante: AS04, que contiene 3-0-desacyl-4'-monofosforil lípido A (MPL)3 (50 µg) e hidróxido de aluminio hidratado ($Al(OH)_3$) (0,5 mg).

Indicaciones, eficacia, seguridad e inmunogenicidad de las vacunas frente al VPH

La mejor fuente para consultar los datos de las vacunas frente al VPH es las respectivas Fichas Técnicas (FTs), ambas actualizadas en 2014[3, 4]

Gardasil®:

Indicaciones

• Es una vacuna para uso a partir de los 9 años de edad para la prevención de:
- Lesiones premalignas (cervicales, vulvares y vaginales) y cáncer cervical causalmente relacionados con ciertos tipos oncogénicos del VPH
- Verrugas genitales (condilomas acuminados) relacionadas causalmente con tipos específicos de VPH.

Posología

• De 9 a 13 años:
- Gardasil® puede ser administrado de acuerdo con un esquema de 2 dosis, 0,5 ml en los meses 0 y 6. Si la 2ª dosis es administrada antes de los 6 meses después de la 1ª dosis, una 3ª dosis debe ser administrada.
- Alternativamente, Gardasil® puede ser administrado de acuerdo a un esquema de 3 dosis (0.5 ml en los mes 0, 2 y 6). La 2ª dosis debe ser administrada al menos 1 mes después de la 1ª dosis y la 3ª dosis debe ser administrada al menos 3 meses después de la 2ª dosis. Las tres dosis deben ser administradas en el período de 1 año.

• De 14 años o más: Gardasil® debe ser administrado de acuerdo a un esquema de 3 dosis (0.5 ml en los mes 0, 2 y 6). La 2ª dosis debe ser administrada al menos 1 mes después de la 1ª dosis y la 3ª dosis debe ser administrada al menos 3 meses después de la 2ª dosis. Las tres dosis deben ser administradas en el período de 1 año.

• Gardasil® debe ser administrada por inyección intramuscular. El lugar preferente es el área deltoidea del brazo o el área anterolateral superior del muslo. No debe ser administrada intravascular ni intradérmica ni subcutánea.

Cervarix®:

Indicaciones

• Es una vacuna para uso a partir de los 9 años de edad para la prevención de lesiones premalignas (cervicales, vulvares y vaginales) y cáncer cervical causalmente relacionadas con ciertos tipos oncogénicos del VPH

Posología

• De 9 a 14 años:
- Dos dosis cada una de 0.5 ml en los meses 0 y 6.
- Flexibilidad: Segunda dosis entre 5 y 7 meses después de la 1ª dosis

• De 15 años en adelante:
- Tres dosis cada una de 0,5 ml en los meses 0, 1 y 6.
- Flexibilidad: Segunda dosis entre 1 y 2,5 meses después de la 1ª dosis. Tercera dosis entre 5 y 12 meses después de la 1ª dosis

• Si a cualquier edad la 2ª dosis es administrada antes del 5º mes después de la 1ª dosis, la 3ª dosis debe ser siempre administrada.
• Cervarix® es para inyección intramuscular en la región deltoidea.

A DESTACAR:

- Indicación de uso a partir de los 9 años de edad, sin límite superior.
- Ninguna alusión a que ser o no sexualmente activa o haber sufrido o no infección previa por VPH condicione la administración de la vacuna:
  - Esta vacuna ha dejado de ser exclusivamente para pre-adolecentes sin relaciones sexuales.
- "Lesiones causadas por ciertos tipos oncogénicos", alusión a la protección cruzada, protección frente a tipos de VPH no vacunales: protección frente a tipos filogenéticamente próximos a los vacunales que amplía sustancialmente el espectro protector de la vacuna.
- Protección frente a cáncer cervical, sin especificar tipo histológico, escamoso o glandular: el adenocarcinoma de cérvix muestra en los registros tendencia consolidada al incremento, dada la ineficacia frente a él de la prevención secundaria basada en citología y colposcopia.
- Para Gardasil®, protección frente a verrugas genitales, sin precisar sexo, hombres y mujeres.
- La incorporación a las FTs de los esquemas de aplicación a 2 dosis.

Estos son los principales datos de **eficacia, seguridad** e **inmunogenicidad** que constan en las FTs de ambas vacunas:

Gardasil®[2]

• Eficacia

Mujeres 16 - 26 años:

· Población por protocolo (PP): Tres dosis, naïve a tipos relevantes de VPH, sin violaciones del protocolo.
· Frente a CIN 2/3 y AIS por tipos 16/18: 98.2 (95%IC:93.5-98.8)
· Frente a VIN 2/3*: 100% (95%:67.2-100)
· Frente a ValN2/3*: 100% (95%:5.4-100)
· Frente a VG*: 99% (95%:96.2-99.9)

* Por tipos vacunales
AIS: Adenocarcinoma in situ; VIN; Neoplasia intraepitelial de vulva; ValN; Neoplasia intraepitelial de vagina
VG: Verrugas genitales

· Población por intención de tratar (ITT): Al menos 1 dosis, cualquier estado VPH al reclutamiento. Esta población se aproxima en su estado a la población general con respecto a la prevalencia del VPH.
· Frente a CIN 2/3 y AIS por tipos 16/18: 51.8 (95%IC:41.1-60.7)
· Frente a VIN 2/3*: 73.3% (95%:40.3-89.4)
· Frente a ValN 2/3*: 85.7% (95%:37.6-98.4)
· Frente a VG*: 80.3% (95%:73.9-85.3)

* Por tipos vacunales

· Protección global frente al volumen de enfermedad cervical VPH relacionada. En mujeres naïve a los 14 tipos comunes de VPH y que presentaron una citología negativa al reclutamiento, reducción de la incidencia de:
· CIN 2/3* o AIS*: 42.7% (95%IC:23.7-57.3)
· VG*: 82.8% (95%IC:74.3-88.8)

* Por tipos vacunales o no vacunales de VPH

Protección Cruzada

El estudio no fue diseñado para el análisis de resultados frente a tipos individuales no vacunales de VPH.

