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Abstract

Lesions after blunt cervical trauma could be, infrequently, associated with complications that require a discussion under clinical and legal medical point of view. Vertebral artery dissection as a serious consequence of a cervical trauma is a rare complication of patients with blunt injury mechanisms. Artery lesions could be frequently initially unrecognized or they may present a variety of symptoms ranging from a simple pain involving neck to ischemic lesions and cerebral ictus. Arterial dissection can cause ischemic stroke either by thromboemboli forming at the site of injury or as a result of hemodynamic insufficiency due to severe vascular stenosis or occlusion.

In medical literature several injury hypotheses which may cause a dissection of the arterial walls of vertebral arteries have been analyzed. Among them, repeated micro-traumatism which, acting on already altered wall, cause the
Vertebral artery injury and third-party liability: the wrongful attack to whiplash injury, L.27/12 (G.U. n.71 del 24.03.12)

dissection. Some jobs or sports are characterized by this risk because they imply frequent and repeated flexo-extension movements or head rotations. Also a single minor trauma, such as a blunt cervical trauma following car accident, could cause the dissection of the vertebral arterial wall.

The case reported concerns a 43 year-old man who suffered a bruising trauma following a car accident (a bumper-to-bumper crash with an articulated lorry). The reported symptomatology consisted of pain along the rachis and on the back on the neck and a diagnosis of cervical whiplash was made. After the worsening of the symptomatology, neurological tests revealed right hemiataxia and dysarthria. Succeeding MRI scanning with angiographic sequences revealed a dissection of the left vertebral artery with a hyperdense lesion of the right cerebellar hemisphere, as an outcome of an infarct in the area of a postero-inferior cerebellar artery. Vertebral artery stretch during trauma is a possible pathogenic mechanism that could explain some aspects of the whiplash symptom complex and serious consequences.

At the present this issue shows many controversial points from a pathogenetic point of view. The described uncertainties and the rareness of this kind of injury may explain the “superficiality” of a doctor giving first-aid to a patient with cervical whiplash and “generic” symptoms and it could be related to possible economical benefits consequent from insurance indemnity.

However the persistence of symptoms or the negative evolution of the same suggests that it wasn’t the “usual whiplash invented for compensation purposes” and that late complications of an injury of the walls of encephalic arteries must be taken into serious consideration specially under clinical point of view.

Abstract

Le lesioni derivate da un trauma da “colpo di frusta” possono essere, sia pure infrequentemente, associate a complicanze che per gravità non possono non rappresentare oggetto di discussione, oltre che dal punto di vista clinico, anche sul piano medico legale. La dissecazione dell’arteria vertebrale come conseguenza di un trauma cervicale è un evento raro, che, clinicamente può passare inosservata o presentarsi in modo improvviso con una sintomatologia variegata e costituita dal semplice dolore al collo sino alla comparsa di lesioni ischemiche cerebrali e ictus. La dissecazione arteriosa a carico delle arterie vertebrali può determinare una lesione ischemica sia con meccanismo tromboembolico sia determinando un’insufficienza emodinamica dovuta a stenosi od occlusione. Rispetto alle modalità lesive sono state avanzate svariate ipotesi idonee a causare la dissecazione delle pareti vasali dell’arteria vertebrale. Tra queste vengono annoverati i microtraumatismi ripetuti, come avviene in alcune mansioni lavorative o in determinati sport, che, agendo su una parete già alterata, determinano la dissecazione. La lesione della parete vasale può anche derivare da un unico trauma, anche di relativa modesta entità, come nel caso del colpo di frusta del rachide cervicale.

Il caso in discussione tratta di un uomo di 43 anni che riportava un colpo di frusta del rachide cervicale a seguito di tamponamento da parte di un autoarticolato, essendo la vittima alla guida del proprio automezzo. Solo a distanza di qualche tempo le immagini dell’angio-RM rivelarono la dissecazione delle pareti dell’arteria vertebrale sinistra con gli esiti di infarto all’emisfero cerebellare destro, corrispondente al territorio della arteria cerebellare posteriore inferiore. Dal punto di vista ezio-patogenetico la spiegazione presenta ancora aspetti da chiarire e le relative incertezze che ne derivano, così come l’infrequenza di tali lesioni traumatiche, possono giustificare un comportamento “superficiale” da parte del sanitario che presta le prime cure e che nell’ottica di un trauma banale trascura segni obiettivi e strumentali utili a prevenire la successiva comparsa di complicanze. Tale atteggiamento è talora connesso al fatto che il colpo di frusta cervicale è troppo spesso associato alla ricerca di benefici economici a carattere risarcitorio da parte del paziente con o senza la compiacenza del medico stesso. Tuttavia il persistere di una sintomatologia o l’evoluzione negativa del caso deve far ritenere che non si tratti del “solito colpo di frusta” con finalità lucrative e l’insorgenza di un complesso di sintomi sospetti deve essere presa in seria considerazione prima di tutto sul piano clinico, oltre che, in seconda battuta, sul piano medico-legale.
Introduction

Vertebral artery dissection ad a consequence of a trauma occurs in approximately 1% of all patients with blunt injury mechanisms, and it could be frequently initially unrecognized or it may present a variety of symptoms ranging from a simple pain involving neck to ictus. Arterial dissection can cause ischemic stroke either by thromboemboli forming at the site of injury or as a result of hemodynamic insufficiency due to severe stenosis or occlusion (1).

In the most serious hypotheses, diagnosis is often rapid, while in the other cases subtle symptoms such as vertigo (57%), unilateral facial paresthesia (46%), cerebellar signs (33%) and visual field defects (15%) could produce initial diagnostic doubts related and they may imply also a wrong clinical assessment (2).

In medical literature several injury hypotheses which may cause a dissection of the arterial walls of vertebral arteries have been analyzed. Among them, repeated microtrauma which, acting on already altered wall, cause the dissection: for example, it has been noticed that some jobs such as drivers or some sports such as tennis, sailing and archery are characterized by this risk because they imply frequent and repeated flexo-extension movements or head rotations (3).

The vessel wall injury may also derive from a single trauma, such as whiplash injury to the cervical rachis or manipulations of the rachis during chiropractic treatment. The first case is quite rare, while the second one is reported in many academic articles, perhaps also in order to point out the requirement of a specific technical training or to safeguard said technique from subjects who practice it without a qualification (4,5,6).

Case report

In Legal Medicine experience it is quite frequent to assess the outcomes of cervical whiplash. Almost all of them with limited permanent consequences, as shown by the studies with numerous events of this kinds. Sometimes and depending on the seriousness of initial injuries, some more complex cases are brought to our notice, as it is the case reported below. This case refers to a 43 year old man who suffered a bruising trauma following a car accident (a bumper-to-bumper crash with an articulated lorry). A diagnosis of cervical whiplash was made a peripheral hospital. The reported symptomatology basically consisted of pain along the rachis and on the back on the neck, in addition to an understandable state of anxiety related to the recent trauma.

The medical history did not reveal any previous illness, with the exception of moderate arterial hypertension. The patient led a normal life, did not regularly play any sport and had a sedentary job. After the impact, he did not lose consciousness. On his own admission, the visit at the hospital was mainly a precaution. The routine X-ray examination of the cervical rachis did not show any skeleton alterations, but only limited alterations due to arthrosis.

He was prescribed to wear a rigid collar for approximately ten days and anti-inflammatory drugs in case of need. On the days following the trauma, besides the persistence of the painful symptomatology, the patient started to show dizziness, sensation of visual acuity blurring and fatigue. The doctor prescribed a further period of rest and pain-relieves in case of need. It is hereby highlighted that the patient never underwent any kind of physical therapy; in particular, he never underwent chiropractic. In order to spent a period at rest, the patient stayed in a resort for a short time. Worried by the worsening of his symptomatology, he went to a nearby hospital where he underwent some neurological tests, which revealed right hemiataxia and dysarthria. An MRI scanning with angiographic sequences revealed a dissection of the left vertebral artery with a hiperintense lesion of the right cerebellar hemisphere, as an outcome of an infarct in the area of the postero-inferior cerebellar artery. He was treated with just a symptomatic therapy and rest, as previously recommended. Close clinical follow ups revealed a favourable evolution with minimum cerebellar signs.

In his report, forensic doctor admitted the causal relationship with the car accident and an indemnity. The causal relationship between the accident and the vascular injury was justified in particular with a criterion of chronological order and on the basis of the lack of provable pre-existing vascular alterations which could explain the artery injury.

Discussion

The case analysis cannot set aside anatomical reference which are indispensable to explain the dissection of the arterial wall.
The course of vertebral arteries rends them particularly vulnerable to injury from mechanical trauma. In general, from their entry at approximately C6, the vertebral arteries ascend within transverse foramina of the cervical vertebrae, where they are enclosed and relatively fixed. They are thus protected for most of their extracranial course until their exit from C2. To damage to this part of vertebral artery required large traumatic forces. The artery passes through the C2 intervertebral foramen to the more laterally located intervertebral foramen of C1. At their exit from C2, the vertebral artery is exposed to large shear and tensile forces during cervical movement, in particular rotation and lateral flexion.

The walls of the vertebral artery, like all human blood vessels, consists of three layers and the composition of the vertebral artery varies among its length, probably in response to the different demand along its course. The different stiffness of each of the three layers may contribute to the complications from minor trauma as well as from manipulation (7) or whiplash trauma (8), even though the review of the literature has led to criticized this kinds of conclusions.

Therefore, Haneline et al (9), maintained that a healthy vertebral artery cannot be damaged by traumas of this order (the author refers in particular to chiropractic manoeuvres, whose “damaging capacity” is assimilated to that of cervical whiplash).

As far cervical whiplash is concerned, it has been highlighted that several symptoms related to it cannot always find a valid explanation. However, it has been assumed that vertebral artery stretch during trauma is a possible pathogenic mechanism that could explain some aspects of the whiplash symptom complex (9).

According to Bassi and Lattuada (10), also in the forms with a traumatic aetiology such as those under discussion, the dissection of the arterial wall presupposes a pre-existing anomaly on it, or even a genetic predisposition related to connective tissue disorders (10,11).

Conclusions
At the present the issue shows many controversial points from a pathogenetic point of view. The described uncertainties and the rareness of this kind of injury may explain the “superficiality” of a doctor giving first-aid to a patient with cervical whiplash and “generic” symptoms, such as those reported in the case under discussion. This not careful behavior is not guilty and could be related to possible economical benefits consequent from insurance indemnity.

However the persistence of symptoms or the negative evolution of the same must suggest that it wasn’t the “usual whiplash invented for compensation purposes”.

This conclusion is also related to the act n.27/12, which reformed the article n.139 of “Codice delle Assicurazioni” (relating insurance liability), with the aim of restrict abuses and unjustifiable economical benefits.

In the case reported, the conclusion was definitely favorable and the case was resolved also under the point of view of medical jurisprudence. However late complications of an injury of the walls of encephalic arteries must be taken into serious consideration specially under clinical point of view.
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CAROTID BODY PARAGANGLIOMA: EARLY DIAGNOSIS

PARAGANGLIOMA CAROTIDEO: UNA DIAGNOSI PRECOCE

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Key words: neuroendocrine tumors, paraganglioma, carotid

Parole chiave: tumori neuroendocrini, paraganglioma, carotide

Abstract

Background: Paragangliomas (PGLs) are rare neuroendocrine tumors which arise from the extraadrenal chromaffin tissue of the autonomous nervous system, located in the carotid body or glomus (CB). This is a little corpuscle localized at carotid bifurcation; it contributes to regulating blood pressure, cardiac and respiratory frequency by giving information to the nervous system bodies located in the brain stem. Histologically, PGLs remind of the CB normal architecture, with clusters cells known as Zellballen, highly vascularized. Rarely secreting vasoactive amines, come more often to clinical observation as a mass located at the mandibular angle, asymptomatic. Based on the size and relationship with the surrounding vascular structures, are divided into three groups according to the Shamblin classification.

Case report: 57 year old patient, smoker. Reports about a year the appearance of vertigo associated with cold sweat and general malaise that lasts about 20 min which were resolved spontaneously (blood pressure in association with these episodes is high with maximum values recorded for 180/110 mmHg) He is submitted to a Holter instrumental investigations including blood pressure, ECD of the neck vessels (TSA), then it was performed an MRA of the neck. The patient underwent surgery The final histological examination showed a “paraganglioma composed of nests of chromogranin positive cells with round nuclei and finely dispersed chromatin with abundant eosinophilic, granular cytoplasmic portion”.

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Discussion and Conclusions: The PGLs are rare neoplasms, with an incidence of 0.012%. Very rarely (5% of cases) the patients come to medical attention for the appearance of a "pressor amine syndrome" with tachycardia, palpitations, flushing, hypertensive crisis, dizziness, malaise, diarrhea, amino-linked activity consequences of PGLs secreting. According to the Shamblin classification are divided into three groups based on the size and relationships contracted with the surrounding vascular structures (group III belong to the larger and forms persistently adherent to the carotid bifurcation). In most cases, the patients having a PGLs come to medical attention for the appearance of a mass in the lateral region of the neck, at the mandibular angle, often completely asymptomatic. When the tumor reaches considerable size, may be responsible for nerve deficits (especially for X, XI and XII nerves), dysphagia, neck pain. Early diagnosis of PLGs asymptomatic and small, reduces the risk of perioperative lesions of the cranial nerves and carotid arteries. In our case, early identification was made possible by the biological and functional characteristics of the tumor and the consequent clinical manifestations, allowing to carry out the surgery safely for the patient. Despite the size of PLG taken into account, it was ranked to the Shamblin group I.

Abstract

Introduzione: I chemodectomi (o paragangliomi) carotidei (CC) sono rare neoplasie che originano dalle cellule chemorecettive del glomo carotideo (GC). Il GC è un corpuscolo localizzato a livello della biforcazione carotidea; contribuisce alla regolazione della pressione arteriosa, della frequenza cardiaca e respiratoria inviando informazioni ai centri nervosi regolatori situati nel tronco encefalico. Istologicamente i CC ricordano la normale architettura del GC, con cellule organizzate in clusters detti Zellballen, altamente vascolarizzati. Raramente secernenti amine vasoattive, giungono più spesso all’osservazione clinica come una massa localizzata a livello dell’angolo mandibolare, asintomatica. Sulla base delle dimensioni e dei rapporti con le strutture vascolari circostanti vengono suddivisi in tre gruppi sec. La classificazione di Shamblin.

Caso Clinico: Pz di 57 aa, fumatore. Riferisce da circa un anno la comparsa di vertigini oggettive associate a sudorazione algida e malessere generale della durata di circa 20 min che regrediscono spontaneamente (la pressione arteriosa in concomitanza di tali episodi risulta elevata con valori massimi registrati di 180/110 mmHg). Viene sottoposto ad indagini strumentali tra cui un Holter pressorio, un ECD dei vasi epiaortici (TSA) e Angio-Rm del collo. Il pz viene sottoposto ad intervento chirurgico. L’esame istologico definitivo evidenzia un “paragangioma costituito da nidi di cellule cromogranina positive con nucleo rotondo e cromatina finemente dispersa, con abbondante quota citoplasmatica eosinofila e granulare”.

Discussione e Conclusioni: I CC sono neoplasie rare, con un’incidenza dello 0.012%. Secondo la classificazione di Shamblin vengono suddivisi in tre gruppi sulla base delle dimensioni e dei rapporti che contraggono con le strutture vascolari circostanti. Nella maggioranza dei casi i pz portatori di un CC si presentano all’attenzione del medico per la comparsa di una massa in regione laterale del collo, a livello dell’angolo mandibolare, spesso del tutto asintomatica. Quando la neoplasia raggiunge notevoli dimensioni, può rendersi responsabile di deficit nervosi (soprattutto a carico dei nn X, XI e XII), disfagia, dolore cervicale. Molto più raramente (5% dei casi) i pz giungono all’attenzione del medico per la comparsa di una "pressor amine syndrome" con tachicardia, palpitation, flushing, crisi ipertensive, vertigini, malessere generale, diarrea, legata all’attività amino-secerente dei CC. La diagnosi precoce di CC asintomatici e di piccole dimensioni riduce i rischi perioperatori di lesioni a carico dei nervi cranici e delle arterie carotidi. Nel nostro caso, la precoce identificazione è stata permessa dalle caratteristiche biologiche e funzionali del tumore e dalle conseguenti manifestazioni cliniche, consentendo di condurre l’intervento chirurgico in tutta sicurezza per il paziente. Nonostante le dimensioni del CC preso in considerazione, lo classificavano al I gruppo di Shamblin.
Background

Paragangliomas (PGLs) are rare neuroendocrine tumors which arise from the extraadrenal chromaffin tissue of the autonomous nervous system, located in the carotid body or glomus (CB). This is a little corpuscle localized at carotid bifurcation; it contributes to regulating blood pressure, cardiac and respiratory frequency by giving information to the nervous system bodies located in the brain stem. Histologically, PGLs remind of the CB normal architecture, with clusters cells known as Zellballen, highly vascularized. Rarely secreting vasoactive amines, come more often to clinical observation as a mass located at the mandibular angle, asymptomatic. Even more rarely they behave as malignant lesions giving distant metastases. Based on the size and relationship with the surrounding vascular structures, are divided into three groups according to the Shamblin classification (1) (Tab. 1).

**Tab.1 - Shamblin Classification**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>small tumors, with poor adhesion to the carotid artery, with cleavage plane</td>
</tr>
<tr>
<td>Type II</td>
<td>larger tumors, with adequate adhesion to the arterial wall and partial involvement of the origin of the internal and external carotid</td>
</tr>
<tr>
<td>Type III</td>
<td>full involvement of the bifurcation, with considerable adhesion to the arterial wall, with difficult cleavage plane</td>
</tr>
</tbody>
</table>

Case Report

57 year old patient, smoker. Reports about a year the appearance of vertigo associated with cold sweat and general malaise that lasts about 20 min which were resolved spontaneously (blood pressure in association with these episodes is high with maximum values recorded for 180/110 mmHg). He is submitted to a Holter instrumental investigations including blood pressure, which documents “mean daytime systolic and in 24 hours values more than reference ones”, and ECD of the neck vessels (TSA), which highlights at the right carotid bifurcation nodularity, size 27mm X 17mm. Then it was performed an MRA of the neck which “confirms the presence of nodularity at the carotid bifurcation of the size of 27mm X 20mm (Fig. 1), with moderate post-contrast enhancement and that displaces the external and internal carotid with no stenosis; this nodularity is also not infiltrating the surrounding tissues” (Fig. 2).

The patient underwent surgery. The surgery, conducted in loco-regional anesthesia, consisted of the cleavage of the “nodularity” from the carotid bifurcation after hemostasis with metal clips of glomus vessels and removal of this nodularity, in its entirety, without the need for clamping of the carotid arteries. The final histological examination showed a “paraganglioma composed of nests of chromogranin positive cells with round nuclei and finely dispersed chromatin with abundant eosinophilic, granular cytoplasmic portion” (Fig. 3). In the follow-up to one year the patient no longer has presented episodes of vertigo or feeling generally unwell, and a new Holter investigation including blood pressure has documented the normalization of blood pressure both day and night average values while the control of TSA Doppler ultrasound showed no evidence of disease recurrence.
Fig. 1 - Right glomus tumor: long and transverse sections without contrast

Fig. 2 - Right glomus tumor: long and transverse sections without contrast

Fig. 3 - Paragangioma
Discussion

PGLs are neuroendocrine structure located in the adventitia carotid bifurcation, posterior-medial side. It is sensitive to hypoxia, acidosis and hypercapnia; its stimulation results in increased frequency and respiratory rate and a rise in blood pressure through vasoconstriction and the production of circulating catecholamines. The PGLs are rare neoplasms, with an incidence of 0.012% (2).

Are generally between the fourth and fifth decade of life. The average size is of 4.5 cm x 3.5 cm x 3 cm but can grow up to 15 cm and a weight of 200 g. According to the Shamblin classification are divided into three groups based on the size and relationships contracted with the surrounding vascular structures (group III belong to the larger and forms persistently adherent to the carotid bifurcation).

In most cases, the patients having a PGLs come to medical attention for the appearance of a mass in the lateral region of the neck, at the mandibular angle, often completely asymptomatic. When the tumor reaches considerable size, may be responsible for nerve deficits (especially for X, XI and XII nerves), dysphagia, neck pain (3).

Very rarely (5% of cases) the patients come to medical attention for the appearance of a "pressor amine syndrome" with tachycardia, palpitations, flushing, hypertensive crisis, dizziness, malaise, diarrhea, amino-linked activity consequences of PGLs secreting (4). The biological behavior of PLGs, characterized by their tendency to grow and gradually incorporate the surrounding vascular and nerve structures, justifies their complete removal whenever they are identified (5, 6).

Conclusions

Early diagnosis of PLGs asymptomatic and small, reduces the risk of perioperative lesions of the cranial nerves and carotid arteries (2).

Unfortunately, most of the PLGs, when identified, belongs to group II or III Shamblin, making the operation much more difficult (7).

In our case, early identification was made possible by the biological and functional characteristics of the tumor and the consequent clinical manifestations, allowing to carry out the surgery safely for the patient. Despite the size of PLG taken into account, it was ranked to the Shamblin group I.
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EXPOSURE TO ASBESTOS AND LUNG CANCER: A CASE REPORT.

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Key words: asbestos, adenocarcinoma, cancerogenesis, TLV-TWA

Parole chiave: amianto, adenocarcinoma, cancerogenesi, TLV-TWA

Abstract

In Greek ἀμίαντος (asbestos) means immaculate and incorruptible and ἀσβήστος (asbestos) perpetual and inextinguishable. The knowledge of its particular characteristics and its applications dates back to ancient times, for example, Egyptians already used it for embalming.

Industrial use of asbestos dates back to the late nineteenth century, following the discovery of large Canadian deposits in Quebec (1877). The later discovery of important deposits in South Africa (crocidolite, chrysotile, amosite), Russia (chrysotile), United States (chrysotile), Australia (crocidolite) and Finland (anthophyllite), Italy (chrysotile) favoured its spreading and use on a large scale.
Exposure to asbestos and lung cancer: a case report.

Asbestos has been a well known confirmed human carcinogen since 1992, but before that date it was widely and regularly used for its insulating properties and its resistance. Exposure to asbestos appears associated to several diseases, such as pulmonary fibrosis, asbestosis (characterized by typical lung lesions), and neoplasms such as pleural and peritoneal mesothelioma and pulmonary adenocarcinoma. To put the blame of a disease on exposure to asbestos, however, diagnostic criteria are needed, ranging from the discovery of asbestos fibers in lung parenchyma to an array of radio-immuno-histo-chemical findings, to the duration and extent of exposure, etc. Here is a case report of lung cancer attributed to exposure to asbestos, which reconstructs the history of the patient in a critical analysis of the diagnostic criteria. Data have been discussed in the light of the current knowledge, with the support of a scrupulous literary review, which lead us step by step along the evolution of our achievement about the carcinogenicity of asbestos. Mr P (1932-2002) worked for a transport tramway company at the routine maintenance and repairs and died for lung adenocarcinoma. Scientific information worldwide produced about asbestos and its effects on human health are abundant, but it can’t be assumed that what is now universally recognized and taken for granted was recognized and taken for granted and with the same diffusion in past years and in the years during which Mr. P worked (1955-1992). Hence, there is no certainty of the diagnosis of the lung primitive adenocarcinoma attributed to Mr. P because the diagnostic criteria suggested by the international literature have not been strictly applied. There are no clinical or instrumental or laboratory signs that can be considered as indicators of the effect of exposure to asbestos: pulmonary fibrosis, asbestosis, pleural plaques, asbestos fibers, asbestos corpuscles, and the hypothesis of a possible cause and effect relationship is not supported by valid data.

Abstract

In greco la parola amianto significa immacolato e incorruttibile e asbesto perpetuo ed inestinguibile. La conoscenza delle sue particolari caratteristiche e l’utilizzo risalgono a tempi antichissimi, ad esempio già gli Egizi lo utilizzavano per l’imbalsamazione.

L’impiego industriale dell’amianto risale agli ultimi decenni dell’Ottocento in seguito alla scoperta dei vasti giacimenti canadesi del Quebec (1877). La successiva scoperta d’importanti giacimenti anche in Sudafrica (crocidolite, crisotilo, amosite), Russia (crisotilo), Stati Uniti (crisotilo), Australia (crocidolite) e Finlandia (antofillite), Italia (crisotilo) ne favorì la diffusione e l’uso su vasta scala. L’amianto è un noto cancerogeno riconosciuto dal 1992, ma prima di questa data veniva ampiamente e regolarmente utilizzato per le sue proprietà isolanti e di resistenza. L’esposizione ad asbesto risulta correlata a diverse patologie, quali fibrosi polmonare, asbestosi (caratterizzata da lesioni polmonari tipiche), e neoplasie quali mesotelioma pleurico e peritoneale ed adenocarcinoma polmonare. Per attribuire una patologia all’esposizione ad amianto però occorrono dei criteri diagnostici, che vanno dal ritrovamento delle fibre di asbesto nel parenchima polmonare ad una batteria di reperti radio-immuno-isto-chimici, alla durata ed all’entità dell’esposizione, etc. Riportiamo un case report di neoplasia polmonare attribuita ad esposizione ad amianto, in cui viene ricostruita la storia del paziente in un’analisi critica dei criteri diagnostici. I dati vengono ridiscussi alla luce delle conoscenze attuali, con il supporto di una review della letteratura che ci accompagna attraverso l’evoluzione delle conoscenze concernenti la cancerogenicità dell’amianto. Il Sig. P nato nel 1932 e deceduto nel 2002 per adenocarcinoma polmonare, ha lavorato occupandosi della manutenzione ordinaria e straordinaria di mezzi tramviari aziendali. Le informazioni scientifiche che sono state prodotte in tutto il mondo sull’amianto/asbesto ed effetti sulla salute umana sono copiose, ma non si può ritenere che quanto oggi è scontato ed universalmente riconosciuto lo fosse anche negli anni passati e con la stessa diffusione di oggi e negli anni durante i quali il Sig. P ha prestato servizio, per cui non è stato possibile chiarire con certezza l’ezioologia della malattia. Non vi è quindi certezza della diagnosi di adenocarcinoma primitivo del polmone attribuito al Sig. P in quanto non sono stati applicati rigorosamente i criteri diagnostici suggeriti dalla letteratura internazionale. Non risultano segni clinici, strumentali o di laboratorio che possano essere presi in considerazione come indicatori di effetto di esposizione ad amianto: fibrosi polmonare, asbestosi, placche pleuriche, fibre di amianto, corpuscoli di asbesto, e l’ipotesi di un’eventuale relazione causa ed effetto non è supportata da dati validi.
Background

In Greek ἀμίαντος (asbestos) means immaculate and incorruptible and ἀσβήστος (asbestos) perpetual and inextinguishable. The knowledge of its particular characteristics and its applications dates back to ancient times, for example, Egyptians already used it for embalming.

Industrial use of asbestos dates back to the late nineteenth century, following the discovery of large Canadian deposits in Quebec (1877). The later discovery of important deposits in South Africa (crocidolite, chrysotile, amosite), Russia (chrysotile), United States (chrysotile), Australia (crocidolite) and Finland (anthophyllite), Italy (chrysotile) favoured its spreading and use on a large scale. Actinolite and tremolite are considered little commercial relevance pollutants.

Until 1930, relatively small amounts of asbestos have been used (338,783 tonnes in 1930), but quantities have gradually increased over the following decades until reaching 5,159,000 tons in 1978.

In 1969, Canada supplied 45.9% of the world production. USSR followed with 26.8%, South Africa with 7.9%, China with 5%, other countries followed with minor shares.

The physico-chemical properties of asbestos and its intrinsic properties - nonconducting, insulating, anti-vibration, spinnable in fabric and fire retardant material - have facilitated its use in many fields of production and have led to an extensive use. Here its application fields:

- Construction: asbestos-cement slabs (Eternit), tiles, pipes, decoration, fire retardant panels, spray application for insulating plasters;
- Shipbuilding industry: insulating and fire-fighting coatings;
- Aviation industry: insulating and fire-fighting coatings;
- Railway industry: insulating and fire-fighting coatings;
- Automotive industry: brake and friction linings, insulating applications;
- Plastics industry: additives, various artifacts reinforcing;
- Chemical industry: filter and gaskets for various functions, thermosetting and thermoplastic resins;
- Metal Industry: guards and protective clothing, insulators for furnaces, boilers, etc.;
- Asbestos textile industry: textiles, tapes, ropes, twines, yarns, upholstery;
- Other: coveralls and protective fire or heat resistant clothing, papers, cardboards, electrical insulators, paints, talc.

This material was widely used for its characteristics of technical utility until the time of its ban that dates back to 1992.

Scientific information worldwide produced about asbestos and its effects on human health are abundant, but it can’t be assumed that what is now universally recognized and taken for granted was recognized and taken for granted and with the same diffusion in past years and in the years during which Mr. P worked (1955-1992).

Analysis of literature data, including the most recent, allows us to provide an updated overview on the subject; we thought it essential to plot the over time numerical trend of publications of international literature on health effects of asbestos exposure.

The number of censused papers is less than ten until 1964, about one hundred from 1972 to 74, about 150 until 1978. Since 1982 there has been a growing interest and with an average production per year of about 350 scientific papers. There are two peaks in 1982 and 2001 respectively with 430 and 562 publications.

In these works effects on human health due to exposure to asbestos are identified and defined:

- Diffuse interstitial fibrosis or parenchymal asbestosis;
- Non-malignant pleural diseases or pleural asbestosis (thickening, plaque effusions);
- Hands and forearms skin lesions (warts);
- Asbestos related cancer disease (mesothelioma, lung cancer).
Case Report
Mr. P (1932-2002) died of lung adenocarcinoma, worked for a transport tramway company at the routine maintenance and repairs. Mr. P was hospitalized in April 2001, with a history of hypertension since the age of 52 associated with ischemic heart disease; he had had night dyspnea for 6 months with sudden awakenings; former smoker, 20 cigarettes/day since he was young, he had given up smoking when 50. A Chest radiography performed during hospitalization showed "round opacity in right field." He underwent bronchoscopy in the apical segment of the lower lobe that pointed out modest extrinsic compression of about 2 mm from the apex where thickened and whitish mucosa appeared. The tumor markers were "negative." Sputum cytological examination revealed: "material consisting of numerous neutrophils and some squamous epithelial cells exempt from significant atypia". He performed T.A.C. total body revealing: "negative skull; a round solid formation with inhomogeneous enhancement with diameter of about 8 cm between the posterior segment of the upper lobe and the apical segment of the lower right lobe of the lung. Costal pleura is involved with loculated pleural effusion. Two nodular tumefactions related to the pulmonary veins lymph nodes. Upper abdomen negative." Lung biopsy with needle aspiration revealed: "Using ultrasound guidance we proceed to needle aspiration for cytological examination (SIC) of the parenchymal tumefaction located at the right lung." The discharge diagnosis was "adenocarcinoma of the lower lobe of the right lung on transthoracic needle biopsy. Ischemic heart disease ". No mention of cytological examination report.

The patient was hospitalized again in December 2001. Pulmonary function tests revealed a ventilatory insufficiency of obstructive type. Chest radiography showed "opacity with irregular margins in the apical segment of the lower right lobe, striae of connection with the hilum with retraction of the area; stapling of the right diaphragmatic pleura, prominent hilum, not active pleural effusions. Mr. P was therefore subjected to an intervention for right pneumonectomy. A standard chest radiography performed after surgery showed "outcomes of right pneumonectomy with leveled residual cavity, no left pleuroparenchimal injury; right pleural drainage." The patient was discharged in December 2001 in good condition, and in the documentation of hospitalization there was no mention of the histological examination on removed lung.

In August 2002, the patient underwent a new hospitalization for metastatic lung cancer: "Liver metastases. Episode of atrial fibrillation. Pericardial effusion. Suspected metastases of soft tissue on right supraclavicular region and dyspnea." T.C. total body showed "skull negative; chest: results of right pneumonectomy, pericardial effusion, no alteration in the left lung; abdomen showed 22 mm hepatic nodule hypothesis of injury repetitive, 16 mm retro peritoneal nodule." Echocolor-doppler-rate showed an EF 40% and moderate pericardial effusion.

Discussion
In order to realize whether the cause of his death could be an occupational disease, we analyzed the data in our possession, drawing some considerations.

1. Diagnostic certainty of neoplastic disease:

Here are the salient data obtained from the clinical documentation. Actually in medicine there are quality criteria that must be met when talking of lung cancer diagnosis which in this case have not even been considered.

It is clear that the diagnosis of adenocarcinoma is said to come from an initial examination defined cytologic but the report is missing. Cytological examination is known, to be an investigation with many limitations and possibilities of error. We read in the record, "histological examination: poorly differentiated adenocarcinoma of the lung" but no proof is present, so that it is legitimate to wonder if the words cytological examination stand for histological examination by needle aspiration. However, even if it were a histological examination, the reporting of an examination of this type should present indications about the amount of material taken, the type of staining and fixatives used, the centrifugation, the storage etc. And there’s still the difficulty of distinguishing the histotype of a tumor which is then defined as poorly differentiated, but without objective data to be used as criteria. The table shows the classification of histological types of adenocarcinoma with molecular characteristics.
For cancers that require cytological and histological examination it is also important to choose the fragment/s to be examined (1).

One possible source of error may be due to the analysis of a fragment, not representative of the disease. This is clear from the study by Nigrisoli (2). He examined 1490 samples at the cryostat, and found that the causes of failure are mainly due to errors of macroscopic sampling and secondly to a misunderstanding of the histological examination. These factors may explain the poor diagnostic accuracy (3).

If histological examination had shown a suspicion of primitive adenocarcinoma, this tumor should have to be distinguished from a metastasis of adenocarcinoma with a different source, -eg colon or rectum through immunohistochemical investigations at least. Regarding to immunohistochemistry offers the pathologist the opportunity to increase the rate of diagnostic accuracy, especially in the cases of biopsy representative of poorly differentiated neoplasms (4, 5), above all when it comes to needle aspiration exam which is also less accurate than histological examination on biopsy.

In cases of poorly differentiated lung carcinoma, a panel of immunophenotypic characterization of first line could allow to lean towards a particular and specific histotype.

Notwithstanding rare exceptions the coexpression of cytokeratin 7 and thyroid transcription antigen factor-1 (TTF-1), together with the negativity for cytokeratin 20, cytokeratin 5/6, high molecular weight cytokeratins and for p63, might allow to facilitate a diagnosis of adenocarcinoma (6, 7). According to Tsuta (8), the combination of cytokeratin 5/6 and TTF-1 is the most valid immunohistochemical combination for the diagnosis of a lung adenocarcinoma.
Many authors (8, 9, 10, 11, 12) argue that the tumor immunohistochemical characterization is important for a differential diagnosis. According to Turner (2012) the analysis of immuno-histochemical markers is essential for the differential diagnosis between adenocarcinoma and other types of cancers, pulmonary, non-pulmonary and metastatic (13). According to Ye (14, 15) and many authors (16, 17, 18) the study of immunohistochemical markers is useful to distinguish primary lung adenocarcinoma from adenocarcinoma of other sites that has metastasized in the lung, especially in cases of poorly differentiated adenocarcinoma (18). According to Saleh (19) immunocytochemical investigations have a significant role in the differential diagnosis between adenocarcinoma and metastasis.

Other clinical tests, such as lower abdomen CT, useful to exclude the presence of primary tumors in other locations, were not performed.

It is well known that:

a. the diagnosis must be made on the autopic workpiece in the presence of different samples to differentiate the lung carcinoma from a possible other cancer or a secondary tumor that has metastasized to the lung.

b. in the presence of surgical specimen the immunohistochemical investigations are also useful to support a differential diagnosis.

c. in the absence of asbestosis it would be necessary to search the mineral fibers in the biological material, or directly into the lung parenchyma or in the lavage bronchioloalveolar liquid, or with optical microscopy could help as well as scanning or transmission electron microscope.

d. it is therefore known that differential diagnosis of lung adenocarcinoma is not obvious and simple at all.

The markers mentioned in the medical record were negative and it was not specified what markers they were, the cytological and / or histological examination are not reported out and confirmed by immunohistochemical investigation as it should be done. Nothing confirms that the disease was a primary poorly differentiated lung adenocarcinoma and not a different type of lung cancer or a metastasis of a tumor originated elsewhere and first identified in the lung before being evident in other organs (see hypotheses of liver metastatic repetitions).

2. Carcinogenicity of asbestos: although asbestos carcinogenicity is unquestionable, it is also true that the knowledge, work hygiene or compensation legislations, as well as the international scientific databases became acknowledged in the years following those in which Mr. P worked (1955-1992) and commonly accepted in Italy years later. Legislation has in fact evolved thanks to the gradual diffusion of scientific knowledge.

3. Presence of asbestos in the workplace: Mr. P. worked continuously from 1955 to 1992 at the maintenance and repair of various types of rail vehicles, first as a workman (Class II, Class I, selected Class I ...) and then as foreman.