· Protección frente a CIN2/3 y AIS. Población VPH naïve para tipos específicos

· Tipos 31-45	43.2%	95% IC:12.1-63.9
· Tipos 31-33-45-52-58	25.8%	95% IC:4.6-42.5
· 10 tipos no vacunales de VPH	23.0%	95% IC:5.1-37.7
· 16 tipos no vacunales de VPH	29.1%	95% IC:9.1-44.9

Mujeres 24 – 45 años

· Eficacia combinada frente a infección persistente, verrugas genitales, lesiones vulvares y vaginales, CIN de cualquier grado, AIS y cáncer cervical por tipos vacunales:
· PP: 88.7% (95%IC: 78.1-94.8)

· ITT: 47.2% (95%IC: 33.5-58.2)

Reducción de procedimientos terapéuticos cervicales

Al final del estudio, Gardasil® los redujo en las siguientes proporciones:

· Población VPH naïve: Naïve a los 14 tipos comunes de VPH y citología negativa al reclutamiento: 41.9% (95%IC:27.7-43.7)
· ITT: 23.9 (95%IC:15.2-31.7)

Hombres 16 – 26 años

· Población PP. Protección frente a
Lesiones genitales externas*: 90.6% (95%IC:70.1-98.2)
Verrugas genitales*: 89.3% (95%IC:65.3-97.9)
PIN 2/3*: 100% (95%IC:-52.1-100)
*Por tipos vacunales
PIN: Neoplasia intraepitelial de pene

· Población ITT. Protección frente a
Verrugas genitales*: 68.1% (95%IC: 48.8-79.3)* Por tipos vacunales
· Sub-análisis en hombres homosexuales (MSM). Eficacia frente a AIN 2/3:
Población PP
Por tipos vacunales: 74.9% (95%IC:8.8-95.4)
Por tipos 16-18: 86.6% (95%IC:0.0-99.7)
Población ITT
Por tipos vacunales: 54.2% (95%IC:18.0-75.3)
Por tipos 16-18: 57.5% (95%IC:-1.8-83.9)

AIN: Neoplasia intraepitelial de ano

• Seguridad

A partir de la experiencia acumulada en los ensayos clínicos y en el control de la aplicación clínica, la reacción adversa más comúnmente es la reacción local (rubor, prurito, dolor) en el sitio de inyección (77% de los vacunados durante los 5 primeros días post-vacunación) y cefalea (16.6%). Otras reacciones frecuentes (por encima del 10% de casos) son las náuseas y la fiebre. Todas fueron ligeras y de moderada intensidad.

La urticaria se presentó en escasas ocasiones (entre > 1/10.000 y < 1/1.000 casos) y el broncoespasmo en muy escasas ocasiones (< 1/10.000 casos)

Se han comunicado en registros pasivos casos de mareos, Síndrome de Guillain-Barré, síncope con movimientos tónico-clónicos o artritis. Al ser informes voluntarios procedentes de una población de volumen no conocido, no es posible estimar de forma fiable su frecuencia o establecer su relación con la exposición a la vacuna.

• Inmunogenicidad

Los **porcentajes de seropositividad** medidos por un ensayo tipo-específico (cLIA) contra los 4 tipos vacunales al mes 1 post primera dosis fueron:

· Mujeres de 16 a 26 años:
Anti-VPH 6: 99.8%
Anti-VPH 11: 99.8%
Anti-VPH 16: 99.8%
Anti-VPH 18: 99.5%

· Mujeres de 24 a 45 años:
Anti-VPH 6: 98.4%
Anti-VPH 11: 98.1%
Anti-VPH 16: 98.8%
Anti-VPH 18: 97.4%

Los niveles en los individuos de la cohorte placebo que habían aclarado una infección previa (seropositivos / PCR negativos) fueron sustancialmente menores que los inducidos por la vacuna.

Entre el 97.4 y el 99.9% de los hombres vacunados seroconvirtieron para los cuatro tipos vacunales al mes de recibir la vacuna.

Persistencia de la seropositividad

· Mujeres 16 – 26 años: Seguimiento 60 meses. Porcentajes de seropositividad:
Anti-VPH 6: 90%
Anti-VPH 11: 95%
Anti-VPH 16: 98%
Anti-VPH 18: 60%

· Mujeres 24 – 45 años: Seguimiento medio 4 años. Porcentajes de seropositividad:
Anti-VPH 6: 91.5%
Anti-VPH 11: 92.0%
Anti-VPH 16: 97.4%
Anti-VPH 18: 47.9%

· Hombres 16 – 26 años: Seguimiento medio 2,9 años. Porcentajes de seropositividad:
Anti-VPH 6: 88.9%
Anti-VPH 11: 94.0%
Anti-VPH 16: 97.9%
Anti-VPH 18: 57.1%

· En los estudios de seguimiento a largo plazo las mujeres de 16-45 años y los hombres de 16-26 que era negativos al cLIA estaban todavía protegidos frente a la enfermedad clínica.

Memoria Inmune

Un subgrupo de mujeres vacunadas con Gardasil® que recibieron una 4ª dosis 5 años después del final de su vacunación presentaron una rápida y potente respuesta anamnésica que provocó títulos de anticuerpos anti-VPH superiores a los que se habían obtenido en el mes 1 post-vacunación.

Cervarix®[3]

• **Eficacia**

Mujeres 15– 25 años

· Frente a CIN 2+por tipos 16/18

Población ATP: Tres dosis, DNA – / sero – mes 0 y DNA – mes 6 a tipos 16/18: 94.9 (95%IC:87.7-98.4)
Población TVC: Al menos 1 dosis, cualquier estado VPH al reclutamiento. Incluye mujeres con o sin infección VPH actual o pasada. Esta población se aproxima en su estado a la población general de mujeres entre 15 y 25 años: 60.7 (95%IC:49.6-69.5)

· Frente a CIN2+ por cualquier tipo de VPH:

Población TVC: 33.1% (95%IC:22.2-42.6)
Población TVC naïve: Al menos 1 dosis. Citología negativa y DNA – para 14 tipos oncogénicos de VPH y sero – para tipos 16/18 al reclutamiento: 64.9% (95%IC:52.7-74.82)

Protección Cruzada

· Protección frente a CIN2+. Población ATP

Tipo 31	87.5%	95% IC:68.3-96.1
Tipo 33	68.3%	95% IC:39.7-84.4
Tipo 39	74.9%	95% IC:22.3-93.9
Tipo 45	81.9%	95% IC:17.0-98.1
Tipo 51	54.4%	95% IC:22.0-74.2

Mujeres de 26 años o más

· Eficacia frente a infección persistente por VPH a 6 meses, marcador subrogado relevante para cáncer cervical:

Población ATP: 82.9% (97.7%IC: 52.8-96.1)
Población TVC: 47% (97.7%IC: 25.4-62.7)

Reducción de procedimientos terapéuticos cervicales

· Al final del estudio, Cervarix® los redujo en las siguientes proporciones:

Población TVC naïve: 70.2% (95%IC:57.8-79.3)
Población TVC: 33.2 (95%IC:20.8-43.7)

• **Seguridad**

La reacción adversa más frecuentemente observada después de la administración de la vacuna fue el dolor y el rubor en el sitio de la inyección, 78% de todas las dosis. Otras reacciones muy frecuentes (por encima del 10% de casos) fueron las mialgias y la cefalea. Reacciones frecuentes (entre > 1/100 y < 1/10 casos) fueron los síntomas gastrointestinales, el prurito, la artralgia y la fiebre (> 38º).La mayoría de estas reacciones fueron de severidad leve o moderada y de corta duración.

Las infecciones respiratorias y los mareos aparecieron en muy escasas ocasiones (entre > 1/1000 a <1/100 casos).

Se han comunicado en registros pasivos casos de linfadenopatías, reacciones anafilácticas, angioedema, sincope o reacciones vasovagales, a veces acompañadas de movimientos tónico-clónicos y mareos. Al ser informes espontáneos, no es posible estimar de forma fiable su frecuencia.