There are no data that allow to determine whether and to what extent the patient was exposed to asbestos environmental pollution. The environmental surveys showed the presence of asbestos fibers in very low concentrations, between 0.01 and 0.12 fibers/cc. These measurements were made, however, in areas different from those where the employee worked. It is also missing the official documentation stating the time spent in various environments where asbestos could be present, or the effective exposure of the worker (as already said, in fact, there are only generic and conflicting testimonies; environmental surveys were carried out on workplaces different from those in exam, and showed levels well below TLV and STEL).
<table>
<thead>
<tr>
<th>TLV-TWA Limit value for exposure to chrysotile (daily average)</th>
<th>175 f/cc</th>
<th>1948-1967 ACGIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)</td>
<td>12 f/cc</td>
<td>1968-71 ACGIH</td>
</tr>
<tr>
<td>TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)</td>
<td>5 f/cc</td>
<td>1972-79 ACGIH</td>
</tr>
<tr>
<td>TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)</td>
<td>2 f/cc for chrysotile. 0,5</td>
<td>1980-83 ACGIH</td>
</tr>
<tr>
<td>TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)</td>
<td>f/cc for amosite. 0,2 f/cc for crocidolite. 2 f/cc for other</td>
<td>Legislative Decree no. 277/91, Art. 31, paragraph 1, letter A</td>
</tr>
<tr>
<td>TLV-TWA Limit value of exposure to amphiboles and mixtures containing amphiboles (daily average)</td>
<td>0,1 f/cc</td>
<td>Legislative Decree no. 277/91, Art. 31, paragraph 1, letter B</td>
</tr>
<tr>
<td>TLV-TWA</td>
<td>0,1 f/cc</td>
<td>DLgs 81/08 smi</td>
</tr>
<tr>
<td>TLV-TWA</td>
<td>0,1 f/cc</td>
<td>ACGIH</td>
</tr>
</tbody>
</table>

4. Chronological criterion: it is known that the latency period of adenocarcinoma is not univocal and it’s impossible to predict it in a single individual because of the influence of different confounding factors (20);

5. Qualitative and quantitative criteria on causation: we note that the criteria which allow to attribute to asbestos the hypothetical lung adenocarcinoma found in the de cuius are completely missing.

a- The radiological investigations carried out provide results in which any indicator of suspected asbestos-related disease (pulmonary fibrosis which is an early sign of pneumoconiosis, asbestosis, pleural plaques, rounded atelectasis) is not mentioned.

b- Lung function exams show an obstructive picture (typical of smoking and not of dust related diseases) no sign of restriction typical of exposure to asbestos.

c- Lung malignancies due to causes other than asbestos (smoke, etc.) do not histologically differ from an asbestos-related cancer, so the existence of a cause-and-effect relationship is to be supposed following criteria scientifically valid.

The difficulty of etiological attribution of lung cancer to asbestos is responsible for heated medical - legal debates, while for pleural mesothelioma the causal role of asbestos is admitted in extremely low doses (21), as regards the cause-effect relationship between asbestos exposure and lung cancer, it is generally believed a cumulative exposure function, with an estimated increase in the risk of 1% for each fiber / ml-years of exposure (22).

The presence of which, besides indicating occurred exposure, allows to quantify the exposure itself and to estimate the risk of neoplastic disease, especially in absence of a concomitant asbestos related pathology as asbestosis. From these premises it is easily deduced that the use of semi-invasive methods, such as bronchoscopy with collection of liquid
Exposure to asbestos and lung cancer: a case report.

coming from broncho-alveolar washing, or really invasive methods as transbronchial biopsy procedures would allow to
to better define the actual load of fibers; these procedures are often necessary if there is a suspicion of an asbestos-related
neoplastic disease (23).

According to the Helsinki Consensus Conference in 1997 (24) strict criteria must be met to talk about asbestos related
lung cancer, even when it is established that we are dealing with a primary lung cancer. Here are these criteria:
simultaneous presence of asbestosis radiologically (absent in this case) or histologically diagnosed, positivity of
indicators related to the counting of asbestos corpuscles and fibers: 15,000 asbestos corpuscles (AC) per gram of dry
pulmonary tissue, 2 million or more of amphibolic asbestos fibers per gram of dry pulmonary tissue (counting fibers of
length>= 5 uM or 5 million counting shorter fibers), or counting corpuscles or fibers in a range compatible with that of
asbestosis, or a higher concentration of particles> 1/ml of bronchoalveolar lavage fluid and other. In this particular case
these criteria are not met and the presence of these indicators is not even reported nor is the exposure quantified in
some way, therefore it is impossible to talk about asbestos-related disease diagnosis and it is impossible to claim which
the qualitative-quantitative causation criterion is.

In conclusion, signs of asbestos-related lung disease (interstitial fibrosis, asbestosis, atelectasis, etc.) are absent, and
personal or pollution specific measures that allow to quantify a subject's actual exposure to asbestos are absent, and
there is no use of indicators of cumulative dose (none of this exists in the documentation). These signs consist of
asbestos corpuscles and / or of bare fibers; the search for these indicators must be made in the bronchoalveolar lavage
fluid with the most convenient methods, in particular with electron microscopy for fibers mineralogical examination, that
allows to have an idea of past exposure. If histological preparations are available, a better characterization of cumulative
asbestos exposure seems to derive from the use of the above indicators in combination with the search for asbestos-
induced fibrotic lesions (23). They should also be mentioned in the histological examination report.
This to be noted that even if asbestos can be correlated with adenocarcinoma, cigarette smoking alone without any
effect attributable to asbestos, may have caused the cancer as an efficient and decisive cause, and many authors in
literature associate cigarette smoking with the onset of adenocarcinoma (25, 26, 27, 28, 29, 30, 31).

The concentration is not absolutely suitable in that far below the current law TLV and therefore it is erroneous talking
about continuous exposure to high doses of asbestos for over 35 years.

6. Modal criterion on causality: if modal criterion had been met, we should have also found asbestos fibers, asbestos
corpuscles, pleural plaques, pulmonary fibrosis or full-blown asbestosis.

7. Criterion for the exclusion of other causes: it is true that the action of smoking is synergistic to that of asbestos but in
this case there is no reasonable likelihood of damage resulting from asbestos exposure since there is no clinical or
laboratory or radiological sign of asbestos exposure. It’s highly unlikely that this particular lung cancer might be caused
by a dose below the TLV fixed by the legislator, who believes that below this value there is not a legitimate chance of
developing cancer.

As already mentioned we underline that cigarette smoking alone without any effect attributable to asbestos may have
caused the tumor as an efficient and decisive cause, so we can rule out that the disease diagnosed as lung cancer may
be connected to asbestos exposure.

Conclusions
There is no certainty of the diagnosis of the lung primitive adenocarcinoma attributed to Mr. P because the diagnostic
criteria suggested by the international literature have not been strictly applied.
There are no clinical or instrumental or laboratory signs that can be considered as indicators of effect of
asbestos exposure: pulmonary fibrosis, asbestosis, pleural plaques, asbestos fibers, asbestos corpuscles;
The hypothesis of a possible cause and effect relationship is not supported by valid data.
The etiological diagnosis must be in fact supported by tests such as the specific immunohistochemical tests.
Exposure to asbestos and lung cancer: a case report.

References

Exposure to asbestos and lung cancer: a case report.


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FORENSIC ASPECTS OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

ASPETTI MEDICO-LEGALI DELLA MEDICINA ALTERNATIVA E COMPLEMENTARE (CAM)

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Parole chiave: Complementary and Alternative Medicine, normativa italiana, Sistema Sanitario Nazionale

Abstract

Background: Currently, in Italy the professions - which are divided into regulated and unregulated - can be an alternative to traditional employment, or complementary to it. In the recent years arised the phenomenon of not recognized professional associations, so that the NCEL (National Council for Economy and Labour) compiled a list called «Database on professional association», made from about 200 associations, 42 of which included in the category "Unconventional Medicine". However, since the work done outside of professional associations is living a situation of lack of consideration, it would be necessary to recognize a proper dignity also to the activities performed outside of a register.

Objectives: In this study the authors examine the current Italian legislation related to the use of alternative medicine practices in order to illustrate the need for a definitive legal framework of the subject setting clear rules for the use of unconventional treatments.
Recently, in the Anglo-Saxon world came into force the acronym CAM (Complementary and Alternative Medicine), a group of different medical and therapeutic practices which are not part of the group of conventional medicine, but not even are in contrast to this.

In the wake of this new acronym, also in Italy is becoming increasingly common use to define these medical practices with the expression of "Integrated Medicine".

**Methods:** The authors analyze the possibility to integrate the practices of conventional medicine with traditional medicine in public clinics, making by example the experimental model of some regions such as Emilia Romagna and Tuscany. Furthermore, looking at the last Judgment on the case "Di Bella," the authors emphasize that, despite the widespread national practices of alternative medicine, the latter must be supported by evidence of how effective these can be in order to be provided by public clinics and therefore be borne by the NHS.

**Results and Conclusions:** Whereas the unconventional practices are areas that are fully and legitimately part of the professional health, it is desirable to come to a permanent legal framework in this area, setting clear rules for unconventional treatments, in order to guarantee to citizens who choose such treatments the competence of those who practice them and to the same professionals the opportunity to stand out from figures without adequate experience.

**Abstract**

**Introduzione:** Attualmente, nello scenario italiano le libere professioni - che si dividono in regolamentate (protette o riconosciute) e non regolamentate - possono essere alternative al tradizionale lavoro dipendente, oppure complementari ad esso.

Negli ultimi anni è emerso il fenomeno delle associazioni professionali non riconosciute, tanto che il CNEL ha stilato una lista di "Banca dati sulle associazioni professionali" composta da quasi 200 associazioni, tra cui 42 comprese nella categoria "Medicine non Professionali". Tuttavia, dato che il lavoro svolto al di fuori degli ordini professionali vive una situazione di scarsa considerazione, sarebbe necessario riconoscere un'adeguata dignità anche all'attività professionale svolta al di fuori degli Albi professionali.

**Obiettivi:** In questo studio gli Autori esaminano l'attuale normativa italiana relativa all'utilizzo delle pratiche di medicina alternativa allo scopo di illustrare la necessità di un definitivo inquadramento normativo della materia che stabilisca regole certe per l’utilizzo dei trattamenti non convenzionali.

Recentemente, nel mondo anglosassone è entrato in vigore l’acronimo CAM (“Complementary and Alternative Medicine”), ovvero un gruppo variegato di pratiche mediche e terapeutiche che non rientrano nell’alveo della medicina convenzionale, ma che non si pongono nemmeno in contrapposizione con la "Medicina Convenzionale", intesa come medicina accademica. Sulla scia di questo nuovo acronimo, anche in Italia sta diventando sempre più comune definire tali pratiche con l’espressione di "Medicina Integrata".

**Metodi:** Gli Autori analizzano la possibilità di integrare le pratiche di medicina non convenzionale con la medicina tradizionale all’interno degli ambulatori pubblici, portando ad esempio il modello sperimentale di alcune Regioni, quali l’Emilia Romagna e la Toscana. Inoltre, esaminando l’ultima Sentenza sul caso "Di Bella", sottolineano come, nonostante la larga diffusione a livello nazionale delle pratiche di medicina alternativa, queste ultime devono essere supportate da prove di effettiva efficacia affinché possano essere erogate da ambulatori pubblici e, di conseguenza, essere a carico del Servizio Sanitario Nazionale.

**Risultati e Conclusioni:** È auspicabile che si approdi ad un definitivo inquadramento normativo della materia che stabilisca regole certe per i trattamenti non convenzionali, in modo da garantire ai cittadini che optano per tali
trattamenti la professionalità di chi li pratica e agli stessi professionisti la possibilità di distinguersi da figure prive di adeguata professionalità.

In conclusione, considerando che le pratiche non convenzionali costituiscono un settore che legittimamente e a pieno titolo rientra nell’ambito dell’attività professionale sanitaria, l’integrazione delle pratiche non convenzionali all’interno del sistema convenzionale della medicina garantirebbe ai cittadini la più alta libertà di scelta terapeutica, assicurando loro il più elevato livelli di sicurezza e di correttezza di informazione.

Background

Currently, in Italy professions are part of a complex universe: in fact, flowing in the type of self-employment, can be also alternative to traditional employment, or complementary to it.

In addition, in accordance with current legislation, professions are divided into regulated and unregulated.

Among the former there are protected professions, that cannot be exercised without being put on the register and being part of an association, which manage the control of the activity; and the recognized professions, governed by law and for which it’s required to be put on the register or lists but does not include to be part of an association.

Instead, unregulated professions, while being part of an important social and economic reality, are not subject to public regulation, although they are present on the job market and are represented only by their associations (1).

Table 1

<table>
<thead>
<tr>
<th>Professions</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arts, technical sciences</td>
<td>25</td>
</tr>
<tr>
<td>Business communications</td>
<td>18</td>
</tr>
<tr>
<td>Business services</td>
<td>52</td>
</tr>
<tr>
<td>Unconventional medicine</td>
<td>42</td>
</tr>
<tr>
<td>Sanitary</td>
<td>19</td>
</tr>
<tr>
<td>Psychological care</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>196</strong></td>
</tr>
</tbody>
</table>

For over ten years, the NCEL (National Council for Economy and Labour) began to pay attention particularly to emergent professions and compiled a list called «Database on professional association», made from 196 associations, so categorized (table 1).

In particular, the category of «unconventional medicine» includes a total of about 100,000 members: music therapists, teachers of feldenkrais method, natural hygienists iridologists heilpraktiker, naturopaths, holistic energy experts, shiatsu operators, body energy techniques, yoga experts, pranotherapists, flower therapists, herbalists, analysts of body connexion, kinesiologists, foot reflexology experts, biotherapists, integrated medicine experts.

Therefore, also thanks to the NCEL, in the recent years there has been a real phenomenon of not recognized professional associations, very relevant on a quality and quantity level, as well as for the social importance assumed.

In our country, since the work done outside of professional associations is living a situation of lack of consideration, and its lack of regulation exposes the State to the risk of infringements by the European Union, it would be necessary to recognize a proper dignity also to the activities performed outside of a register (2).
Non Conventional Medicine (NCM) versus Complementary and Alternative Medicine (CAM)

The National Federation of the Associations of Doctors and Dentists (FNOMCeO) in 1995 used the term "alternative medicine or practice" to refer to «...all those practices that claim to cure using methods other than those verified by the official testing of medical science...» (3).

With the overall definition of "Non Conventional Medicine" (MNC), instead, means that set of therapeutic methodologies that goes from acupuncture / traditional Chinese medicine to homeopathy, from homotoxicology to ayurvedic medicine, from chiropractic to osteopathy, from herbal medicine to anthroposophic medicine, from naturopathy to reflexology, from aromatherapy to chromotherapy, from Shiatsu to pranotherapy, from macrobiotics to yoga, from emoterapia to music therapy, ending with gemmotherapy: this is a very heterogeneous group of healing practices - some of which are secular tradition, other relatively recent introduction - which fall outside the common activities of medicine and in recent years are enjoying a growing interest in the Western world (4).

Between these, the first nine were selected by OMS, by the European Parliament and approved by the same FNOMCeO in the National Council of May 18, 2002 - as "relevant" on the Italian territory, because most desired by the population and because they have a solid foundation, although most often purely empirical (5, 6).

In the Code of Medical Ethics of 2006 - particularly in Chapter IV on diagnostic tests and treatments – there are limits and roles for the use of Non-Conventional Practices: «...The use of unconventional practices can not be separated from respect for the decorum and dignity of the profession and is expressed in the exclusive area of direct and non-delegable responsibility of the medical professional. The use of unconventional practices must not steal the citizen to specific treatments and scientifically established and requires more detailed information and acquisition of consent. It is forbidden the doctor to cooperate in any way or to facilitate the exercise of third parties not doctors in the field of so-called unconventional practices...» (7).

The reason for the growing interest in the NCM is mainly due to their requirements: the centrality, complexity and wholeness of the person according to a "holistic" approach, which emphasizes in particular the interaction between body and mind, the personalized therapy to the individual patient; the vision of the disease as a phenomenon resulting from an imbalance inside the body, for which the purpose is to restore the harmony of the person; finally, the belief that, using these medicines, is heading towards a lower risk of toxicity than the classical pharmacological remedies industrial (8).

The term "Unconventional", therefore, is currently in Italy the name most commonly used, in this way, however, these treatment methods seem to be in opposition to the "Conventional Medicine", understood as academic medicine.

To overcome this problem, in recent years in the Anglo-Saxon world has entered into force the acronym CAM. This acronym stands for the "Complementary and Alternative Medicine", which is a group of diverse medical and therapeutic practices that are not part of the group of conventional medicine (9, 10).

In the wake of this new acronym, certainly more representative and appropriate from precedents, also in Italy is becoming increasingly common use to define these medical practices with the expression of "Integrated Medicine". That medicine combines the values expressed by citizens with the doctor’s professional and any other health care professional, satisfying the criteria of social justice and maximum sustainability. Among the virtues of Integrated Medicine include: the reasonableness of the use of scientific knowledge and understanding of the situations and problems of the individual, relational sensitivity to promote mutual understanding, the ability to listen to and value the opinion of the patient (11).

Difference between the International Standards and the Italian Standards: from a "tolerant" system to an "exclusive" system

While most of the countries of the European Union joins to a "tolerant" system that opting for scientific medicine, accepts some NCM, Italy still adheres to an "exclusive" system.

In fact, in a such "tolerant" system the NCM found various forms of legal regulation and for some time alongside therapies officers, while the Italian "exclusive" type recognizes only the figures of medical graduates, dentists and degrees in the health professions and in none of these training programs there is place for teaching of NCM (12).
The heterogeneity of unconventional treatments legislation in the various Western world countries and the increasing use of NCM led the European Parliament to adopt in 1992 a "Motion for a resolution" (13) in which it was stressed the precise identification and classification of "medicine and non-conventional therapies."

In addition, the 29.05.1997, the European Parliament adopted the "Resolution on the status of non-conventional medicine" (14) that, accepting the previous proposal, promoted a significant health policy of openness to unconventional practices, calling on member states a commitment in the process of recognition of these methodologies (15). In particular, it was stressed the importance of giving patients a wide choice of treatment, an adequate level of security and complete information on the quality, effectiveness and risks of these procedures.

In addition, the European Parliament has guaranteed an economic appropriation to continue scientific studies on non-conventional therapies, requiring each member state a positive commitment to integration of CAM in official medical practice.

Despite the numerous proposal that have occurred in the recent decades, currently in Italy there is no legislation governing the practice of Non-Conventional Medicine. In fact, during the recent legislatures, have been examined by Parliament legislative proposals that have not yet had a complete definition.

For example, in 1997 with the proposed law entitled «Discipline of unconventional therapies and the establishment of registers of operators unconventional», it was recognized the diagnostic and therapeutic value of nine NCM and the establishment of specific courses in the degree program in Medicine, post-graduate courses of specialization and registers for professionals.

Despite numerous attempts, even this proposed law was passed. The result is a paradox, as currently the NCM are carried out mostly privatized regime, mainly by professionals, medical or otherwise, with training not officially recognized. These professionals can not use the title of specialists and sometimes prescribe drugs sold without adequate rules that regulate the marketing.