• **Inmunogenicidad**

Porcentajes de seropositividad: Mujeres de 9 a 55 años

Un mes post-tercera dosis, más del 99% de las que recibieron Cervarix® fueron sero-positivas para anticuerpos (Ac) anti 16/18 (Ensayo ELISA).

Las mujeres sero – o sero + al inicio alcanzaron títulos similares de Ac post-vacunación.

Los títulos de Ac inducidos por la vacunación fueron más altos que los observados en mujeres previamente infectadas por VPH pero que habían aclarado su infección.

Persistencia de la seropositividad:

· Mujeres de 15 a 25 años

92 mujeres seguidas más de 8,9 años: 100% (95%IC:96.1-100) seguían seropositivas para Ac anti 16/18 medidos por el ensayo ELISA.

El mantenimiento de los títulos de Ac se sitúa al menos 10 veces por encima del observado en las mujeres que han aclarado la infección natural.

· Mujeres de 26 años o más

100% de seropositividad frente al VPH 16 y 99.4% frente al VPH 18 48 meses después de la 1ª dosis de Cervarix®, con niveles menores que en mujeres de menos de 25 años, pero más altos que los producidos por la infección natural.

Memoria Inmune

Un grupo de mujeres vacunadas con Cervarix® que recibieron una 4ª dosis 6,8 años después de la 1ª dosis presentaron una respuesta anamnésica para los tipos vacunales, con niveles superiores a los observados después de recibir la 3ª dosis.

Inmunogenicidad en mujeres HIV +

Una cohorte de 22 mujeres HIV – y otra de 42 HIV + recibieron vacunación con Cervarix®. Todas serocovirtieron

para los dos tipos vacunales, manteniéndose positivas al mes 12 de seguimiento. Los títulos de Ac fueron más bajos en las mujeres HIV +.

La relevancia clínica de esta observación es desconocida.

A DESTACAR:

- Todos los datos recogidos están referenciados en la Fichas Técnicas de ambas vacunas: que los Agencias Europea y Española del Medicamento las hayan aceptado y publicado representa la máxima garantía de calidad.
- Los rangos de eficacia y seguridad de ambas vacunas están en el nivel más alto si se comparan con los de las otras vacunas disponibles frente a otras enfermedades infecciosas.
- La seguridad de las vacunas VPH está bajo control permanente en su actual proceso de aplicación clínica en más de 120 países en todo el mundo mediante registros activos y pasivos controlados por los principales Agentes Sanitarios Nacionales y Supra-Nacionales.
- La última revisión[5] para ambas vacunas confirma su alta seguridad y reasegura el positivo balance riesgo / beneficio de la vacunación VPH

Efectividad y eficiencia de las vacunas frente al VPH

• Efectividad

La medición de la efectividad – reproducción en la aplicación clínica de los resultados obtenidos en el ensayo clínico – exige dos condiciones:

- Existencia de registros previos de la patología cuya prevalencia / incidencia vamos a medir.
- Puesta en marcha de procedimientos de vigilancia epidemiológica y registro de las variables relacionadas con los objetivos preventivos de la vacuna.

El país con adecuación máxima a estas necesidades es Australia, país pionero en la introducción de la vacunación VPH en programas de Salud Pública. Además, las coberturas alcanzadas allí superan claramente el mínimo exigido para que la efectividad – y la eficiencia – sean alcanzadas, un 70%[6, 7]

En la historia natural de la patología VPH dependiente, el marcador clínico más precoz es la VG; después, la alteración citológica, a continuación la neoplasia intraepitelial y finalmente el CC. Este ha sido el proceso de determinación progresiva de la efectividad que se ha seguido y ha sido publicada.

- Efectividad frente a verrugas genitales

Se ha demostrado en varios países (Nueva Zelanda, USA, Alemania, Suecia, Bélgica, Dinamarca, Francia) pero han sido los grupos australianos los que la han documentado y demostrado de forma más rotunda. El programa público de Australia, que ha usado Gardasil®, ha alcanzado en primera dosis una cobertura del 83% y en tercera del 70%[6] en chicas entre 12 y 17 años. En la última publicación del grupo[8] se comunica un descenso del 85% en las consultas y en los tratamientos de VG en las cohortes vacunadas, comparado con la tendencia estable del período pre-vacunación. Este descenso no se detectó en mujeres de más edad. Además, se registró en el mismo período un descenso del 70,6% en las consultas por VG en hombres de 15-24 años, no registrado en años anteriores: es la inmunidad de grupo, por el que en un colectivo con alta cobertura, las personas no vacunadas se benefician de la inmunidad que las vacunadas han desarrollado.

En el Reino Unido se ha detectado[9] una reducción de los diagnósticos de verrugas genitales entre 2008 y 2011 del 13.3% en chicas de 16-19 años, con un pico del 20.8% en las de 17 años. Estos descensos se correlacionaron positivamente con las coberturas vacunales con Cervarix®. No se observaron descensos para otras infecciones genitales y en mujeres de más edad. Es probable que la explicación a este dato inesperado no esté en la protección cruzada frente a los tipos 6 y 11, sino en que en un estudio de seguimiento a 4-6 años post-vacunación con Cervarix® o Gardasil® se demostró[10] que los niveles de células T/CD4 para los tipos 6 y 11 eran similares para ambas vacunas: 0.045% vs 0.045%; 0.051% vs 0.033%, respectivamente.

- Efectividad frente a resultados citológicos anómalos

También en Australia los registros del programa público de aplicación de Gardasil® aportan el siguiente dato[11]: Tasa de lesión intraepitelial de alto grado en mujeres no vacunadas: 15.3 x 1.000 personas/año; en vacunadas, 11.9, 95%IC: 0.65-0.88, una apreciable reducción del número de estos resultados citológicos.

- Efectividad frente a diagnósticos de neoplasia intraepitelial

Nuevamente disponemos de datos al respecto del programa australiano[11]. Las mujeres no vacunadas presentaron una tasa de CIN2+ por 1.000 personas/año del 6.4; las vacunadas con Gardasil®, del 4.8, 95%IC: 0.58-0.91, reducción significativa.

También significativa es la reducción comunicada por el programa público de Escocia[12], que usa Cervarix®, al analizar sus tasas de diagnóstico de CIN3 en las cohortes vacunadas. La reducción se detecta en las lesiones por tipos vacunales 16 y 18 y también por tipos no vacunales 31, 33 y 45.

• **Eficiencia**

Las últimas revisiones publicadas[13, 14], de la OMS y del grupo de Quebec, referencia mundial, confirman que en los países desarrollados los modelos más recientes confirman que vacunar a las chicas pre-adolescentes es altamente eficiente (coste-efectivo).

Una comunicación reciente[15] del grupo de Quebec concluía que:

· Vacunar en programas públicos a mujeres de 19-26 años produce resultados conflictivos.

· La vacunación a chicos no es eficiente con coberturas altas en chicas, dada la inmunidad de grupo.

· El uso de 2 dosis incrementará sustancialmente la eficiencia.