In addition, with regard to the training of these "operators", in Italy the curriculum of the Faculty of Medicine and Graduate Schools does not provide any course of instruction, then, the training in question are assigned to private institutions that organize postgraduate master and short courses (8).

A possible step forward: draft laws of 2011 on homeopathy, traditional Chinese medicine and acupuncture

The National Health System, having felt the need to take into consideration the NCM, in Article 9 of Legislative Decree 229/1999 - about the matching funds of the NHS - cited among the additional benefits, while failing included among the essential levels of assistance (LEA).

The next step took place during the National Council of FNOMCeO of 18 May 2002, where it was stated that «...the exercise of these medicines and unconventional practices in should be considered a medical act...» and that they were only «...the doctor and the dentists are the only health actors that can identify patients susceptible of a benefit ... the only people qualified to make diagnosis, to prepare the appropriate treatment plan and monitor the implementation of the same patient...».

The EU, has long been committed to ensuring an adequate level of protection, competitiveness and innovation in the field of health, issued in 2006 the "Directive on drugs," which had as its target the alignment between all Member States, including Italy, regarding regulatory and commercialization of new classes of drugs. In Italy, however, despite the EU Directives, the administrative act concerning the authorization to record new homeopathic medications - although provided by Community legislation - has not been formalized to date (16).

To avoid this, in Parliament were deposited many draft laws with the intention to achieve a legal recognition of CAM, without reaching definitive results also due to the continuous intervention of the National Bioethics Committee (17) - that at a meeting of 18 March 2005 had ruled unfavorably against Alternative and Complementary Medicine - and the Italian Episcopal Committee (IEC), who had spoken out against Oriental Disciplines for reasons of religious-theological.

With the above-mentioned «Resolution and Guidelines on Medical and Non-Conventional practices» in 2002 integrated with the «Guidelines for training in medicine and unconventional practices...» - approved by the National Council FNOMCeO of December 12, 2009 - shows that the exercise of non-conventional medicines and practices must be exercised exclusively by the surgeon and dentist, given to patients who may actually benefit from them, after adequate information and acquisition of an explicit informed consent, must also be the subject of educational initiatives to be included in Continuing Medical Education programs (18).
On 6 April 2011 were presented in the Senate two draft laws relating to traditional Chinese medicine and acupuncture and homeopathy in order to regulating the exercise of these CAM (19).

Proposal for integration with traditional medicine in public clinics: Experimental Model in Tuscany and Emilia Romagna.

The so-called "alternative medicine" (NCM), still gives rise to a number of reasons a large interest among many citizens and health professionals, are not regulated in Italy by an adequate regulatory framework that clearly identifies, it delimits the scope usability and define the criteria for qualifying persons authorized to exercise them, and are not included in the offer of the National Health Service.

In fact, the national context is characterized by a substantial regulatory gap and the failure of many attempts to define a framework law in past legislatures. The NCM are not included in the National Health Service (20) and do not appear in the list of integrative activities that may be provided a fee by the local health as outpatient services.

Currently they are working on an integrated version of these projects, but there is still no law defined at national level, while the Regions have become independent. In fact, against this increasing popularity of MC, the Regions have taken the initiatives in an attempt to regulate a very diverse sector, especially in the Health Service. In fact, even on the basis of changes to Title V of the Constitution (21), some Regions have adopted specific initiatives in the NCM, with very different approaches. In some cases, reference to NCM were introduced within the Regional Health Plans, in other have been set regional structures as a reference (committees, observers, technical and scientific committees, etc.), or have been funded research programs or have been promoted and carried out information campaigns and training for doctors and other health professionals.

In many areas, such as, Lombardy, Emilia Romagna, Tuscany, Piedmont and Lazio are provided at public clinics or credited performance of MC, particularly acupuncture and homeopathy.

The most advanced Region in the field of NMC promotion is undoubtedly Tuscany, who entered with a resolution Acupuncture, Homeopathy-Homotoxicology, Herbal Medicine and Manual Medicine among medical practices of essential levels of assistance, in practice would be payable by the NHS on request of Family Doctor, and each of them is granted a specific tariff. This makes it possible to guarantee the right of public access to these therapies and to develop research.

In addition, the Tuscany Region has decided to implement other measures such as regulating the training of doctors who practice Complementary Medicine, guaranteeing the quality of services; including representatives of the MC in the Regional Health Council and the Health Councils of hospitals and universities and approving a supplementary agreement to the activities of specialist outpatient care, so that the local health authorities may have qualified professionals.

So, the Tuscany Region has set up a constant monitoring of the MC to evaluate their effectiveness and to enable the integration of those techniques that improve the health of citizens and at the same time allow proper allocation of available resources (22).

Even the Emilia-Romagna is one of the regions most active; in fact, has enacted specific legislation, has set up an observatory for non-conventional medicine (OMNCER) with qualified experts and, above all, has promoted a program of research for the integration of NCM in the Regional Health Service (SSR) (23).

A recent Judgment on the "Di Bella" method.

Among the various forms of alternative medicine, between 1997 and 1998 the "MDB" (or "multitattamento Di Bella", abbreviated MDB) was the subject of great attention by the Italian media. The MDB is an alternative therapy for the treatment of cancer, with no scientific evidence about its foundations and its effectiveness (24).

The reasons for such a great resonance are to be found in the attraction that inevitably involves any alleged therapeutic solution to a problem that for its size (in Italy the cancer diagnosis are more than 250,000 per year) and gravity (representing 30% of death causes in 5-year survival of 40%) results in a strong emotional burden and suffering. On the other hand, the interest aroused by the so-called non-conventional therapies appears to involve more people if it is true that, as recent investigations (25), more than 30% of people resort to this type of treatment.

The founder of this method began research on cancer in 1963 and four years later he began experimenting on some patients. In 1977 introduced the Somatostatin in its multitherapy for the alternative treatment of tumor masses and for the prevention of metastases.
Although in 1996 the Commission had considered the National Cancer therapy without scientific validation and despite a 1998 judgment of the Constitutional Court had expressed negatively, under the weight of the media coverage (26) and of the social alarm given by the case, the trial was authorized by the Government on 10.01.1998. It is interesting in this connection to quote a passage from the judgment that the Constitutional Court issued about MDB «...Where ... there is the possibility of a treatment proven already valid and the claim that the State should be required to provide for free other medical services, or purporting to be effective, it would not be reasonable. The consequences of free individual choices about the preferred treatment cannot fall, in fact, on the National Health Service, because it ignores the role and the responsibilities of the State through the organs of the scientific-technical health with regard to testing and certification effectiveness, and not harmful, pharmaceutical substances and their therapeutic use for the protection of public health » (27).

Shortly after the 11 multicenter studies of phase II were activated (to assess whether a particular treatment is able to reduce the size of tumor masses in a significant number of patients) on eight types of neoplasms. The final evaluation was entrusted to the Italian Study Group for the Di Bella Multitherapy trial which concluded that the experiments had not produced any evidence to justify further clinical trials. The phase II study, therefore, showed how the MDB did not have sufficient clinical activity to warrant further investigation, ie the phase III.

Indeed, the choice of a phase II trial was dictated by important ethical and practical reasons. A Phase III trial would, in fact, led to the involvement of a large number of patients. The subject for a long period of time expected to thousands of patients to a treatment where the level of effectiveness was, a priori, not known, he would have violated basic ethical constraints. In addition, the journal Cancer reported that patients treated with the Di Bella therapy lived on average less than those treated with traditional therapies of proven effectiveness (28) and also pointed out that such treatment was not without side effects (29).

Despite the failure of the trial, the public is getting closer and closer to this alternative medicine (30) and greater emphasis in journalism and television was given to Dr. Di Bella, culminating with, February 15, 1998, in a demonstration by 15,000 supporters Di Bella to obtain the free of such therapy.

In the years following, the experimentation suffered a new setback, because, in 2003, the Chamber of Deputies approved a measure to address the government for the purposes of a new experimentation of the method (31), but in 2005 came a new rejection by National Institute of Health. To date, the method is publicized through various websites by the children who have also set up a foundation (32).

Recently, namely 26 February 2012 the method Di Bella is back in the discussions with the decision of a Judge of the Labour Section of the Court of Bari, Mary Procoli that upheld the appeal brought by a cancer patient who asked to be treated with the method devised by the professor.

With this ruling, the judge reiterated the right of the patient to use against the tumor the cocktail of drugs based on somatostatin developed by physiologist Modena. The Court of Bari has in fact upheld the request of a patient requiring the «ASL to grant immediate disbursement and free drug treatment».

However, the judgment in favour with Di Bella method was short-lived, in fact, the General Manager of the Local Health Authority, Dominic Colasanto, he immediately signed a resolution to proceed on appeal and appeal the judge's decision.

Indeed, a recent Judgment of the Court of Appeals for the Labour Court of Bari, Mary Procoli that upheld the appeal brought by a cancer patient who asked to be treated with the method devised by the professor.

Accordingly, that judgment confirms that, despite the broad national dissemination practices alternative medicine, the latter must be supported by evidence of actual effectiveness so that they can be provided by public clinics and, therefore, be borne by the National Health Service. If it is true that you can not prevent a patient to choose what type of care follow - the right to health and the good health is a primary and fundamental right of the individual - is equally undeniable that the groundlessness of a subjective right to the public Health should take an active part in the administration of therapies whose effect is not scientifically recognized (33).

About the problem of limited resources and the basic levels payable had already expressed in 1995 the Constitutional Court: «...In the presence of limited resources and reduced availability of funds accompanied by the need for reorganization of the national budget, it is unthinkable to be able to spend without limitation, having regard only to the needs, whatever its seriousness and urgency it is vice versa spending have to be commensurate with the actual financial...» (36).
resources, which affect the quality and the level of health care and to be determined after evaluation of priorities and compatibility and taking into account, of course, the fundamental need to protect the right to health, certainly not compromised by the measures now under consideration...» (34). Therefore, the ordinances which had been given the drug delivery of the Di Bella therapy had completely disregarded peaceful principles in the legal and health.

In conclusion, the Di Bella case is testimony to the deep discomfort that invests the doctor-patient relationship, suffering from a general lack of confidence in the medical profession that is born, on the one hand, by the progressive loss of a direct dialogue with the patient and, on the other the conviction of the infallibility of human progress. Any medical failure is now interpreted as a serious fault of health. This distrust is the scenario of the praetors jurisprudential orientation, where a proven medical treatment but, unfortunately, sometimes fallible, oppose practices of uncertain efficacy, whose greatest merit is made by the alleged but never shown improved quality of life, perhaps due to the interruption of a multidrug high doses, rather than the effectiveness of the Di Bella cure (33).

Considerations and Conclusions

On the basis of the now increasing use of alternative medicine practices, the result is more and more the need for the doctor to know at least culturally juggle the conventional and non-conventional therapies, limited, at least in cases where there is a demonstration for the latter efficacy or better tolerability. And that includes consideration of the recent case law orientation has shown on the issue of medical responsibility, preferring even the appearance of increased risks choice of treatment chosen. In fact, we must not neglect the possibility of a request for compensation in the event that, following a conventional treatment, damage will occur iatrogenic (such as might result from sustained of corticosteroids, NSAIDs, antibiotics) that could have been avoided by using - with the same effect - an unconventional treatment (12).

It follows, therefore, the need for the Italian University institutionally delegated to the training of health workers enter in the programming of degree courses in Medicine and Surgery at least the conceptual premises and technical aspects of implementing unconventional treatments, for which now there is a scientific validation (35) and, above all, the establishment by the Orders provincial registers of physicians who practice this type of care.

Recently, in the wake of the increasing spread of "Complementary and Alternative Medicine", some Italian universities have established master on the CAM most recognized in the scientific field. In particular, the Department of Social Medicine, Faculty of Medicine, University "Sapienza" of Rome has established a Master's Degree entitled "Acupuncture and Herbal Medicine integration of Traditional Chinese Medicine and Western Medicine" (36, 37). In addition, as "Sapienza" also other Italian universities - in particular Bologna, Trieste, Cagliari (38) and Siena (39) play master level II primarily on acupuncture, herbal medicine and homeopathy.

The University of Bologna, in recent years, has launched two courses of higher education which was also attended by health workers of the Regional Health Service, taking advantage of contributions provided by the Regional Programme on NCD. One of the two advanced courses on the subject of NCM promoted by the University of Bologna, entitled "Integration of knowledge in conventional and unconventional medicine", was organized by the Faculty of Medicine in the academic year 2006-2007. It is aimed at health professionals or not, and aims to develop the skills necessary to guide the choices of health care organizations in NCMs. The other course is offered by the University of Bologna, Department of Sociology and is titled "Sociology of Health and non-conventional medicine" (40, 41).

It is desirable, therefore, to arrive to a final regulatory framework of the area setting clear rules for unconventional treatments, in order to ensure to the citizens who opt for such treatments the professionalism of those who practice them and the same professionals the ability to distinguish by figures without adequate professional.

In conclusion, then, whereas unconventional practices are areas that are legitimately full and falls under the professional care, the integration of unconventional practices within the conventional system of medicine guarantees citizens the highest freedom of choice of treatment, giving them the highest levels of safety and correctness of information (42).
References
1. Art. 2222 c.c.: Contratto d’opera (Capo I: disposizioni generali; Capo II: delle professioni intellettuali risp.); artt. 2229 e seguenti c.c.: Professioni intellettuali.
17. Siamo ancora lontani dalla possibilità di una completa integrazione con le medicine convenzionale; infatti, il 23 aprile del 2004 il Comitato Nazionale di Bioetica ha bocciato il riconoscimento alle pratiche di medicina di medicina non convenzionale, perché prive di basi scientifiche. La decisione presa dal Comitato ha, innanzitutto, due effetti immediati: impedisce che le medicine alternative possano diventare materia d’insegnamento all’università o in corsi di formazione accademica e vieta la presenza di loro rappresentanti vengano nominati nel Consiglio superiore di sanità, il massimo organo tecnico consultivo del ministero della Salute. E cade come un fulmine a ciel sereno sulla paventata possibilità di riconoscere una serie di discipline alternative, soprattutto per quello che riguarda il rimborso delle spese mediche da parte del Servizio Sanitario Nazionale.
19. Disegni di Legge 6 aprile 2011, n. 2672-2673:
   - Articolo 1: disciplina l’esercizio della CAM in questione nell’ottica del riconoscimento del pluralismo nella scienza e della ricerca scientifica;
   - Articolo 2: prevede l’istituzione, presso gli ordini provinciali dei medici, degli odontoiatri, dei farmacisti e dei veterinari, di appositi registri di esperti in tali discipline;
   - Articolo 3: istituisce, presso il Ministero della Salute, una Commissione permanente per la disciplina di tali CAM, con funzione consultiva presso il medesimo Ministero e con ilo compito principale di promuovere la corretta divulgazione delle tematiche sanitarie inerenti alle materie in questione e le attività di ricerca, anche al fine di riconoscere nuove discipline terapeutiche;
   - Articolo 4: prevede la possibilità dell’accreditamento delle associazioni, società scientifiche ed enti privati di formazione ai fini della diffusione delle suddette Medicine Complementari;
Articolo 5: stabilisce che il Ministero dell’Istruzione, dell’Università e della Ricerca istituisca corsi di formazione post-laurea al fine del rilascio della qualifica di esperti in omeopatia e medicina tradizionale cinese e agopuntura;

Articolo 6: prevede la possibilità per lo Stato e le Regioni di procedere all’individuazione di nuove discipline complementari;

Articolo 7: reca il principio del consenso informato, ovvero che il paziente che decide di sottoporsi a tali trattamenti, sia preventivamente informato dal medico circa diagnosi, prognosi, scopo e natura del trattamento sanitario proposto, comprensivo di benefici, rischi ed eventuali effetti collaterali ad esso legati.


21. Art. 3 Legge Cost. 18 ottobre 2001, n. 3: “... Sono materie di legislazione concorrente quelle relative a: rapporti internazionali e con l’Unione europea delle Regioni; commercio con l’estero; tutela e sicurezza del lavoro; istruzione, salva l’autonomia delle istituzioni scolastiche e con esclusione della istruzione e della formazione professionale; professioni; ricerca scientifica e tecnologica e sostegno all’innovazione per i settori produttivi; tutela della salute; alimentazione; ordinamento sportivo; protezione civile; governo del territorio; porti e aeroporti civili; grandi reti di trasporto e di navigazione; ordinamento della comunicazione; produzione, trasporto e distribuzione nazionale dell’energia; previdenza complementare e integrativa; armonizzazione dei bilanci pubblici e coordinamento della finanza pubblica e del sistema tributario; valorizzazione dei beni culturali e ambientali e promozione e organizzazione di attività culturali; casse di risparmio, casse rurali, aziende di credito a carattere regionale; enti di credito fondata e agrario a carattere regionale. Nelle materie di legislazione concorrente spetta alle Regioni la potestà legislativa, salvo che per la determinazione dei principi fondamentali, riservata alla legislazione dello Stato...”.


30. Un sondaggio dell’epoca sulla rivista Toscana Medica rilevava che l’85% degli italiani era favorevole alla cura Di Bella.


32. Prof. Di Bella, criteriologia MDB, principi attivi, terapia, farmaci, monitoraggio, effetti collaterali, aspetti legali, diritti dei pazienti disponibili on line all’indirizzo: http://www.metododibella.org/it.


37. Second Level Master’s degree of CAM to 3 addresses: ”Traditional Chinese Medicine with Acupuncture, Homeopathy, Herbal Medicine". University of Rome and Bologna FIAMO (Italian Federation Associations and


40. Integrazione fra saperi convenzionali e non convenzionali in medicina, disponibile on line all’indirizzo: www.unibo.it/Portale/Offerta+formativa/AltaFormazione/20072008/Integrazione fra saperi convenzionali e non convenzionali in medicina.


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DNA QUANTIFICATION BY REAL TIME PCR AND SHORT TANDEM REPEATS (STRs) AMPLIFICATION RESULTS

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Key words: Quantification, Real Time PCR (qPCR), Short Tandem Repeats (STRs)

Parole chiave: Quantificazione, Real Time PCR (qPCR), Short Tandem Repeats (STRs)
Abstract

Determining the DNA amount in a forensic sample is fundamental for PCR-based analyses because if on one hand an excessive amount of template may cause the appearance of additional or out-of-scale peaks, by the other a low quantity can determine the appearance of stochastic phenomena affecting the PCR reaction and the subsequent interpretation of typing results. In the common practice of forensic genetics laboratories, the quantification results provided by Real Time PCR (qPCR) assume the role of “boundary line” between the possibility for a given DNA sample to be subjected or not to the subsequent analytical steps, on the basis of an optimal amount of DNA in the range indicated by the manufacturer of the specific commercial kit.