A DESTACAR:

- La efectividad y la eficiencia únicamente se alcanzan con coberturas vacunales superiores al 70%.
- Si no hay registros previos y programas de seguimiento controlado de las cohortes vacunadas no puede medirse el impacto vacunal en la población.
- Disponemos de datos concluyentes procedentes de las mejores fuentes que confirman que la vacunación frente al VPH es altamente efectiva y eficiente.

Novedades más relevantes de las vacunas frente al VPH

La medición de la efectividad – reproducción en la aplicación clínica de los resultados obtenidos en el ensayo clínico – exige dos condiciones:

· Vacunación post-tratamiento de lesiones intraepiteliales

Una revisión presentada en EUROGIN 2013 16 resumía los porcentajes de reducción de CIN2 y VG demostrados después de la vacunación post-tratamiento:

CIN2:	Cervarix®	88.2%	Gardasil®	64.9%
VG:			Gardasil®	63%

La crítica de que se trataba de un análisis retrospectivo con calidad limitada de evidencia, fue solventada en una publicación posterior[17] en la que en un estudio prospectivo y aleatorizado se demostró, después de un ajuste multivariado, que no vacunar con Gardasil® post-LEEP es un factor independiente de riesgo para recidiva:

HR: 2.8, 95%IC: 1.3-6.0, p<0.01.

· Protección de Cervarix® frente a infecciones oral y anal

Eficacia de Cervarix® en mujeres de 18 a 25 años:

- Frente a infecciones orales por tipos 16/18. 93% (95%IC: 63-100). Seguimiento medio, 4 años[18]

- Frente a infección anal por tipos 16/18: 83.6% (95%IC:66.7-92·8)[19]

· Nueva indicación de Gardasil® frente a cáncer anal

En resolución del 25 de Abril de 2014 (EMA/CHMP/253675/2014)[20] el Comité para Productos Medicinales para Uso Humano (CHMP) de la Agencia Europea del Medicamento (EMeA) acordó una recomendación positiva de modificación de la autorización de venta de Gardasil®. El CHMP adoptó la siguiente nueva indicación:

Gardasil® es una vacuna para uso a partir de los 9 años de edad para la prevención de:

- Lesiones premalignas (cervicales, vulvares y vaginales), lesiones premalignas anales y cáncer cervical y anal causalmente relacionados con ciertos tipos oncogénicos del VPH

- Verrugas genitales (condilomas acuminados) relacionadas causalmente con tipos específicos de VPH.

Se espera que esta recomendación del CHMP de la EMeA sea incorporada de forma inmediata a una nueva FT de Gardasil®

· La vacuna nonavalente

En dos comunicaciones a EUROGIN 2013[21, 22] se presentaron los primeros datos de inmunogenicidad, eficacia y seguridad de la vacuna nonavalente (tipos de VPH 6, 11, 16, 18, 31, 33, 45, 52, 58) de Merck /SPMSD.

• **Eficacia**

En población PP, eficacia del 96.7% (95%IC: 80.9-99.8) frente a CIN/VaIN/VIN 2/3 y del 97.1% (95%IC: 91.8-99.2) frente a CIN/VaIN/VIN de cualquier grado, etiológicamente relacionados con los tipos 31/33/45/52/58. La eficacia frente a las lesiones por los tipos 6/11/16/18 no fue inferior a la generada por la vacuna tetravalente.

- **Inmunogenicidad y seguridad**

  · En chicas y chicos de 9 a 15 años y en mujeres de 16 a 26 años la vacuna mantuvo un alto perfil de seguridad, sin acontecimientos adversos serios causalmente relacionados, con un 90.8% de reacciones locales (85.1% para la vacuna tetravalente).

  · Más del 99% de los sujetos vacunados seroconvirtieron para los 9 tipos a niveles similares en todos los grupos incluidos, con niveles de anticuerpos comparables a los de la vacuna tetravalente.

RECORDATORIO FINAL PARA UNA BUENA PRÁCTICA

- La educación de la población en la aplicación conjunta de vacunación VPH y cribado de cáncer de cérvix rediseñado es una obligación de los ginecólogos.
- Recibir consejos adecuados relativos a las nuevas estrategias preventivas del cáncer de cérvix es un derecho de las mujeres.

Cain JM for the FIGO Working Group on Combating Cervical Cancer: Control of cervical cancer: women's options and rights. Int J Gynaecol Obstet 2009; 106: 141-3

Conflicto de Intereses: El primer autor, Javier Cortés, ha recibido becas de viaje y/o de investigación y honorarios por conferencias y/o asesorías de GSK y SPMSD.

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ESTUDI DE CASOS

Varón de 50 años, VIH positivo, con trombopenia y rectorragias

50-year-old VIH positive male, with thrombocytopenia and rectal bleeding

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Resumen

Se trata de un varón de 50 años, VIH no controlado, que ingresó en el hospital por un shock séptico de origen respiratorio. Además presentaba episodios repetidos de rectorragias sin objetivar causa pese a pruebas diagnósticas dirigidas, así como trombopenia persistente. Se realizaron pruebas endoscópicas invasivas sin encontrar la causa, así como pruebas de imagen abdominal (TAC y aortografía) que no mostraron alteraciones. Ante una PCR para CMV positiva en sangre se administró tratamiento con foscarnet, persistiendo las rectorragias y la trombopenia. Ante la persistencia de las rectorragias, se valoró intervención quirúrgica, que se desestimó dado el alto riesgo quirúrgico. El caso se presenta en el foro de las sesiones clinicopatológicas del Hospital Universitario Son Espases.

Abstract

This is a case of a 50-year-old VIH positive male with no medical monitoring, who was admitted to the hospital with septic shock due to an underlying respiratory cause. He also presented repeated rectal bleedings of unknown origin and thrombopenia. Upper and lower endoscopies, abdominal CAT scans and aortography were all negative. Treatment with foscarnet was started after a CMV positive serum -PCR with no improvement. Surgery was not considered, given the high surgical risk. The case is discussed in the context of a clinicopathological general session at Son Espases Universitary Hospital.

Caso clínico

Varón de 50 años, ex-consumidor de drogas vía parenteral, enolismo activo. Coinfectado por VIH y VHC sin control médico. Recibe metadona como tratamiento habitual.

Ingresado por shock séptico secundario a neumonía neumocócica complicado con empiema pleural que precisó de colocación de tubo de drenaje. Tratado con cefepime y clindamicina y posteriormente con penicilina. La carga viral del VIH fue 273 copias/ul y los CD4 de 24cel/ul. Inició tratamiento antirretroviral y cotrimoxazol profiláctico.

Presentó un primer episodio de rectorragia por lo que se realizaron una gastroscopia, que no visualizó alteraciones, y un TAC abdómino-pélvico que no evidenció sangrado. Por aparición de lesiones herpéticas perianales y orales se iniciaron Aciclovir y Fluconazol, y por neumonía basal derecha, piperacilina/tazobactam y ciprofloxacino, con buena evolución de las lesiones y recuperación respiratoria completa.