However, some studies have shown the possibility to obtain STR typing results even with an extremely low DNA concentration or, paradoxically, equal to zero (1). Regardless of the amount of DNA used for the quantification of the testing sample, specific software are able to use the standard curve to calculate concentration values far below the manufacturer’s reported optimal detection limit (0.023 ng/μL). Consequently, laboratories have to face the critical decision to interrupt the analyses giving up the possibility to obtain a genetic profile -although partial- or to try the amplification of the extract with the awareness of the interpretation issues that this implies.

The authors will present the quantification results obtained by qPCR performed on numerous samples collected from items of forensic interest, subjected to DNA extraction using magnetic beads. Following the quantification step, the extracts were subjected to DNA amplification and STR typing using last generation commercial kits. Samples that showed quantification values below the limit of detection for the method were included in the analysis in order to check the existence of a correlation between the DNA quantification results by qPCR and the possibility of obtaining a genetic profile useful for identification purposes.

Our study, performed on 558 samples from forensic casework items, has shown a correlation between the DNA amount resulted from qPCR analysis and the possibility of obtaining a genetic profile useful for identification purposes. In spite of the increasing sensitivity of last generation commercial kits for STR analysis, as demonstrated by the ability to detect allelic peaks from extremely low DNA quantities (with concentrations far below the limit of detection for the specific quantification kit, even corresponding to 0 or “Undetermined”), the results obtained show a correlation between qPCR quantification values and STR typing results. Thus the qPCR method confirms being today a useful and valid instrument for both qualitative and quantitative evaluation of genetic samples for human identification purposes.
The best-case scenario in forensic casework would undoubtedly involve the possibility of obtaining -from a specific DNA sample- a complete, balanced and high-quality genetic profile. However, the real laboratory practice involves in most cases challenging samples containing low quantity or low quantity DNA.

Determining the amount of DNA in a forensic sample is fundamental for PCR-based analyses because if on one hand an excessive amount of template may cause the appearance of additional or out-of-scale peaks, by the other a low quantity can determine the appearance of stochastic phenomena affecting the PCR reaction and the subsequent interpretation of typing results.

In the common practice of forensic genetics laboratories, the quantification results provided by Real Time PCR (qPCR) assume the role of “boundary line” between the possibility for a given DNA sample to be subjected or not to the subsequent analytical steps, on the basis of an optimal amount of DNA in the range indicated by the manufacturer of the specific commercial kit.

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In this study, the quantification results by qPCR performed on several samples collected from items of forensic interest are compared with the corresponding typing profiles of the Short Tandem Repeats (STRs), in order to check the existence of a correlation between the DNA quantification results by qPCR and the possibility of obtaining a genetic profile useful for identification purposes.

Methods

The analyses were conducted on 2 of forensic casework items consisting in:

- A wool scarf whose length was mt 2.00;
- A cotton handkerchief whose size was cm 84 x 54.

Laboratory tests

The samples were indicated with the numbers 1-509 as for the scarf, and 510-558 as for the handkerchief.
On each sample a generic blood test was performed by reactive strips containing dimethyl-dihydro-peroxysan and a colorimetric indicator (tetramethylbenzidine) that turns to green-blue color in presence of haemoglobin (Combur Test® E, Roche Diagnostics GmbH, Mannheim, Germany). On the samples that resulted positive for this analysis, the human species blood test was performed using the Hexagon OBTI kit (Human- Diagnostics Worldwide, Wiesbaden, Germany). This is an immunochromatographic test that uses monoclonal antibodies that form a “sandwich” complex with human haemoglobin (hHB), if present in the testing sample. This complex appears as a blue line on the membrane, thus permitting a visual interpretation of the result.

The results of these tests are shown in Table 1.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Num. of positive samples for the blood diagnosis test</th>
<th>Num. of positive samples for the human species blood test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarf</td>
<td>429</td>
<td>429</td>
</tr>
<tr>
<td>Handkerchief</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

- **Cytological analyses**

Further laboratory analyses were performed on a small fragment of each sample (n.1-558) in order to highlight the possible presence of cellular elements.

The search for cellular elements was performed by a cytocentrifugation technique using the Cytospin 3 (Shandon) instrument, that uses the centrifugal force in order to isolate and prepare a single layer of cells on specific microscope glass slides and, at the same time, is able to preserve the cell integrity. Each sample was washed by repeated pipetting in a volume of 90 μl of extraction tampon (TE). The entire volume was then charged on the sterile, single-use cytocentrifuge rack and subjected to sedimentation using the following parameters: time 5’, speed 800 rpm. All the procedure was performed at room temperature.

After the cytocentrifugation, in order to highlight the possible presence of cellular elements, each sample was colored with Hematoxylin (Vector Laboratories, CA. Cat. H-3401), a basic colorant generally used to highlight (in blue color) acid cell structures as the endoplasmic reticulum and the nucleic acids contained in the cell nucleus. The excess of color was removed with water and each sample was then analysed at the optic microscope ZEISS Axioskop 2 plus with a magnification of 20X. No cell elements were present in the analyzed samples.

- **DNA extraction**

Fragments of each sample were collected with sterile scissors and tweezers, then separately placed into 1,5 mL tubes and subjected to the DNA extraction procedure with the commercial kit DNA IQ™ System (Promega Corporation, Madison, WI, USA). This kit is specifically designed for forensic genetics laboratories; it allows DNA isolation using paramagnetic beads and can be used for extracting DNA from a great variety of samples, including dry stains and biological fluids (2). The DNA extraction procedure was performed following the manufacturer’s protocol:

1. cut sample and place in a microcentrifuge tube;
2. add 250 μL of prepared Lysis Buffer and incubate at 70°C for 30’;
3. transfer Lysis Buffer and sample into DNA IQ™ spin basket, centrifuge at maximum speed (13000 rpm) for 2’;
4. remove spin basket and add 7 μL of resuspended resin; vortex and incubate at room temperature for 5’;
5. vortex and place in the magnetic stand; carefully discard solution without disturbing resin;
6. wash with 100 μL of prepared Lysis Buffer;
7. wash three times with 100 μL of 1X Wash Buffer;
8. with the tube in the magnetic stand and the lid open, air-dry the resin at room temperature for 5’-10’;
9. add 30 µL of Elution Buffer and incubate at 65°C for 5';
10. remove tubes from heat, vortex and place on magnetic stand;
11. remove the DNA solution and put into a new tube;
12. store the DNA extract at +4°C.

- **DNA quantification by quantitative PCR or “Real Time PCR” (qPCR)**

For the quantification of the DNA extracts, the technique called quantitative PCR or “Real Time PCR” was used with the Applied Biosystems 7500 Real Time PCR instrument.

The Quantifiler® Duo DNA Quantification Kit (Applied Biosystems, Foster City, CA, USA) was used for the DNA samples analysis as it allows the simultaneous identification of the total human DNA and the human male DNA contained in a sample. The results obtained with this kit allow knowing if the extract contains a sufficient amount of DNA in order to proceed with the STR (Short Tandem Repeat) analysis and can be used to determine the relative amount of male and female DNA in the tested sample. This kit also includes a specific internal control (IPC) that highlights the presence of inhibitors that can affect the results of the PCR. The IPC is a synthetic DNA sequence that cannot be found in nature. The analyzed genes are the following: the Ribonuclease P RNA Component H1 (RPPH1) and the SRY gene, respectively used to amplify human DNA and male human DNA.

- **Sample preparation for Real Time PCR**

A reaction mix was prepared for each DNA sample and each standard curve point, as shown in Table 2.

**Table 2 - Reaction mix for each sample to be analyzed by Real Time PCR**

<table>
<thead>
<tr>
<th>Component (included in the kit)</th>
<th>Quantity in microlitres (µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantifiler Duo Primer Mix</td>
<td>10.5</td>
</tr>
<tr>
<td>Quantifiler Duo PCR Reaction Mix</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>23.00</td>
</tr>
</tbody>
</table>

The necessary quantities of the components were prepared in sterile polypropylene tubes and 23 µl of the reaction mix were dispensed in each well of the 96-well reaction plate for Real Time (MicroAmp Optical 96-well reaction plate, Part number N801-0560, Applied Biosystems), then 2 µl of standard DNA, 2 µl of testing DNA and 2 µl of Non-Template Control (NTC) were added into the corresponding well as to obtain a final reaction volume of 25 µl/sample.

Before being processed, the plates were centrifuged at 300 rpm for about 30 seconds in order to remove air bubbles in the wells.

The qPCR reaction parameters are shown in Figure 1:
The standard curve was created using 8 known DNA concentrations (included in the kit). The concentration range goes from 50 ng/µl (point 1) to 0,023 ng/µl (point 8). A duplicate for each standard point was used (Figure 2).
- Analysis of the DNA extracts (samples n. 1-558)
Each sample was analyzed in duplicate. The analysis of the internal control (IPC) revealed no inhibition of the PCR reaction. In fact, the Ct value of the IPC was always included in the range between 28-31, as it should be in normal conditions. In other words, from our analysis it is possible to exclude the presence of inhibitors in the PCR reaction that could affect the DNA amplification in the analyzed samples.

- STRs amplification and typing
The following commercial kits for DNA amplification were used: AmpFISTR® NGM SElect™ PCR Amplification kit (Applied Biosystems, Foster City, CA, USA); PowerPlex® ESI 17 System and PowerPlex® ESX 17 System (Promega, Madison, WI, USA).
Here the manufacturer’s amplification protocol for each kit is reported, with the indication of the reaction volume per sample. The DNA amplification was performed with a DNA Thermal Cycler GeneAmp PCR System 2720 (Applied Biosystems).

**AmpFISTR® NGM SElect™ PCR Amplification kit**
- 10 μl of AmpFISTR® NGM SElect™ Master Mix;
- 5 μl of AmpFISTR® NGM SElect™ Primer Set;
- 10 μl of DNA;
Final reaction volume 25 μl

**PowerPlex® ESI 17 System**
- 5 μl of PowerPlex® ESI 5X Master Mix;
- 2.5 μl of PowerPlex® ESI 17 10X Primer Pair Mix;
- Up to 17.5 μl of DNA;
Final reaction volume 25 μl

**PowerPlex® ESX 17 System**
- 5 μl of PowerPlex® ESX 5X Master Mix;
- 2.5 μl of PowerPlex® ESX 17 10X Primer Pair Mix;
- Up to 17.5 μl of DNA;
Final reaction volume 25 μl

The amplified DNA samples were then prepared for autosomal STRs typing by Capillary Electrophoresis:

**NGM SElect kit**
- 24.5 μl of Hi-Di™ Formamide;
- 0.5 μl of GeneScan™ 600 LIZ™ Size Standard;
- 1.5 μl of DNA (PCR product);
Final reaction volume 26.5 μl

**ESI 17 and ESX 17 kit**
- 24.5 μl of Hi-Di™ Formamide;
- 0.5 μl of CC5 Internal Lane Standard 500 (ILS 500);
- 1.5 μl of DNA (PCR product);
Final reaction volume 26.5 μl

An ABI PRISM 310 Genetic Analyzer (Applied Biosystems) was used for the DNA analysis.
The electrophoretic run parameters varied according to the specific kit (Table 2) and the electropherograms obtained were analyzed with the GeneMapper ID v3.2.1 software.

Results
The results of the genetic analyses (STRs typing) in comparison with the DNA concentration revealed by qPCR are the following:
- 0 or “Undetermined”: 0% of complete profiles (n=0 over 77 samples);
- between 0 and 0.023 ng/μL: 1.18% of complete profiles (n=5 over 423 samples);
- 0.023 ng/μL and up: 100% of complete profiles (n=58 over 58 samples).

Discussion and Conclusions
Determining the DNA amount in a forensic sample is fundamental for PCR-based analyses because if on one hand an excessive amount of template may cause the appearance of additional or out-of-scale peaks, by the other a low quantity can determine the appearance of stochastic phenomena affecting the PCR reaction and the subsequent interpretation of typing results (3, 4, 5).

Forensic advances with Real Time PCR have allowed qPCR quantification methods to become more wide-spread. This quantification technique allows determining with high accuracy and sensitivity the starting DNA amount in the tested sample during the PCR reaction. The quantification is performed using a fluorescent probe that permits an evaluation of the PCR product amount at each reaction cycle. Thus, the fluorescent signal intensity that is measured during the PCR reaction exponential phase allows determining the DNA quantity that was present at the beginning of the reaction.

The best point for measuring the fluorescence (through the comparison between the testing sample and samples with a known concentration used as standards) in relation to the cycle number is the PCR exponential phase, in which the relation between product quantity and starting DNA amount is more reliable. The qPCR instruments use the Cycle Threshold (Ct) for these calculations: the Ct value is the point at which the signal fluorescence overcomes an arbitrary threshold level, thus the smaller the number of cycles needed to exceed this threshold the higher the DNA template amount in the reaction.

Finding a minimum quantitation value that would predict STR success could save forensic examiners a great deal of time and money. This would assure that attempting to amplify STR loci from DNA with quantitation measurements at or below the minimum value would consistently be unsuccessful and would not result in any typable STR loci upon subsequent CE analysis. Examiners could then reliably choose to stop analysis of any sample that has a quantitation value at or below the minimum value. However, samples whose quantitation values fall below the limit of detection for this method may give an inaccurate quantitation result that is not reproducible upon a second analysis. This could explain the occurrence of full STR profiles from “undetected” samples, as well as the lack of any STR loci from several detected samples (1).

Our study, performed on 558 samples from forensic casework specimens, has shown a correlation between the DNA amount resulted from qPCR analysis and the possibility of obtaining a genetic profile useful for identification purposes (i.e. a complete profile).

In spite of the increasing sensitivity of last generation commercial kits for STR analysis, as demonstrated by the ability to detect allelic peaks from extremely low DNA quantities (with concentrations far below the limit of detection for the specific quantification kit, even corresponding to 0 or “Undetermined”) (6), the results obtained show a correlation between qPCR quantification values and STR typing results in terms of identification capacity in a forensic context. Thus the qPCR method confirms being today a useful and valid instrument for both qualitative and quantitative evaluation of genetic samples for human identification purposes.
**Table 3 - Program parameters for the electrophoretic runs**

<table>
<thead>
<tr>
<th>Kit</th>
<th>Module</th>
<th>Inj.secs</th>
<th>Run °C</th>
<th>Run time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NGM SElect</strong></td>
<td>GS STR POP 4 (1 ml) G5v2.md5</td>
<td>5</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td><strong>ESI 17/ESX 17</strong></td>
<td>GS STR POP 4 (1 ml) G5v2.md5</td>
<td>5</td>
<td>60</td>
<td>28</td>
</tr>
</tbody>
</table>
DNA quantification by real time PCR and short tandem repeats (STRs) amplification results

References

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SERIOUS AND FATAL ACCIDENTS IN 2011 IN IMMIGRANT WORKERS: CONSIDERATIONS ON THE PHENOMENON AND PREVENTIVE MEASURES

INFORTUNI GRAVI E MORTALI NEL 2011 IN LAVORATORI IMMIGRATI: CONSIDERAZIONI SUL FENOMENO E MISURE PREVENTIVE

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Key words: accident, migrant workers, prevention

Parole chiave: infortunio, lavoratori immigrati, prevenzione

Abstract

Background: Traumatic events or serious injury, or death occurring to foreign nationals are mostly events of nature work, and the competence to indemnify working accidents (and occupational diseases) is attributed to INAIL. An accident at work is defined as a traumatic event which occurred through the intervention of a violent cause during the work, determining a worker's personal injury identified in a temporary incapacity, permanent disability, (allowance for damage between 1 and 5%, with a lump sum payment for the damages of between 6 and 15%, with monthly income for damages equal to or greater than 16%) or death. In recent years, Italy has shown a general reduction in the number of harmful events and fatalities, and this was also the case for foreign workers, but in the face of such data has highlighted the persistence of a significant number of serious multiple injuries and deaths.
**Objectives:** To evaluate the possible additional risk factors and possible preventive measures.

**Methods:** The present study investigated the time course of serious and fatal injuries in foreign workers from 2008 to 2011, and in more detail the events for the year 2011, taking into account the business sector, the methods of the event, the spatial distribution and the nationality of the workers, examining the data obtained from the Annual Reports INAIL. For the serious injury is highlighted a progressive decrease in foreign workers during the years 2008 to 2011, in industry and services and, to a lesser extent, in agriculture. Data on fatalities instead show a substantial stability in the number of them, both in percentage and in numerical values.

**Discussion:** It’s possible that the factors that contribute to an increased risk of serious and fatal events in foreign workers can be: the imperfect knowledge of the Italian language, the lack of specific training in relation to occupational hazards, the irregularity and uncertainty that often characterizes their work activities, excessive consumption of alcohol, which can lead to higher risks of some occupations in itself dangerous.

**Conclusions:** The main objective is to remain an "effective preventive action" as an essential element to reduce accidents and occupational diseases. Prevention must take place in a business activity that is inspired by the values of "social responsibility."

In this prevention work is fundamental to the involvement of all public and private institutions involved in the health and safety of the workplace, primary care physicians and hospitals, universities, advocacy organizations and associations representing; it’s also important to try to make companies aware of the costs of unsafe, informing also the economic benefits related to a policy of prevention.

**Abstract**

**Introduzione:** Gli eventi traumatici con lesioni gravi o gravissime o mortali occorsi a cittadini stranieri sono in gran parte di natura lavorativa, e la competenza di indennizzare gli infortuni lavorativi (e le malattie professionali) è attribuita all’INAIL. Per infortunio sul lavoro si intende un evento traumatico, occorso per causa violenta in occasione di lavoro, determinante nel lavoratore un danno alla persona identificabile in una incapacità temporanea al lavoro, una invalidità permanente (in franchigia per i danni compresi fra 1 e 5 %, con liquidazione in capitale per i danni compresi fra il 6 ed il 15 %, con rendita mensile per i danni uguali o maggiori del 16 %) o la morte.

Lo studio del fenomeno infortunistico lavorativo in Italia ha evidenziato negli ultimi anni una riduzione del numero generale degli eventi lesivi e degli infortuni mortali; è stato riscontrato un decremento di infortuni anche nei lavoratori stranieri, ma a fronte di tali dati si è evidenziata la persistenza di un significativo numero di politraumatismi gravi e di decessi.

**Obiettivi:** Lo scopo di questo lavoro è valutare la possibile presenza di fattori di rischio aggiuntivi nei lavoratori stranieri in Italia e le possibili misure di prevenzione.

**Metodi:** Il presente studio analizza l’andamento nel tempo delle lesioni gravi e mortali dei lavoratori stranieri nel periodo 2008-2011, e più in dettaglio gli eventi relativi all’anno 2011, prendendo in esame il settore di attività, le modalità dell’evento, la distribuzione territoriale e la nazionalità dei lavoratori, esaminando i dati ottenuti dai Rapporti annuali dell’INAIL. Per gli infortuni gravi si è evidenziata una progressiva diminuzione nei lavoratori stranieri nel corso degli anni dal 2008 al 2011, nell’industria e nei servizi e, in misura minore, nel settore agricolo.

I dati sugli incidenti mortali, invece mostrano una sostanziale stabilità del loro numero, sia in percentuale sia in valori numerici.
Discussione: E’ possibile che i fattori che contribuiscono ad un aumentato rischio di eventi gravi e mortali nei lavoratori stranieri possano essere: la conoscenza imperfetta della lingua italiana, la mancanza di formazione specifica in relazione ai rischi professionali, l’irregolarità e l’incertezza che spesso caratterizza le loro attività di lavoro, il consumo eccessivo di alcol, che può portare a rischi più elevati in alcune occupazioni già di per sé rischiose.

Conclusioni: L’obiettivo principale deve rimanere quello di un efficace azione preventiva, quale elemento essenziale per ridurre gli infortuni e le malattie professionali; tale prevenzione deve avvenire all’interno un’attività imprenditoriale che si ispiri ai valori di “responsabilità sociale”. In questo lavoro di prevenzione è fondamentale il coinvolgimento di tutte le istituzioni pubbliche e private operanti nel settore della salute e della sicurezza nei luoghi di lavoro, medici di base e ospedali, università, gli enti di patrocinio e le associazioni rappresentative; è inoltre fondamentale cercare di rendere consapevoli le aziende dei costi legati alla non sicurezza, informando anche dei benefici economici legati ad una efficace politica di prevenzione.

Background
Traumatic events, serious injury or death occurring to foreign nationals are mostly events of nature work. The competence to indemnify working accidents (and occupational diseases) is attributed to INAIL. An accident at work is defined as a traumatic event which occurred through the intervention of a violent cause during the work, determining a worker’s personal injury identified in a temporary incapacity, permanent disability, (allowance for damage between 1 and 5%, with a lump sum payment for the damages of between 6 and 15%, with monthly income for damages equal to or greater than 16%) or death. The study of injuries working in Italy in recent years has shown a reduction in the overall number of harmful events and fatalities. It was found a decrease of injury even in foreign workers, but in the face of such data is shown to persist for a significant number of serious multiple injuries and fatalities. However, is difficult to estimate the number of injuries of varying severity, caused by illegal foreign workers who are not reported for fear of retaliation, dismissal, discrimination of various kinds.

Objectives
The purpose of this study was to evaluate the possible presence of additional risk factors in the foreign workers in Italy.

Methods
Examining the data obtained from the Annual Reports INAIL (1, 2, 3, 4) is highlighted for the serious injury a progressive decrease in foreign workers during the years 2008 to 2011, in industry and services and, to a lesser extent, in agriculture (Fig. 1).
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

Fig. 1 - Serious injuries (damage equal to or greater than 16%) occurred to foreign workers for the years 2008-2011.

The reasons for this decrease could be attributed to not complaints of injuries (for irregularities or threat of dismissal) and the effect of the economic crisis (with a decrease in the number of workers employed), but also the possible positive effects of the work of prevention so far implemented. Data on fatalities instead show a substantial stability in the number of them, both in percentage and in numerical values (Fig. 2), since it seems closer to reality. Possible causes could be identified in the use of foreign workers not trained in working riskier in substantial inability to prevent the reporting of a deadly event, but also, probably, in ‘emphasis on the risk of abuse of alcohol and other habits subjective.

Fig. 2 - Fatal accidents occurred to foreign workers for the years 2008-2011.
With regard to the sectors most at risk, the data show the prevalence in percentage of serious accidents in the construction sector, followed by transport, services and industry metals (Tab. 1 – Fig. 3). This confirms what has been shown in the general data on the increased risk exposure of construction workers and those who work on the street.

For fatalities, the data show the prevalence in percentages in the construction sector, followed by transport and agriculture. These data confirm what was detectable in the general data on the increased risk exposure for construction workers and for those who work on the road, but also show how in the agricultural sector there is a considerable risk for fatal injuries, mainly due to reversal of agricultural vehicles and falls from a height (Tab. 1 – Fig. 4).

Tab. 1 - Occupational accidents occurring to foreign workers in 2011 and compensated by INAIL, divided for management and main sectors of economic activity.

<table>
<thead>
<tr>
<th>Management / Sector of economic activity</th>
<th>Permanent (grade&gt; = 16%)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Employees State Income</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Industry and Services</td>
<td>392</td>
<td>121</td>
</tr>
<tr>
<td>• Agrindustria</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>• FISHING</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>• ESTRAC. MINERAL</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>• IND. FOOD</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>• IND. TEXTILE</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>• IND. LEATHER</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>• IND. WOOD</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>• IND. PAPER</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>• IND. OIL</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>• IND. CHEMISTRY</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>• IND. RUBBER</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>• IND.TRASFORMAT.</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>• IND. METALS</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>• IND. MECHANICAL</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>• OTHER INDUSTRIES</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>• CONSTRUCTION</td>
<td>120</td>
<td>26</td>
</tr>
<tr>
<td>• TRADE</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>• HOTELS. and REST.</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>• TRANSPORTATION</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>• BUSINESS SERVICES</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>• PUBLIC ADMIN.</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>• HEALTH</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>• PUBLIC SERV.</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>• PERSONAL HOME</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Serious 438</td>
<td>Deadly serious 35</td>
</tr>
</tbody>
</table>

• Permanent Disability (grade> = 16%): 438 cases
  of which: at work: 36
  Ongoing: 70
• Mortals: 135 cases
  of which: at work: 100
  Ongoing: 35
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

Fig. 3 - Accidents at work occurred to foreign workers in 2011 and compensated by INAIL for management and main sectors of economic activity - DISABILITY Permanent (grade ≥ 16%).

Fig. 4 - Accidents at work occurred to foreign workers in 2011 and compensated by INAIL for management and main sectors of economic activity - FATAL INJURY.
With regard to the causes and circumstances of the event, it is necessary to emphasize that there is a problem primarily in the framework for approximately 1/3 of cases (more un-coded / Permanent - Permanent Disability > = 16%: 115 cases, 54 cases death). It should be noted, however, that most serious accidents are caused, in the almost equivalent extent, from falls and loss of control of a machine or machines. These data confirm substantially as the sectors most at risk of serious events are as construction and transport (Tab. 2 – Fig. 5).

For fatalities, data show that about 2/3 of them are caused by loss of control of a machine or machinery, followed by events caused by rupture or collapse and fall, and this confirms that the sectors most at risk of fatal events are the construction industry, transport and agriculture (Tab. 2 – Fig. 6).

<table>
<thead>
<tr>
<th>Event Mode</th>
<th>Permanent (grade ≥ 16%)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diversion electrical problem, explosion, fire</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diversion due to overflow, overturn, loss, sliding, steaming ...</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Broken, burst, slipping, falling, collapse agent material</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Loss of control of all or part of a machine, of a means of transport / handling equipment</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>Fall of person from slipping or stumbling</td>
<td>107</td>
<td>9</td>
</tr>
<tr>
<td>Movement of the body without physical effort</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>Movement of the body with physical effort</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Surprise, fright, violence, aggression threatens</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Other non-encrypted / indefinite</td>
<td>115</td>
<td>54</td>
</tr>
<tr>
<td>TOTAL</td>
<td>438</td>
<td>135</td>
</tr>
</tbody>
</table>

of which:

- during work                                                               368  100
- Ongoing                                                                    70   35
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

Fig. 5 - Serious accidents at work with damage ≥ 16% foreign workers occurred in 2011 and compensated by INAIL known for event mode (%).

Fig. 6 - Fatal accidents at work occurred to foreign workers in 2011 and compensated by INAIL known for event mode (%).
With regard to the regional distribution of events (Tab. 3 – Fig. 7 – Fig. 8), the data show that more than half of serious and fatal accidents are concentrated in Lombardy, Veneto, E. Romagna and Lazio, regions with high employment in the construction industry, tertiary and transport.

**Tab. 3 - Fatal and serious accidents occurring to foreign workers in 2011 and compensated by INAIL for territorial distribution.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Permanent (grade &gt; 16%)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIEMONTE</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>V. D’AOSTA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>LOMBARDIA</td>
<td>83</td>
<td>21</td>
</tr>
<tr>
<td>TRENTINO A.A.</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>VENETO</td>
<td>49</td>
<td>17</td>
</tr>
<tr>
<td>FRIULI V. G.</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>LIGURIA</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>EM. ROMAGNA</td>
<td>65</td>
<td>22</td>
</tr>
<tr>
<td>TOSCANA</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>UMBRIA</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>MARCHE</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>LAZIO</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>ABRUZZO</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>MOLISE</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CAMPANIA</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>PUGLIA</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
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</tr>
<tr>
<td>CALABRIA</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>SICILIA</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>SARDEGNA</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

Fig. 7 - Serious accidents have occurred to foreign workers in 2011 and compensated by INAIL for territorial distribution.

Fig. 8 - Fatal accidents occurred to foreign workers in 2011 and compensated by INAIL for territorial distribution.
With regard to the nationality of foreign workers (Tab. 4 – Fig. 9 – Fig. 10) the data show how the workers most at risk for serious injury are from Romania (workers employed mainly in construction), followed by those from Morocco and Albania; also workers most at risk for fatal accidents originated from Romania and Albania, to a lesser extent from Morocco.

**Tab. 4 - Fatal and serious accidents occurring to foreign workers in 2011 and compensated by INAIL by nationality of origin.**

<table>
<thead>
<tr>
<th>Nationality</th>
<th>Permanent (grade≥16%)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROMANIA</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>MOROCCO</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>ALBANIA</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>MACEDONIA</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>TUNISIA</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>UKRAINE</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>SENEGAL</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>GERMANY</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>EX YUGOSLAVIA</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>SWITZERLAND</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>BANGLADESH</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>FRANCE</td>
<td>9</td>
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</tr>
<tr>
<td>INDIA</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>POLAND</td>
<td>8</td>
<td>3</td>
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<tr>
<td>ARGENTINA</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>EGYPT</td>
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<td>2</td>
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<tr>
<td>MOLDOVA</td>
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<td>BELGIUM</td>
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<tr>
<td>Bosnia and Herzegovina</td>
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<td>0</td>
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<td>BRAZIL</td>
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<td>2</td>
</tr>
<tr>
<td>CHINA</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>OTHER COUNTRIES</td>
<td>72</td>
<td>21</td>
</tr>
</tbody>
</table>
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

Fig. 9 - Serious accidents have occurred to foreign workers in 2011 and compensated by INAIL by nationality.
Discussion
What may be, then, the factors underlying the serious and fatal injuries in foreign workers? It 'possible that the factors that contribute to an increased risk of serious and fatal events in foreign workers can be:
1. the imperfect knowledge of the Italian language;
2. the lack of specific training in relation to occupational hazards;
3. the irregularity and uncertainty that often characterizes these jobs;
4. excessive consumption of alcohol that can lead to higher risks of some occupations in itself dangerous.

Conclusions
The main target must therefore remain an "effective preventive action" as an essential element to reduce accidents and occupational diseases. Prevention must take place in a business activity that is inspired by the values of "social responsibility."

In this' prevention work is fundamental to the involvement of all public and private institutions involved in the health and safety of the workplace, primary care physicians and hospitals, universities, advocacy organizations and associations representing; the latter, in particular, can play a crucial role in the full integration of foreign citizens in the workplace and protection in case of accidents and occupational diseases, accounting for through new knowledge and training for workers in different cultures and traditions, sometimes forced to operate in unsafe environments and in situations of discrimination. It 'also important to try to make companies aware of the costs of unsafe, informing also the economic benefits related to a policy of prevention (5, 6, 7, 8, 9, 10, 11, 12, 13).
Serious and fatal accidents in 2011 in immigrant workers: considerations on the phenomenon and preventive measures

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OBSTRUCTIVE SLEEP APNEA SYNDROME: RELATIONSHIPS BETWEEN SEVERITY AND SEX

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Key words: obstructive sleep apnea syndrome, polysomnography, AHI

Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is a pathological condition characterized by frequent episodes of collapse of the structures of the upper airways with interruption of airflow and reduction of oxygen saturation in arterial blood.

Its incidence is equal to about 4% in men and 2% in females in the population up to 65 years of age.

The severity of OSAS is determined by an index that relates the number of apneic events per hour of sleep “apnea-hypopnea index” (in English AHI: apnea-hypopnea index).

As the muscle tone of the body ordinarily relaxes during sleep, and the airway at the throat is composed of walls of soft tissue, which can collapse, it is not surprising that breathing can be obstructed during sleep.

Common signs of OSA are unexplained daytime sleepiness, restless sleep, and loud snoring (with periods of silence followed by gasps). Less common symptoms are morning headaches, insomnia, trouble concentrating, mood changes such as irritability, anxiety and depression, forgetfulness, increased heart rate and/or blood pressure, decreased sex drive, unexplained weight gain, increased urination and/or nocturia, frequent heartburn or gastroesophageal reflux disease, and heavy night sweats.
The gold standard for the diagnosis of OSAS is considered the polysomnography.

**Objectives:** The aim of our study is to evaluate the influence of sex in the presentation of the disease.

**Methods:** The sample was undergone to a visit for the evaluation of any anatomical abnormalities of the first airways, which can cause or aggravate the disease. Patients was subjected to a questionnaire for the evaluation of disorders which achieve to disease with the compilation of the Epworth evaluation scale, which measure the frequency with which the patient tends to fall asleep during the daily activities. We utilized also the polysomnography for the diagnosis and staging of the disease.

**Results:** The analysis of the results obtained allows us to observe that the ratio between the apnea/Hypopnea number for hour and sex is not statistically significant (p>0,05), despite the prevalence of OSAS is greater in males than in females, with a ratio of 3:1.

**Discussion and Conclusions:** Our study has allowed us to observe that the frequency of submission of OSAS is greater in male than female with a ratio of 3:1, while the severity of the disease does not appear related to sex. Thus, our study confirms the existing data in the literature showing a ratio of 5:1 in the presentation of the disease in males than in females.

**Abstract**

**Introduzione:** La sindrome delle apnee ostruttive del sonno (OSAS) è una condizione patologica caratterizzata da frequenti brevi episodi di collasso delle strutture delle vie aeree superiori durante il sonno, con conseguente interruzione del flusso aereo che comporta la riduzione della saturazione di ossigeno nel sangue arterioso. La severità dell’ OSAS è determinata da un indice che mette in relazione il numero di eventi di apnea per ora di sonno “apnea-ipopnea” (in inglese AHI: apnea-ipopnea). Dal momento che la muscolatura del corpo si rilassa normalmente durante il sonno, le prime vie aeree, composte da pareti di tessuto molle che può collassare, non è sorprendente che la respirazione possa essere ostruita durante il sonno. Segni comuni di OSAS sono: sonnolenza diurna, sonno agitato e forte russamento (con periodi di silenzio seguiti da rantoli). Sintomi meno comuni sono mal di testa, insonnia mattutina, difficoltà di concentrazione, cambiamenti di umore come irritabilità, ansia e depressione, perdita di memoria, aumento della frequenza cardiaca e/o della pressione sanguigna, diminuzione del desiderio sessuale, aumento di peso inesplicabile, aumento della minzione e/o nicturia, pirosi gastrica frequente o malattia da reflusso gastroesofageo, e sudorazioni notturne pesanti. Il gold standard per la diagnosi di OSAS è considerata la polisonnografia.

**Obiettivi:** Lo scopo del nostro studio è la valutazione della prevalenza di uno dei due sessi nello sviluppo e nella gravità di presentazione della patologia.

**Metodi:** Abbiamo sottoposto il campione ad esame obiettivo per evidenziare la presenza di eventuali anomalie anatomiche che potessero causare o aggravare la patologia. Infine, è stata utilizzata la polisonnografia per la diagnosi e stadiazione della patologia.

**Risultati:** L’analisi dei risultati ottenuti ha permesso di osservare che il rapporto tra numero di apnee/ipopnee per ora di sonno ed il sesso non è statisticamente significativo (p>0,05), nonostante la prevalenza dell’OSAS nel sesso maschile sia maggiore che nel sesso femminile, con un rapporto di 3:1.
Obstructive sleep apnea syndrome: relationships between severity and sex.

**Discussion e Conclusioni:** Il nostro studio ha permesso di osservare che la frequenza di presentazione dell’OSAS è maggiore nel sesso maschile rispetto a quello femminile con un rapporto di 3:1, mentre la gravità della patologia non appare correlata al sesso. Quindi, la nostra ricerca conferma i dati già presenti in letteratura che mostrano un rapporto di 5:1 nella presentazione della patologia nei maschi rispetto alle femmine.

**Background**
The obstructive sleep apnea syndrome (OSAS) is characterized by episodes of partial obstruction (hypopnea) or complete (apnea) of the upper airway. Its incidence is equal to about 4% in men and 2% in females in the population up to 65 years of age (1, 2). The severity of OSA is determined by an index that relates the number of apneic events per hour of sleep “apnea-hypopnea index” (in English AHI: apnea-hypopnea index). A value of AHI of less than 5 is considered normal. A value between 5 and 15 classifies the OSAS in a mild form, a value between 15-30 defines the moderate and a value greater than 30 characterizes the severe sleep apnea (3, 4). The gold standard for the diagnosis of OSAS is considered the polysomnography (5, 6).

**Objectives**
The aim of our study was to evaluate the prevalence of one of the two sexes in the development and severity of presentation of Obstructive Sleep Apnea Syndrome.

**Methods**
The study has been developed at the Complex Operative Unit of Phoniatrics of the Policlinico Umberto I in Roma. We enrolled 193 patient, 57 female and 136 male, aged between 21 and 77 years from September 2010 to July 2011. It was carried out a careful history that concern accessories disorders associated to OSAS. Sample was undergone to a visit for the evaluation of any anatomical abnormalities of the first airways, which can cause or aggravate the disease. Patients was subjected to a questionnaire for the evaluation of disorders which achieve to disease with the compilation of the Epworth evaluation scale, which measure the frequency with which the patient tends to fall asleep during the daily activities. Sample was divided into two groups according to sex. Each group, then, was further divided into four groups according to age. All patients were submitted to nocturnal polysomnographic home examination by Embletta ® X100 for the identification and quantification of episodes of apnea/Hypopnea during sleep and elaboration of the AHI (Apnea/Hypopnea Index). In male patients, the mean AHI was 31.8 (range 18.2 to 45.5), while in females is 30.05 (range 14.3 to 41.8).

**Statistical Analysis**
To evaluate the correlation between AHI, sex and age was conducted a χ² analysis.

**Results**
Statistical analysis of data of the ratio between AHI, age and sex is not statistically significant (p>0,05). The average AHI estimated for age group does not differ significantly from average AHI estimated for sex. OSAS is present in male of all ages with a peak of more frequent between 40 and 70 years; in females is present only after 40 years, with a peak between 55 and 70 years (Graphic 1, 2).
Obstructive sleep apnea syndrome: relationships between severity and sex.