Analíticamente destacaron valores de hematocrito y plaquetas mantenidos en torno a 26% y 12.000, respectivamente, y aumento de GGT con hiperbilirrubinemia de 11.6 a expensas de la directa en sucesivas determinaciones. La PCR de citomegalovirus en sangre fue positiva, por ello recibió Foscarnet al que se añadió Metronizazol ante la posibilidad de tratase de una colitis pseudomembranosa.

Para el estudio de la plaquetopenia se realizó mielograma, que fue hipocelular con representación de las 3 series, y baciloscopias de médula ósea que fueron negativas. Se solicitó estudio microbiológico de heces que fue negativo, nueva gastroscopia que siguió sin en-

contrar hallazgos, y TAC de abdomen con contraste que objetivó dilatación del rectosigma y colon descendente con líquido en su interior. No se pudo progresar en la colonoscopia por abundantes restos hemáticos, pero la mucosa rectal visualizada era de aspecto normal.

Pocos días después presentó un nuevo episodio de rectorragia. El angioTAC mostró distensión del marco cólico sin imágenes de sangrado; tampoco se pudo progresar en una nueva colonoscopia y la aortografía abdominal fue normal.

A pesar del esfuerzo terapéutico persistieron las rectorragias y la plaquetopenia. Se rechazó cirugía por deterioro del estado clínico del paciente, que finalmente fue *exitus*. Se solicitó necropsia para determinar el origen de la trombopenia y las rectorragias

Discusión

El síndrome de reconstitución inmune consiste en el empeoramiento de una infección/tumor oportunista tras la recuperación del sistema inmune con el inicio de tratamiento antirretroviral (TARGA). Se suele presentar entre la primera semana hasta 5 meses después[1]. En nuestro caso es posible que juegue un papel importante.

La plaquetopenia es muy frecuente en pacientes VIH. Su incidencia está relacionada con el grado de inmunosupresión. Se puede clasificar en:

Primaria: causa más frecuente. Ocasionalmente se resuelve una vez iniciado TARGA. La médula ósea es normal o con elevado número de megacariocitos. Se ha postulado la coexistencia de producción inefectiva junto con un aumento de destrucción periférica[2]. Nuestro mielograma muestra hipocelularidad; junto a la ausencia de mejoría con tratamiento hace sospechar que puede haber otra causa.

Púrpura trombótica trombocitopénica[3]: clínicamente incluye plaquetopenia, anemia hemolítica, fiebre y alteraciones neurológicas y renales. Su baja incidencia y el hecho de que sólo presente plaquetopenia la hace improbable.

Secundaria:
La causa más frecuente son fármacos, que no explicarían la hemorragia digestiva.

El hiperesplenismo secundario es difícil de explicar ya que el TAC no informa de esplenomegalia.

El Sarcoma de Kaposi (SK) y el linfoma pueden explicar los dos signos guía por lo que se incluyen en el diagnóstico diferencial.

Una sepsis bacteriana puede dar trombopenia pero no explica el sangrado digestivo. Otras infecciones, como la Ehrlichia o la Babesia, no están descritas en nuestro medio.

El toxoplasma no es causa de hemorragia digestiva baja (sólo un caso en la literatura en forma de diarrea[4]. La Leishmaniasis visceral puede afectar al tracto gastrointestinal, sobre todo a nivel de intestino delgado (aunque hay casos descritos en colon[5]); en contra no existe esplenomegalia, muy frecuente en esta patología (80% de los casos), y tiene una médula ósea sin parásitos (sensibilidad: 70-90%[6]).

Tanto Histoplama como Coccidioidis son endémicos en zonas de América y África, por tanto altamente improbables en este caso.

Tabla I

Proceso patológico	Esófago	Estómago	Intestino delgado	Colorectal
Inflamación/ulceración	Idiopático Medicamentoso	Gastritis no específica	Enteropatía VIH	Enteropatía VIH Idiopático
Infección viral	CMV Herpes simple	CMV	CMV	CMV Herpes simple
Protozoos y Helmintos		Cryptosporidium	Giardia Cryptosporidium Isospora Microsporidia Strongiloides	---
Bacterias		MAC	MAC	*Clostridium difficile* Salmonella Shigella *Campylobacter* Espiroquetas
Hongos	Candida sp. *Turulopsis glabrata*	*Cryptococcus neoformans*	*Histoplasma capsulatum*	*Cryptococcus neoformans* *Histoplasma capsulatum*
Neoplasias	SK	SK LNH	SK	SK LNH

Las micobacterias, tuberculosa (TBC) y atípicas (MAI), y el Citomegalovirus explicarían la plaquetopenia y sangrado digestivo por lo que se mantienen en el diagnóstico diferencial.

La afectación gastrointestinal es frecuente en pacientes VIH (hasta un 50%). En 2011 se revisaron[7] los hallazgos endoscópicos y anátomo-patológicos del tracto gastrointestinal en pacientes VIH (**Tabla I**).

Si nos centramos en los hallazgos a nivel de colon de la **Tabla I** y los combinamos con las causas de plaquetopenia nos podríamos quedar con el siguiente diferencial:

Patología infecciosa
- Tuberculosis diseminada
- MAC
- CMV

Patología neoplásica
- SK
- LNH

Otras causas:
- PTI + colitis infecciosa
- Sepsis + Neoplasia de colon

La tuberculosis (TBC) es posible por su elevada frecuencia. Se puede dar independientemente del nivel de CD4 y en nuestro caso podría existir riesgo de reactivación (antecedente de "pleuritis"). La clínica del paciente se ajustaría a TBC diseminada. Para su diagnóstico necesitamos la detección del bacilo.

En el caso del MAC, el TAC abdominal puede ser normal hasta en un 25% de los casos[8]. El diagnóstico definitivo se realiza a través del cultivo/ baciloscopia. La baja sensibilidad (30%9) de la baciloscopia en médula ósea hace que no se pueda descartar.

El CMV es probable. Nuestro paciente está en riesgo por su bajo nivel de CD4, viremia positiva para CMV y la afectación del colon es frecuente[10]. La endoscopia es útil para el diagnóstico (VPN de hasta 98%[11]). Aunque nuestro paciente recibió tratamiento para CMV, lo recomendado por expertos[12] son 3-6 semanas.

El papel de la viremia para CMV para el diagnóstico de enfermedad es controvertido. La PCR positiva para CMV, tanto cualitativa como cuantitativa, es factor de riesgo para padecer la enfermedad[13]. Que una viremia positiva equivalga al diagnóstico de enfermedad no está tan claro. En 2007[14] se intentó determinar la sensibilidad, especificidad y los valores predictivos de la PCR cuantitativa (**Tabla II**).

Se ha observado mayor incidencia de neoplasias en pacientes VIH respecto a la población general (excepto el cáncer de próstata).

El SK es el tumor más frecuente en VIH. La afectación gastrointestinal es la presentación extracutánea más frecuente, pudiendo ser el único signo (raro). Los corticoides pueden inducir o exacerbar el SK[15]. A nivel endoscópico se pueden encontrar nódulos hemorrágicos, siendo el diagnóstico definitivo la anatomía patológica.