Furthermore, it is evident that the OSAS is most frequent in the males than females with a ratio of 3:1 (Graphic 3).

**Graphic 1 - OSAS frequency in males divided into age groups**

**Graphic 2 - OSAS frequency in females divided into age groups**

**Graphic 3 - OSAS frequency ratio in males and females**
Discussion and Conclusions
Our study confirms the existing data in the literature that OSAS is more common in males than females with a ratio of 3:1 (7, 8).
The age range of the disease is higher in males than in females. Also there is no a significant correlation between the severity of OSAS, sex and age.
This is a preliminary study that requires an extension of the sample to confirm the data obtained.
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MOBBING: CASE RECORD, GENDER DIFFERENCES, MEDICO-LEGAL ISSUES

MOBBING: CASISTICA CLINICA, DIFFERENZE DI GENERE, ASPETTI MEDICO-LEGALI


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Key words: psychosocial risk, bullying, women's work, adjustment disorder

Abstract

Introduction: The “mobbing syndrome”, due to prolonged harassment at work, requires accurate diagnostic evaluation, both for clinical and medico-legal purposes. The risk related to women’s work has been scarcely investigated.

Objectives: To evaluate with a multidisciplinary approach (occupational physician, psychologist, psychiatrist) the frequency and gender differences of psychiatric disorders due to mobbing (and other forms of work-related stress) in clinical practice.
**Methods:** Between 2001 and 2011, we examined 474 outpatients (273 females, 201 males), aged between 21 and 61 years (average 41.8 years), for suspected psychopathological work-related problems. The diagnostic process included occupational health evaluation, psychological counseling, structured interview for DSM-IV (Diagnostical and Statistical Manual of Mental Disorders), personality test MMPI-2 (Minnesota Multiphasic Personality Inventory-2), psychiatric visit, laboratory and instrumental tests when indicated. The evaluations were mostly based on what the patients reported, due to the fact that it was impossible to directly examine the work environment. Thus, mobbing syndrome diagnoses were formulated in probabilistic terms.

**Results:** A work-related psychiatric disorder was diagnosed in 152 subjects (32% of the whole case series): 37 cases (8%) were probably due to mobbing. The other patients presented work-unrelated psychiatric conditions (28% of cases) or no psychiatric disorders (according to DSM-IV criteria). Among workers with disorders due to mobbing or other forms of work-related stress, the majority (62%) were women, with medium-high education, mostly between 34 and 45 years. The occupations involved were various, with predominance of office work.

**Discussion and Conclusions:** Using a rigorous diagnostic procedure, a psychopathological disorder due to mobbing - or to other forms of occupational stress - is diagnosed in a limited number of patients, mostly women. Thus, caution should be adopted in labeling as “mobbing syndrome” clinical conditions that can show similar manifestations. Such conditions can easily generate conflict with employers, based on unfounded allegations, if superficially assessed. The majority of women with stress-related disorders were between 34 and 45 years: this may be explained by the increased family commitment in this age range, resulting in rise of stressful conditions and working difficulties. The study calls for adequate preventative measures, primarily aimed at protecting women’s work.

**Abstract**

**Introduzione:** La patologia da mobbing, conseguente a vessazioni reiterate in ambito occupazionale, richiede un accurato inquadramento diagnostico, indispensabile non solo ai fini prognostici e terapeutico-riabilitativi, ma anche a scopomedico-legale. Il rischio legato al lavoro femminile risulta scarsamente indagato.

**Obiettivi:** Valutare con approccio multidisciplinare (medico del lavoro, psicologo, psichiatra) la frequenza e le differenze di genere della patologia da mobbing (eda stress lavoro-correlato in genere) nella pratica clinica.

**Metodi:** Tra il 2001 e il 2011, sono state esaminate 474 persone (273 donne e 201 uomini), d’età compresa tra 21 e 61 anni (media:41,8), che riferivano problemi di salute connessa situazioni di mobbing (o comunque di disagio psicologico) in ambito lavorativo. Il percorso diagnostico prevedeva visita specialistica di medicina del lavoro, colloquio clinico-psicologico conintervista strutturata per DSM-IV(Diagnostical and Statistical Manual of Mental Disorders), test di personalità MMPI-2 (Minnesota Multiphasic Personality Inventory-2) in forma intera, visita psichiatrica, accertamenti laboratoristici e strumentali ove indicati. Le valutazioni sono state in massima parte basate su quanto riferito dai pazienti, per l’impossibilità di verificare direttamente l’eventuale esistenza di un clima vessatorio nell’ambiente di lavoro. Le diagnosi di patologia da mobbing sono state quindi formulate in termini probabilistici.

**Risultati:** Un disturbo psichiatrico correlato al lavoro è stato diagnosticato in 152 soggetti (32% della casistica totale): 37 casi (8%) erano verosimilmente dovuti a mobbing. Negli altri pazienti sono state riscontrate condizioni psichiatriche non rapportabili al lavoro (28% dei casi) oppure non è stata formulata diagnosi psichiatrica (secondo i criteri del DSM-IV). Tra i lavoratori con patologiada mobbing o altre forme di stress è stata riscontrata prevalenza femminile (62%), con grado di scolarità medio-elevato; la fascia d’età più colpita era tra i 34 e i 45 anni; le professioni rappresentate sono molteplici, con preponderanza di quelle impiegatizie.
Discussione e Conclusioni: Con un rigorosoinquadramentodiagnostico, un quadro psicopatologico da mobbing - da altre forme di stress lavorativo - è diagnosticato in un numero limitato di pazienti, in prevalenza donne. S’impone quindi prudenza nell’etichettare come “mobbing” situazioni cliniche che tali non sono, anche per prevenire immotivaticontenziosi con i datori di lavoro. La maggioranza delle donne con disturbi stress-correlati erano tra i 34 ed i 45 anni: ciò può essere spiegato dall’incremento degli impegni legati all’ambito familiare durante questa fascia d’età, con conseguente aumento delle condizioni stressanti e maggiori difficoltà lavorative. Lo studio richiama la necessità di adeguate misure preventive, volte soprattutto a tutelare il lavoro femminile.

Background
Mobbing (bullying, moral harassment, psychological violence) is one of the most formidable psychosocial risk factors found in the workplace. It is defined as "any improper conduct that takes place, in particular, through behavior, words, acts, gestures, or writing, which upsets the personality, dignity, physical or psychological integrity of a person, and alters and degrades the working environment" (1). To define a situation as mobbing, it is necessary that the harassing actions be repetitive (according to some Authors, at least once a week for at least six months) (2). Depending on the relationships between victims (“mobbed”) and persecutors (“mobbers”), different forms of mobbagingre defined: "vertical from above" (by employers or superiors), "vertical from below" (unusual, by a lower hierarchical position), "horizontal or among peers" (among workers with similar hierarchical level), "planned or strategic" (within a deliberate corporate strategy aimed at excluding one or more employees), "double mobbing" (in the workplace and family). The attack modalities may involve communication, reputation and/or performance. Other common forms of work-related stress should not be confused with mobbing: antagonism and competitiveness; disputes, character incompatibility, interpersonal conflicts; changes due to company needs; justified disciplinary actions (3, 4, 5, 6).

As in all the situations of reiterated stress, mobbing can exhaust the capacities of individual adaptation, and cause several psychopathological manifestations more or less severe, sometimes irreversible, with repercussions on the somatic sphere. Such a syndrome may include psychosomatic manifestations (insomnia, headache, cardiovascular and gastrointestinal disorders, immunodepression), emotional disturbances (anxiety, anger, crying fits, panic attacks, mood deflection, affective indifference, depersonalization), behavioral disorders (changes in appetite, drugs and substance abuse, self- or hetero-aggressiveness, apathy, changes in sexual behavior up to tolibido disappearance) (4, 5, 6, 7).
The "mobbing syndrome" has not been clearly identified nosologically. Indeed, although several mobbing-related psychopathological conditions are described in scientific literature, both the ICD-10 (International Classification of Disease) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) identify only two stress-related conditions (not necessarily work-related): the Post-Traumatic Stress Disorder (PTSD), and the Adjustment Disorder (AD).
The problem of mobbing and resulting disease has complex medico-legal implications, in the penal, civil, and insurance contexts. During the last few years, the Italian Workers’ Compensation Authority (INAIL) recognized some cases, and included “mental and psychosomatic illnesses due to work organization dysfunctions (organizational coerciveness)” in the list II, group 7, of the new inventory of occupational diseases (Italian Ministry of Labour and Social Policy: Decree 27th April 2004). Thus, an accurate diagnostic procedure is essential not only for clinical (prognostic and therapeutic-rehabilitative) reasons, but also for the possible demonstration of the causal relation between harassment in the workplace and the suffered damage (8, 9).
The European Parliament Resolution of the 20th September 2001 identified women’s work as being arisky area. The EASHW (European Agency for Safety and Health at Work) has long stimulated each country to examine its critical issues regarding gender, health, and safety at work, in order to plan appropriate interventions. A document of the same agency emphasizes that, compared to men, research, prevention and awareness of working women’s risks are underestimated and neglected. In Italy, the article 28 of the Legislative Decree 81/2008 states that gender differences should be properly considered in the evaluation of occupational risks, including "those related to work stress". Nevertheless, in scientific literature there are few studies on gender differences among victims of mobbing or other sources of work-related stress.

Objectives
The present study evaluates the frequency of mobbing syndrome and other non-mobbing-related psychiatric disorders, in patients with working discomfort, undergoing a multidisciplinary diagnostic procedure (occupational physician,
psychologist, psychiatrist). The gender differences, and medico-legal implications, of the diagnosis are then analyzed.

Methods
From 2001 to 2011, 474 patients required a specialist visit at the Occupational Medicine Unit of our Institute for psychological health problems, related, in their opinion, to mobbing (or other forms of work discomfort) in the workplace. The sample consisted of 273 females (58%) and 201 males (42%), aged between 21 and 61 years (average: 41.8). Five subjects (1%) had attended primary school only, 166 secondary school (35%), 227 had a high school diploma (48%), and 76 were university graduated (16%). Three hundred and forty-three patients (72%) were employed in private companies, while the remaining 131 (28%) worked in public institutions. About 12% of the subjects were executives, 15% intermediate managers, 39% clerks, 22% workmen; the remaining 12% had other qualifications.

The diagnostic process, developed by our Unit over the years (11), begins with an evaluation by an occupational health specialist: for each patient a careful work history is collected, as well as family, social, physiological and pathological history; this step is followed by a careful physical examination, in order to identify possible diseases associated with the symptoms of the patient.

It should be specified that the evaluations are mostly based on patient reports, in that our hospital unit cannot (by law) directly verify the existence of harassment in the workplace (a very difficult task, for which sufficiently validated methods are still lacking). Therefore, we formulated the mobbing syndrome diagnoses in probabilistic terms.

The diagnostic protocol then includes: psychological counseling, structured interview for DSM-IV: SCID (Structured Clinical Interview for DSM-IV) axis I and II, a complete personality test MMPI-2 (Minnesota Multiphasic Personality Inventory-2), psychiatric examination, and other laboratory and instrumental tests when indicated.

The structured interview is based on a specific protocol, and attributes specific symptoms, on which the examiner focuses, to the different disease conditions. By giving each patient a severity score, we obtain satisfactory results. For axis I, the process starts with patient’s history and leads to evaluate the presence of psychiatric disorders, such as anxiety and depression. The axis II consists of a self-report questionnaire followed by an interview regarding critical items of the questionnaire, to identify personality disorders and mental retardation.

The MMPI-2, i.e. the updated and standardized version of the MMPI test, is intended to assess the most important structural features of personality and emotional disorders. It includes 567 questions on different topics: general health, neurological conditions, cranial nerves, motility and coordination, sensitivity, vasomotor function, trophism, speech, secretory functions, cardiovascular, respiratory, gastrointestinal and genitourinary systems, habits, family and marital situation, professional activity, education, sexual, social and religious behavior, attitudes towards politics, law and order, morality, masculinity, femininity, presence of depression, manic, obsessive and compulsive disorders, presence of hallucinations, illusions, delusions, phobias, sexual sadistic and masochistic trends. The patient should respond to items with "True" or "False", but all omissions and items with dual response are considered "I don’t know". The usefulness of information obtained through the MMPI-2 depends on the ability of the subject to understand instructions, carry out the required task, understand and interpret the content of the items, and record the answers correctly. To calculate the scores, a computer program and a manual scoring are available. The interpretation of results requires a high level of psychometric, clinical, and professional competence.

The ethical committee of our Institution approved the study protocol, according to the criteria of the Declaration of Helsinki.

Results
As shown in Figure 1, 16 (3%) of the examined patients did not complete the described diagnostic procedures. In 176 subjects (37%) no psychiatric diagnosis (according to the DSM IV criteria) was formulated, while finding altered dynamics in interpersonal relationship with colleagues and concurrent stressful conditions. In 130 patients (28%), we diagnosed a psychiatric disturbance not related to work (depressive and/or anxiety disorder, personality disorder like cluster A and B, dysthymia). Only 152 patients (32%) were affected by work-related psychiatric disorders: among these, 37 (8% of the total; 14 males, 23 females) were likely cases of mobbing, including 2 PTSDs (both females) and 35 ADs (14 males, 21 females). These cases were reported to the judicial and compensation authorities as probable occupational diseases. Other 105 subjects (40 males, 65 females) suffered from work-related anxiety with somatization. Finally, 10 patients (3 males, 7 females) presented AD not consequent to mobbing.

The average age of the 152 patients with a work-related stress disorder was 40.8 years: 45.7 years for males, 39.5 for
females, the latter representing a higher proportion (63%) than men (37%). The majority of the subjects had medium or high education; in particular, 23 patients had graduated from university (15%), 76 had a high school diploma (50%), the remaining 52 attended secondary school (34%), 1 primary school (1%). Regarding work task, 126 subjects (83%) worked in private companies, the remaining 26 (17%) in public administrations; tasks and skills were very different with a clear prevalence of office workers, in which interpersonal relationships and communication are inherently part of the work. The harassment’s length was variable, ranging from 6 months to 15 years.

**Fig. 1 - Distribution of diagnostic conclusions**

![Diagram showing distribution of diagnostic conclusions](image)

**Discussion and Conclusions**

At the end of the diagnostic multidisciplinary procedure, the mobbing syndrome (PTSD or AD) was actually identified, with a reasonable degree of probability, in less than 10% of all patients. This proportion is lower than that described in other Italian case series (12, 13). The discrepancy could be due to different methods in the diagnostic approach or to pre-selection criteria of patients entering the outpatient service. In our series the subjects were referred by the family doctor, while in the study of Monaco (13), for example, the 152 patients had been subject to a previous selection by a group of psychologists: in these subjects, the percentage of mobbing diagnoses was 49%.

A cautionary approach should be adopted in labeling as “mobbing syndrome” clinical conditions that can show similar manifestations; as regards this, the high proportion of psychiatric diseases unrelated to work (approximately one third) must be highlighted. As recently reported in literature (14), these conditions can easily generate litigation with employers, based on unfounded allegations, if superficially assessed. These disputes may lead to worsening of preexisting clinical conditions.

Despite being limited by the lack of direct verification of what was reported by patients (see “Methods”), our data confirm that a rational diagnostic approach (necessarily interdisciplinary) to mobbing is crucial in order to correctly estimate the
true prevalence of this phenomenon (often overestimated by mass-media), and to allow proper identification from a forensic and insurance point of view. Among workers with work-related psychiatric disorders, we found a marked preponderance of females (63%). This gender difference is even more evident in the small group of patients whose psychopathology (PTSD or AD) was mobbing-related: both cases of PTSD, and 21 (out of 35) of AD, were women. The majority of women affected by psychiatric disorders related to occupational stress (including mobbing) was between 34 to 45 years: this can be explained by the increased family commitment in this age range, resulting in rise of stressful conditions and working difficulties (10, 12). Previous investigations of moral violence and gender differences are not univocal. In prison officers, for example, there was no evidence of significant gender differences in the prevalence and modes of bullying practices; some specific types of actions, as the non-allocation of work tasks and exclusion from meetings, were instead found to be more frequent against men than women (15). Research on other professionals has come to similar conclusions, indicating that this kind of bullying is more common in male managerial roles (2). In Turkey, a questionnaire dispensed to a large working population found that, in many and varied employment areas, men are at increased risk of physical aggression, while women are more exposed to verbal, psychological and sexual abuse (16).

According to our data, Bjorkqvist reported that, among mobbing victims (within the university), about 2/3 are women (17). Also, bullying was more commonly reported by women than men (with double frequency) in a survey conducted among businessmen (18). This condition could result from increased exposure to negative actions, lower perceived ability to defend, or to a tendency to more easily define the proper experience as bullying. The female gender is more frequently mobbed also in the series of Work Clinic of Milan, where a diagnostic protocol similar to ours is used (19).

When researching the perception of harassment, it is found that women focus on comments regarding private life and rumors, while men are more involved in activities aimed to discredit the work. A possible correlation between different mobbing modalities and the victims’ gender has also been shown: among women, emotional mobbing is more frequent; among men the strategic kind (4). The bullying behavior against a woman begins, in most cases, when she has just returned from maternity leave and/or needs to frequently leave work to take care of her family. In such cases, it happens that, after making her feel guilty about the (real or alleged) inconvenience related to her absence, the worker is isolated. The hostility to female workers who are entitled to special contractual benefits, such as particular schedules, maternity and expectancies, triggers the bullying phenomenon. Moreover, women more easily report work problems, unlike men who, according to old stereotypes, provide for the family with their work, thus achieving a full satisfaction. Probably because of these reasons, men are more reluctant to disclose problems related to the working environment.

The reasons why women are more targeted by psychological harassment, in our and other case series, may be various, e.g. a more passive attitude (more easily attacked) and rare managerial positions: bullying is mainly exercised by superiors towards subordinates.

The present study highlights the need for preventative interventions. Mobbing and work-related stress prevention begins with proper risk assessment (as required by the article 28 of the Legislative Decree 81/2008), and must involve workers and professionals institutionally appointed to protect their health: employers, prevention technicians, corporate physicians, unions. Ethical behavior should primarily be promoted, to spread trust, tolerance and respect in the workplace (5). The containment of moral violence is based on the possibility of starting a cultural change in interpersonal relationships, values and attitudes (in particular to women).

Acknowledgment
We thank Christin Broughton for linguistic revision.

References
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Mobbing: case record, gender differences, medico-legal issues.