Nuestro paciente tiene factores de riesgo para LNH. La afectación gastrointestinal es la extranodal más frecuente (sobre todo intestino delgado y estómago). El diagnóstico definitivo es anátomo-patológico, aunque pruebas de imagen y endoscópicas podrían ser útiles.

La lista de probabilidades diagnósticas iría encabezada por el CMV, seguido del SK sin poder descartar totalmente ninguna de las otras posibilidades que hemos ido comentando (incluyendo la asociación de varias patologías).

Hallazgos de la autopsia

Examen externo:

Varón de edad media, con ictericia conjuntival y cutánea y marcada caquexia.
Lesión cutánea en pared costal izquierda secundaria al tubo pleural.

Examen interno:

Hallazgos macroscópicos:

A la apertura de la cavidad torácica se observan adherencias pleuro-costales en ambos lóbulos superiores y derrame pleural purulento en cavidad izquierda. El pulmón derecho pesa 450g y el izquierdo 600g, ambos de apariencia congestiva. En LII destaca importante destrucción del parénquima, con área de fistulización bronco-pleural. Hígado micronodular de 1400g. Vesícula biliar marcadamente distendida, con 100-150 ml de contenido biliar, sin cálculos. Vía biliar permeable. Bazo de 170 g, congestivo.

Tabla II

Resultados PCR	Sensibilidad (%) (95% IC)	Especificidad (%) (95% IC)	VPP (%) (95% IC)	VPN (%) (95% IC)
Carga viral (copias/ml)	---	---	---	---
Cualquier viremia	47 (36-60)	89 (80-94)	76 (59-87)	70 (60-78)
≥ 2000	30 (20-44)	96 (89-99)	84 (62-95)	65 (56-74)
≥10.000	17 (9-29)	100 (95-100)	100 (70-100)	62 (53-70)

Esófago con pequeña úlcera mucosa en tercio medio. Estómago e intestino delgado sin particularidades. Marcada dilatación del colon en toda su extensión. A su apertura abundantes restos hemáticos, con numerosas úlceras en colon ascendente y descendente.

Cerebro de 1330 g de peso, con meninges finas y transparentes. A su apertura no se identifican lesiones.

Hallazgos microscópicos:

El área descrita en LII muestra una cavidad quística, no revestida de epitelio. La pared está integrada por numerosos histiocitos, dispuestos en empalizada, sin conformar granulomas. En su interior se observa denso infiltrado inflamatorio neutrofílico con áreas de abscesificación y necrosis (**Figura 1**). Con técnicas histoquímicas de PAS, Grocott y Ziehl-Neelsen no se observan microorganismos. En ambos pulmones se observan células revistiendo espacios alveolares, y en el interior de los mismos, con nucleomegalia e inclusión intranuclear basofílica, que muestran positividad para tinción inmunohistoquímica de CMV (**Figuras 2 y 3**). También se observan signos de daño alveolar difuso en fase organizada, con edema intralveolar, necrosis de neumocitos, fibrosis de los septos y focal proliferación fibroblástica.

La lesión descrita en esófago y las úlceras en colon ascendente y descendente muestran ulceración mucosa,

Figura 1

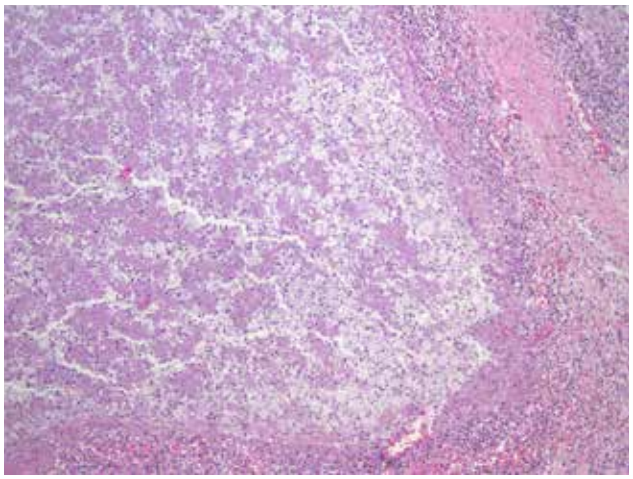


Figura 2

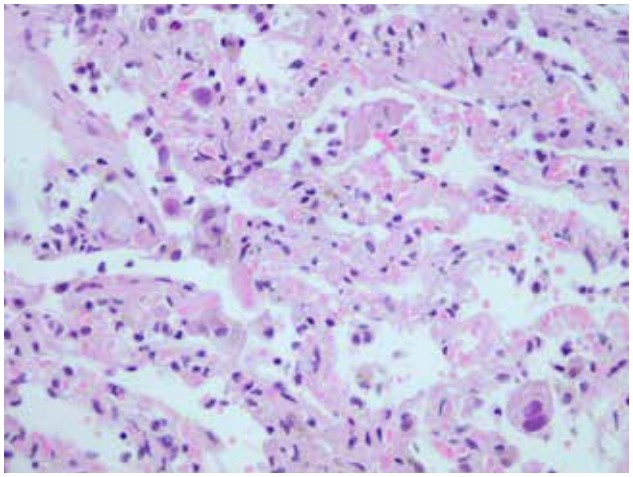


Figura 3

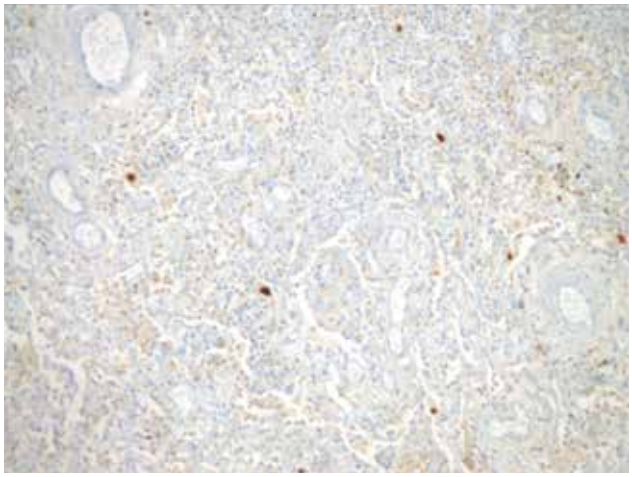


Figura 4

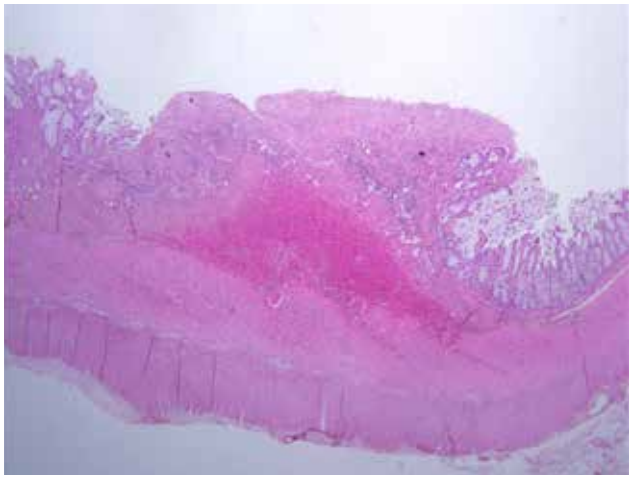
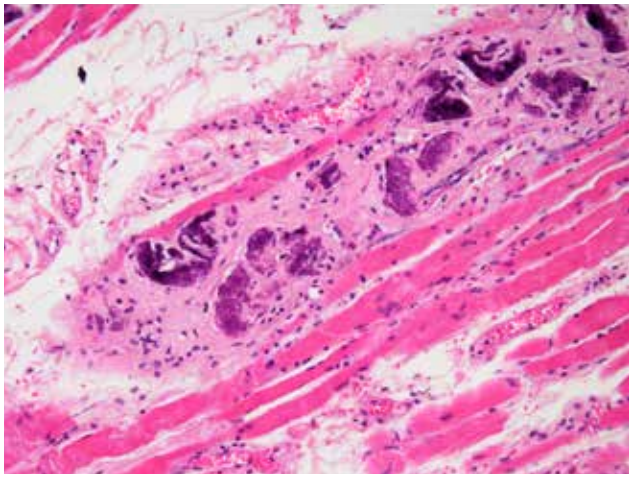


Figura 5



con depósitos de fibrina en la base, infiltrado inflamatorio y proliferación vascular (**Figura 4**). Se identifican aisladas células estromales y endoteliales con nucleomegalia e inclusión intranuclear basofílica, que muestran positividad para tinción de CMV. Tinción para VH8 negativa.

El hígado muestra alteración de la arquitectura normal, con formación de nódulos hepatocitarios de diferentes tamaños separados por septos fibrosos con ligero infiltrado inflamatorio crónico y proliferación ductular. Se observa necrosis isquémica de hepatocitos centronodulares y signos de colestasis. Vesícula biliar autolítica con presencia de colonias bacterianas e infiltrado inflamatorio crónico con polimorfonucleares neutrófilos y depósitos de fibrina en superficie serosa.

Bazo con mala delimitación entre pulpa roja y pulpa blanca, y numerosos macrófagos con pigmento de hemosiderina, probablemente secundario a múltiples transfusiones. Médula ósea hipercelular a expensas de las tres series hematopoyéticas, de aspecto regenerativo.

En fascículos musculares paratiroideos se observa degeneración fibrilar, con atrofia fascicular, núcleos hipertróficos, infiltrado inflamatorio linfohistiocitario y calcificaciones distróficas, sugestivo de miopatía[16] (**Figura 5**).

Diagnósticos de la autopsia

Infección por VIH, categoría C3:
Infección diseminada por Citomegalovirus con:
- Neumonía en ambos pulmones.
- Colitis hemorrágica con megacolon
- Ulceración esofágica.

Neumonía necrotizante en lóbulo inferior izquierdo, en fase avanzada.
- Empiema.

Caquexia intensa
Miopatía calcificada.

Shock séptico/hemorrágico:
Necrosis isquémica hepática
Congestión esplénica.
Daño alveolar difuso em fase avanzada.
Colecistitis crónica agudizada.

Hepatopatía crónica com cirrosis y leve actividad.
Ictericia conjuntival y cutánea.

Diagnósticos

En pacientes inmunodeprimidos puede verse positividad serológica para infección por CMV[17] o aislarse en fluidos corporales en ausencia de enfermedad clínica. Para su diagnóstico definitivo es necesaria evidencia histológica.[18,19] Las células infectadas por CMV muestran cambios citomegálicos con inclusiones intranucleares o citoplasmáticas características. A veces es necesario el uso de tinciones inmunohistoquímicas o de hibridación in situ.

La infección de la mucosa gastrointestinal por CMV ocasiona inflamación, necrosis tisular y compromiso del endotelio vascular, que puede originar daño isquémico. La hemorragia digestiva puede ser masiva[20].

A nivel pulmonar puede producir desde neumonitis intersticial mínima hasta daño alveolar difuso severo, como en este caso.

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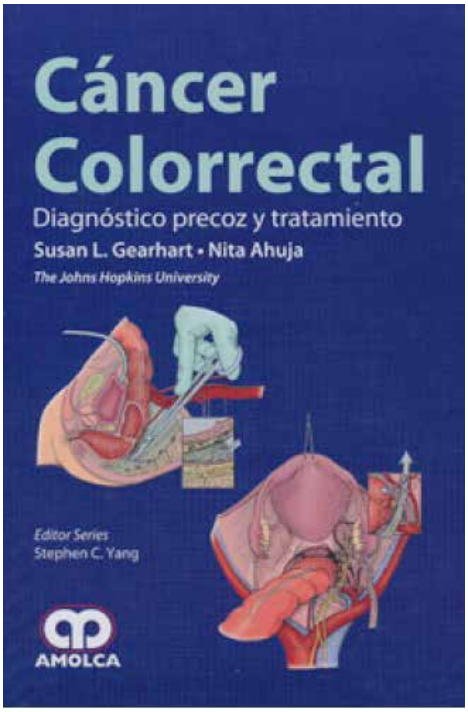
LLIBRES

Cáncer colorrectal. Diagnóstico precoz y tratamiento, de Susan L. Gearhart y Nita Ahuja (eds).

Joan March Noguera

Acadèmic numerari de la Reial Acadèmia de Medicina de les Illes Balears

Aquesta ressenya és un "a mode de" recordatori de l'eminent digestòleg mallorquí i membre de la Reial Acadèmia de Medicina el doctor Antoni Obrador, que tant va fer per la prevenció i el tractament dels càncers colorrectals a Mallorca i que va morir jove víctima d'un càncer.



La publicació objecte de la ressenya ha estat coordinada per les doctores Susan L. Gearhart i Nita Ahuja, professores assistents de Cirurgia i Oncologia Colorrectal al Departament de Cirurgia de la Universitat Johns Hopkins (1876), considerada com la número ú del Estats Units en investigació en ciències, i ha comptat amb un ample ventall de col·laboradors que han redactat els 21 capítols del llibre al llarg de 277 pàgines.

Aquesta publicació, de 2012, és la segona edició en castellà i correspon també a la segona edició nord-americana duta a terme pel grup Editorial Elsevier. Està emmarcada dins d'una col·lecció de publicacions de l'Escola de Medicina de la Johns Hopkins University sobre l'establiment de protocols de prevenció del desenvolupament de diverses malalties.

La tesi central del llibre és que cal augmentar de forma significativa les investigacions per identificar els signes que poden encendre el més prest possible les alarmes de que es pot està desenvolupant un càncer, en aquest cas el càncer colorrectal.

La importància de la crida a la prevenció precoç cal contemplar-la des del fet que els coordinadors d'aquesta publicació son dos cirurgians, és a dir dos professionals que per la seva experiència especialitzada poden tenir una visió clara de que les possibilitats de supervivència a un càncer depenen en primer lloc més del moment en que s'aborda la malaltia que del lloc en que es desenvolupa, encara que això sigui també molt important en aquest moment de les investigacions sobre el càncer.

Així per exemple trobam tres capítols dedicats a la identificació genètica d'indicadors de la prevalença de que una persona pugui desenvolupar un càncer colorrectal: *Cáncer colorrectal y síndromes poliposos heriditarios* del professor Francis M. Giardello de l'Escola de Medicina de la Johns Hopkins University i *Evolució genética de tamizaje* i de l'assessor genètic de l'Escola de Medicina de la Johns Hopkins University Cheryl J. Pendergrass.

Dins aquest grup d'actuacions derivades de la relació entre la genètica i la malaltia trobam també el capítol *Perfilado genético del cáncer colorectal* per Debashish Bose del Departament d'Oncologia Quirúrgica del Centre de Càncer MD Anderson de la Universitat de Texas a Houston i Nita Ahuja.

Igualment important és el capítol titulat *Modificación de conducta y dieta en la prevención de cáncer de colon* elaborat per Sthephanie R. Downing cirurgia general del Departament de Cirurgia del Col.legi de Medicina de l'Howard University de Washington; Emmanouil P. Pappou del Departament de Cirurgia de l'Escola de Medicina de la Johns Hopinks University i la mateixa Nita Ahuja, ja identificada.

De la lectura d'aquests capítols és dedueix, conseqüentment amb els avanços que s'estan produint en el camp de l'identificació genètica d'indicadors, que les persones poden tenir predisposició a sofrir determinades malalties, no tan sols les cancerígenes, i que cal doncs analitzar amb deteniment els costos/resultats d'establir els mapes genètics de les possibles malalties de tots els ciutadans.

Aquests mapes, realitzats en nàixer, servirien perquè des de el principi de les seves vides puguin dur els hàbits més adequats per retardar o impedir l'aparició de les possibles malalties identificades.

Ens trobam, doncs, amb una obra excel·lent per donar als professional de la salut eines per combatre amb possibilitats d'èxit una de les varietats de càncer més estesa en el món, concretament la tercera entre totes les modalitats de càncer.

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LLIBRES

Neuroética. Cuando la materia se despierta, de Kathinka Evers

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Kathinka Evers (n. 1960) hace parte del grupo de filósofos ahora neuroeticistas –en España representados por la respetable filósofa Adela Cortina–. Evers,actualmente trabaja como investigadora en el Centro de Investigación en Ética y Bioética de Uppsala, Suecia, en donde desarrolla temas como ética de la investigación, filosofía de la ciencia e investigación científica.

Esta autora señala un coloquio estadounidense de 2002 como fecha de inicio formal del campo, aunque –denota– ya había publicaciones del neologismo años atrás a cargo de neurocientíficos. Esa primigenia *Neuroética aplicada* –médica– se refería a la ética que debía caracterizar y moldear los desarrollos de las neurociencias (neurofarmacología, imaginología, intervenciones conductistas, etc.) y así su experimentación. Un segundo campo, la *Neuroética fundamental*, puede enfocarse según su definición, hacia las relaciones entre *"arquitectura"* neurológica, pensamiento y juicio moral.

El título describe su asunción sobre este reciente concepto, nueva *"piedra filosofal"* circunstancial de las humanidades. Neologismos tales como Neuroética, Bioética, Biopolítica, Sociobiología, etc., denotan en la actualidad lo que parecen ser nuevos campos del conocimiento. Evers, sin embargo, hace una revisión enmarcando el tema como un potencial *continuum* histórico desde su admirado siglo de las Luces. Hallazgos neurológicos, y un elogio a la interdisciplinariedad componen el núcleo de su propuesta. La obra alcanza un clímax filosófico al rebatir el utilitarista *"sofisma naturalista"*, más correctamente traducido como *"falacia naturalista"* de G.E. Moore (1903), refutado según el relato de la autora, por el filósofo sueco Hägerström en 1911, pero que no obstante aún rige el pensamiento occidental desde la ilustrada Revolución Industrial.

En estas paradojas construye Evers su libro con unos ejes temáticos predominantes. Son elementos constantes en su obra el materialismo ilustrado, el emocionalismo, la epigénesis cultural (como otro factor influyente en la expresión de potencialidades biológicas), una anti-religiosidad activista basada en el debatido Dawkins, y la admirada alusión a filósofos como Hobbes, Hume, el anarquista Kropotkin y F. Bacon. Su estructura discursiva es un tanto franco-céntrica por insumos clave del neurocientífico francés J.P. Changeux –quien ha buscado el puente entre neuroanatomía y ética–, la paleontóloga Patou-Matis y su propia colaboración en el Collège de France. El resultado así tiende a seguir su propia cita, al inicio, sobre el enciclopedista francés Diderot –tampoco médico– en *éléments de Physiologie* cuando afirmaba *"Ocurre que es muy difícil hacer una buena metafísica y una buena moral sin ser anatomista, naturalista, fisiólogo y médico"*.

Es curioso que los médicos no hayan, históricamente, pretendido coaccionar con sus conocimientos biológicos la libertad humana. Pero interfaces disciplinarias como la neuroética propuesta, con un mayor sesgo hacia las ciencias sociales, ofrecen interpretaciones y perfilan pronto el campo, ideológicamente, como *"desafío político" –título de un acápite–*. Se expone igual la Neuroética como respuesta en un mundo que se quisiera mejor de cara a la psicofarmacología y otras neurotecnologías desarrolladas por estamentos militares para aumento de eficacias bélicas. Habría que resaltar –entonces– que esto sucede ante un malestar globalizado según el cual, hay una profusión, un tanto fútil, de desarrollos intelectuales, pues pese a ellos y desde ellos, el mundo no está tan bien y se va hallando aún más problematizado con esas nuevas *"soluciones"* que compone.

Prueba de lo anterior es el abandono de cualquier dilema aplicativo en uno de los capítulos finales titulado *"Usos dobles en un mundo que no es realmente el mejor"* y el mismo final del libro que corroboran dicha fenomenología: *"Es posible que escojamos bien nuestro poder y también evolucionar, tanto biológica como culturalmente, para convertirnos en lo que consideramos criaturas «mejores» que desarrollan sociedades avanzadas. Los valores que seleccionaremos y los métodos que elegiremos desempeñaran un papel esencial para determinar si la clarificación y la comprensión neurocientíficas mejorarán o por el contrario agravaran la difícil situación en la que se encuentran los humanos"*

El llamado a una responsabilidad científica (basada en su adecuación, claridad conceptual y responsabilidad sociopolítica de su aplicación) justifica así pisar el acelerador, omitiendo tácitamente cualquier freno. Sin embargo, a inicios, en el capítulo *"Cuando la materia despierta"* se citan los horrores del darwinismo social y su hija la eugenesia, pseudociencia hecha máquina genocida con el colonialismo inglés y belga, el nazismo, o las descritas medidas de esterilización forzosa de ciudadanos "B" en Suecia hacia 1950…

Se vierte la responsabilidad de estos "desequilibrios" tecnocientíficos al ente abstracto de la ideología y la política, pero al lector se le puede venir una pregunta a la cabeza: ¿Podría el animal político, dejar de ser político?

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