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THROMBOCYTOPENIA AND PREGNANCY

Key words: gestational thrombocytopenia, fetal-neonatal haemorrhage, maternal haemorrhage

Abstract

Gestational thrombocytopenia (GT) is commonly observed in pregnancies with otherwise limited obstetric and hematologic complications. However, few data are available on the natural history of the disease, and on the recurrence of thrombocytopenia in subsequent pregnancies.

37 consecutive patients with GT were enrolled in a prospective study, with a total of 36 pregnancies observed. Vaginal delivery was carried out in 33/41 (80%); two patients were transfused with packed red cells for obstetric hemorrhage (post-partum uterine atony).

Mothers and their related foetuses- newborns were evaluated retrospectively for symptoms and/or signs of external and internal haemorrhage throughout pregnancy and early puerperium, even in relationship with mode of delivery (caesarean section versus spontaneous vaginal delivery). This study according to the literature confirm that all observed cases of GT have an uncomplicated course with no related perinatal and maternal morbidity even in patients with initial platelet count < 75,000/ml independently from the route of delivery.

The Authors conducted a retrospective study concerning maternal platelet count fluctuation during pregnancy and puerperium and its correlation with the newborn’s platelet level in a group of 36 patients referred to the haematology-clinic of the Santo Bambino Hospital, c/o Azienda Ospedaliero-Universitaria Policlinico-Vittorio Emanuele, Catania, Italy for gestational thrombocytopenia (GT) and who delivered at the same hospital during a period of 4 years, from January 2006 to December 2009.
Abstract

Gestational thrombocytopenia (GT) is commonly observed in pregnancies with otherwise limited obstetric and hematologic complications. Thrombocytopenia is defined as a platelet count below 150 x 10^9/l, caused by accelerated platelet destruction or decreased production. It is classified as mild with a platelet count of 100–150 x 10^9/l, moderate at 50–100x10^9/l and severe with less than 50x10^9/l (1).

Thrombocytopenia is second only to anaemia as the most common hematologic abnormality during pregnancy (2). Indeed, a platelet count <150x10^9/l can be observed in 6 to 15% of pregnant women at the end of pregnancy. Thrombocytopenia is usually moderate (<100 x10^9/l in only 1% of women) and often incidentally detected on routine blood count (3).

Gestational thrombocytopenia (GT) is considered the most prevalent cause of thrombocytopenia during pregnancy accounting for about 75% of cases (1). The etiology is unknown, but it is considered to be due to the relative hemodilution of pregnancy, amplified by the capture or destruction of platelets in the placenta (4, 5, 6).

GT is considered a minor form of thrombocytopenia, with no substantial risk of hemorrhage for both the mother and the infant.

Gestational thrombocytopenia is characterized by:

- asymptomatic, mild thrombocytopenia (platelet count >70x10^9/l);
- no past history of thrombocytopenia (except during a previous pregnancy);
- occurrence during the 3rd trimester;
- no fetal / neonatal thrombocytopenia;
- spontaneous postpartum resolution.

Thrombocytopenia can also be associated with several diseases, either pregnancy-related or not, such as preeclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), which represents about 18% of cases, and idiopathic thrombocytopenic purpura (ITP), which is found in about 5% of cases (7). Some rare conditions, such as thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, disseminated intravascular coagulation and others account for about 2% of the total (8, 9) (tab.1).
Thrombocytopenia and pregnancy

Tab. 1 - Causes of thrombocytopenia in decreasing order of frequency during pregnancy

- Incidental or gestational thrombocytopenia
- Pseudothrombocytopenia (laboratory artifact with EDTA anticoagulant)
- Disorders with increased platelet consumption
- Immune thrombocytopenic purpura
- Pregnancy induced hypertension / HELLP syndrome
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Infection-associated (HIV, malaria)
- Drug-induced (heparin, sulphonamides, penicillin, rifampicin, quinine)
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Disseminated intravascular coagulation
- Amniotic embolism
- Disorders with reduced platelet production
- Congenital trombocitopenia
- Aplastic anemia
- Leukaemia
- Drug-induced
- Myelodysplasia

The Authors present here the results of a retrospective study concerning maternal platelet count fluctuation during pregnancy and puerperium and its correlation with the newborn’s platelet levels in a group of 36 patients referred to the haematology-clinic for gestational thrombocytopenia and who delivered in the same Hospital during a period of four years.

Methods
Between January 2006 and December 2009, 36 patients with GT (mean gestational age at diagnosis 5 months ± 3 months) who delivered at the Santo Bambino Hospital, c/o Azienda Ospedaliero-Universitaria Policlinico-Vittorio Emanuele, Catania, Italy were enrolled in this study, after carefully excluding other possible causes of this condition, and evaluated retrospectively. GT was defined as an asymptomatic thrombocytopenia occurring during gestation, in patients with a normal platelet count at the beginning and or immediately before pregnancy and without antiplatelet-antibodies. The presence of EDTA-dependent pseudothrombocytopenia was ruled out by performing platelet count also in samples anticoagulated with sodium heparin and trisodium citrate and by examination of a May-Grunwald stained peripheral smear.

A maternal platelet count was determined at the minimum three times during pregnancy and once after delivery in each enrolled patient and at least once in every relative newborn at birth (first time on cord blood). All patients underwent specific tests for the presence of antiplatelet- autoantibodies.

Maternal thrombocytopenia was pharmacologically treated only for platelet count ≤ 90,000/ml with the following drugs: vitamin C (1-2,5 g/dye) and tranexanic acid (tranex) 2-2.5 g/die, until 3-4 hours before delivery and for two days after birth.

When maternal platelet count was between 50,000 and 60,000/ml, prednisone (deltacortene) 0,5-1 mg/kg/ die was administered antenataly for about 30 days.
Mothers and their related foetuses- newborns were evaluated retrospectively for symptoms and/or signs of external and internal haemorrhage throughout pregnancy and early puerperium, even in relationship with mode of delivery (caesarean section versus spontaneous vaginal delivery).

Results

A total of 36 patients were retrospectively followed, (22 primigravida).
The mean age was 30 ± 2 years.
Only 6 women had developed thrombocytopenia in a previous pregnancy (tab. 2).

Tab. 2

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Primigravide</td>
<td>22</td>
<td>7,92</td>
</tr>
<tr>
<td>Multiparous</td>
<td>14</td>
<td>5,04</td>
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<tr>
<td>Previous gestational thrombocytopenia</td>
<td>6</td>
<td>2,16</td>
</tr>
<tr>
<td>Spontaneous delivery</td>
<td>21</td>
<td>7,56</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>15</td>
<td>5,4</td>
</tr>
</tbody>
</table>

About 45% of the enrolled patients had a caesarean delivery (however only in1 case, patient 14, tab.4, the clinical indication was merely the significant maternal thrombocytopenia and the suspect of a concomitant severe fetal thrombocytopenia by the attending obstetrician, although no maternal antiplatelet-autoantibodies had been identified in this case).
The mean gestational age at the time of diagnosis was 12 ± 3 weeks for the 6 women with a previous history of gestational thrombocytopenia and 28±3 weeks in all the other patients (tab. 3).

Tab. 3 - Gestational age at diagnosis

<table>
<thead>
<tr>
<th>First onset GT</th>
<th>History of previous GT</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 ±3 weeks</td>
<td>12±3 weeks</td>
</tr>
</tbody>
</table>

Initially, when GT was diagnosed in the 36 studied patients, the average platelet count was at the lowest level, 101(± 26,3) x109/l, it increased to108 (±18,8) x109/l subsequently during pregnancy and it went further up, 129 (± 27,3.) x109/l, at the time of delivery, reaching the highest level in puerperium: 154 (± 27,9) x 109/l (fig. 1 and tab. 4).
Fig 1 - Average maternal platelet count fluctuation

![Graph showing average maternal platelet count fluctuation](image)

<table>
<thead>
<tr>
<th>CASE</th>
<th>PLATELED COUNT AT TIME OF DIAGNOSIS</th>
<th>PLATELED COUNT DURING PREGNANCY</th>
<th>PLATELED COUNT AT TERM</th>
<th>PLATELED COUNT PUERPERAL</th>
<th>PLATELED COUNT NEWBORN</th>
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<td>138</td>
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<td>85</td>
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<td>100</td>
<td>116</td>
<td>92</td>
<td>125</td>
<td>123</td>
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</tbody>
</table>
The search for antiplatelet antibodies was negative in all women.

**Tab. 5 - Treatment of thrombocytopenia and type of delivery**

<table>
<thead>
<tr>
<th>CASE</th>
<th>TROMBOCITOPENIA PRIOR TO PREGNANCY</th>
<th>TREATMENT DURING PREGNANCY</th>
<th>DELIVERY TYPE</th>
<th>AUTOANTIBODY</th>
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<td>SVD</td>
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<td>N</td>
<td>SVD</td>
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<td>18</td>
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</table>

* pt with at least one platelet count ≤75 x10⁹/l
Women during pregnancy didn't show any sign of hemorrhage and were given a vitamin supplementation (vitamin C), and tranexanic acid only in the presence of platelet count $\leq 90 \times 10^9/l$, and deltacortene ($0.5-1 \text{ mg/kg/die}$) for platelet count between 50,000 and 60,000/ml. Fetal-neonatal bleeding symptoms were not observed, and only two cases of mild transitory thrombocytopenia were recorded, as reported in tab. 6.

**Tab. 6 - Maternal thrombocytopenia and neonatal complications**

<table>
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<th>CASE</th>
<th>NEONATAL COMPLICATIONS</th>
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<tr>
<td>36</td>
<td>MILD ASYMPTOMATIC TROMBOCITOPENIA</td>
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*: pt with at least one platelet count $\leq 75 \times 10^9/l$; o: therapy during pregnancy; N: no complications
Thrombocytopenia and pregnancy

Discussion
Thrombocytopenia has been more commonly diagnosed in pregnant women in the last 20 years. It may result in bleeding into mucous membranes presenting as petechiae, ecchymosed, epistaxis, gingival bleeding etc. Moreover, bruising, hematuria, gastrointestinal bleeding and rarely intracranial hemorrhage can occur (10).

The diagnosis of ITP is very difficult during pregnancy because its presentation may closely resemble gestational thrombocytopenia (11, 12).

The diagnosis of ITP should be suspected in case of:
- thrombocytopenia discovered before the 3rd trimester or present before pregnancy;
- platelet count <75 x10⁹/l during pregnancy (in our series 7 cases)
- presence of autoantibodies (in our series no cases)
- persistence of thrombocytopenia postpartum (sometimes even thrombocytopenia due to ITP may prompt normalize after delivery).

The Authors found that, despite the defining criteria, GT may include cases with moderate (n=6) and severe (n=1) maternal thrombocytopenia and, although the absence of antiplatelet-autoantibodies, it may be incidentally associated with mild neonatal thrombocytopenia: 2 cases in this series.

The present study confirm that all observed cases of GT have an uncomplicated course with no related perinatal and maternal morbidity even in patient with initial platelet count < 75.000/ml independently from the mode of delivery.

Conclusion
In case of gestational thrombocytopenia a complete normalization of maternal platelet count should be expected during the postpartum period, even if a diagnosis of a concomitant incidental neonatal thrombocytopenia cannot be excluded.

No intervention, such as a foetal platelet count or caesarean section, is necessary. Periodic platelet counts, either once a trimester or every month, are recommended depending on the level of thrombocytopenia.

In cases of thrombocytopenia ≤ 90.000/ml, patients should be given drugs such as: vitamin C (1-1.5 g/die) and tranexanic acid (tranex) 2-2.5g/die to improve platelet count.

In the past, it has been common practice to perform caesar ean section on mothers with severe thrombocytopenia and presence of circulating antiplatelet autoantibodies to lessen the risk of neonatal intracranial haemorrhage due to the trauma of vaginal delivery, especially with foetal platelet counts < 50 x10⁹/l.

In the above clinical scenario , however, caesarean delivery has not been proved to decrease the incidence of either maternal and or neonatal haemorrhage and of course this is particularly true in case of GT as the present study demonstrates.

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References

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XERODERMA PIGMENTOSUM: THE STAR’S SONS. CASE REPORT AND REVIEW OF THE LITERATURE.

XERODERMA PIGMENTOSO: I FIGLI DELLE STELLE. CASO CLINICO E REVISIONE DELLA LETTERATURA.

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Abstract

Xeroderma pigmentosum (XP) is a rare condition inherited as an autosomal recessive trait and it is characterized by photosensitivity, pigmentary changes, premature skin ageing and malignant tumors development resulting from the defect in DNA repair.

The skin cancers, that include squamous and basal cell carcinomas and melanomas, are predominantly caused by exposure to ultraviolet B (UVB) radiation, although UVA cannot be excluded. The mean age of onset of the neoplasms is 8 years of age in XP patients, in contrast of 60 years of age in the general population.

In addition to cutaneous findings, patients often have ocular abnormalities including ectropion, corneal opacities, neoplasms and neurologic abnormalities as ataxia, loss of reflexes, sensorineural hearing loss, dysphagia, and decreasing cognition.

The maximal form of neurological involvement has been defined the De Sanctis-Cacchione Syndrome that is characterized by retarded growth, spasticity and serious intelligence debility. Segmental demyelinisation, microcephaly, inner ear deafness and epilepsy may also be additional neurological signs of xeroderma pigmentosum patients.

XP was described in Vienna by a Hungarian professor of dermatology Moriz Kaposi in 1870 and in 1874 it was first called “xeroderma or parchment skin” while in 1882, the term “pigmentosum” was added to emphasize the striking pigmentary abnormality.
Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the USA. It affects males and females equally and it is frequently symptomatic in childhood.

Xeroderma pigmentosum must be distinguished from other so-called DNA-Repair Deficiency Syndromes as the Cockayne Syndrome (CS) and trichothiodystrophy (TTD) and other rare diseases characterized by pigmentation changes as Erythropoietic Protoporphyria, LEOPARD syndrome, Carney complex and Peutz-Jeghers syndrome. The prognosis of patients with XP includes a high morbidity and early mortality.

Although there is no cure for XP, the skin effects can be minimized by rigorous protection from sunlight and early removal of pre-cancerous lesions. Oral 13-cis retinoic acid has shown to reduce the incidence of epithelial new cancers in XP patients because of retinoids modulate keratinocyte differentiation.

We present the case of a 30-year-old man who was diagnosed with XP at age 9. The first skin lesions had appeared five years, and over time had increased. Other clinical signs included photophobia and loss of eyelashes. Eye examination revealed bilateral corneal opacities and conjunctival chemosis.

We underline the importance of a multidisciplinary approach for the management of patients with XP to prevent the serious complications that this disease can determine.

**Abstract**

Lo Xeroderma Pigmentoso (XP) è una rara patologia ereditaria a trasmissione autosomica recessiva dovuta a un deficit di riparazione del DNA, caratterizzata da fotosensibilità, alterazioni della pigmentazione cutanea, invecchiamento precoce della cute e insorgenza di tumori cutanei maligni.

Questi tumori, che includono carcinomi squamocellulari, carcinomi basocellulari e melanomi, sono prevalentemente causati da esposizione ai raggi ultravioletti B (UVB), anche se gli UVA non possono essere esclusi.

L'età media di insorgenza delle neoplasie è di 8 anni di età, a differenza della popolazione generale dove è di 60 anni.

Oltre alle alterazioni cutanee, i pazienti presentano spesso anomalie oculari quali ectropion ed opacità corneali ed alterazioni neurologiche, come atassia, iporeflessia, ipoacusia neurosensoriale, disfagia ed alterazioni cognitive.

La forma massima di coinvolgimento neurologico è stata definita come sindrome di De Sanctis-Cacchione che è caratterizzata da ritardo di crescita, spasticità e seri deficit cognitivi. Demielinizzazione segmentale, microcefalia, sordità ed epilessia possono essere altri segni neurologici presenti in questi pazienti.

Lo Xeroderma Pigmentoso è stato descritto per la prima volta nel 1870 a Vienna da Moriz Kaposi, un professore ungherese di dermatologia e nel 1874 è stato chiamato per la prima volta ''Xeroderma o pelle a pergamena'', mentre nel 1882, il termine ''pigmentosum'' è stato aggiunto per sottolineare la sorprendente anomalia della pigmentazione.

L'incidenza stimata varia da 1 su 20000 in Giappone a 1 su 250000 negli Stati Uniti. Questa malattia interessa maschi e femmine con la stessa frequenza, e risulta essere spesso sintomatica nella prima infanzia.

Lo Xeroderma pigmentoso deve essere distinto da altre sindromi caratterizzate da deficit di riparazione del DNA come la sindrome di Cockayne (CS) e la tricotiodistrofia (TTD) e da altre malattie rare caratterizzata da alterazioni della pigmentazione come la Protoporfiria eritropoietica, la sindrome di LEOPARD, il complesso di Carney e la sindrome di Peutz-Jeghers.

La prognosi dei pazienti con XP è caratterizzata da un'alta morbilità e da una mortalità precoce.

Sebbene non vi sia alcuna cura per lo XP, le gravi alterazioni della cute possono essere limitate da una protezione solare rigorosa e dalla rimozione precoce di lesioni precancerose. L'acido retinoico 13-cis ha dimostrato di ridurre l'incidenza di tumori epiteliali in pazienti con XP grazie alla sua azione sulla modulazione della differenziazione dei cheratinociti.

Presentiamo il caso di una ragazza di 30 anni a cui è stata fatta diagnosi di XP all'età di 9 anni. Le prime lesioni cutanee erano comparse all'età di cinque anni ed erano aumentate nel corso degli anni. Altri segni clinici erano rappresentati da fotofobia e da perdita delle ciglia. Esame degli occhi rivelava opacità corneali bilaterali e chemosi congiuntivalesi.

Sottolineiamo l'importanza di un approccio multidisciplinare per la gestione dei pazienti con XP per prevenire le gravi complicanze che questa malattia può determinare.
Background
Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by clinical and cellular sensitivity to ultraviolet (UV) radiation, pigmenitary changes, premature skin ageing and neoplasm development (1).
It is the archetype of an expanding family of nucleotide-excision repair (NER) diseases that includes XP itself, the XP variant (XP-V), Cockayne syndrome (CS), cerebro-oculofacial skeletal syndrome (COFS), a mild ultraviolet (UV)-light-sensitive syndrome, trichothiodystrophy (TTD) and some diseases with combined symptoms of XP/CS and XP/TTD (2, 3). XP was described in Vienna by a Hungarian professor of dermatology Moriz Kaposi in 1870 and in 1874 it was first called “xeroderma or parchment skin” while in 1882, the term “pigmentosum” was added to emphasize the striking pigmenitary abnormality (5). Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the USA, and approximately 2.3 per million live births in Western Europe. It affects males and females equally and it is frequently symptomatic in childhood (6).
Genetic defects in XP are heterogeneous, resulting from defects in 8 different genes. Seven of the complementation groups (XP complementation groups A through G) are deficient in nucleotide excision repair, and one group (XP variant) has defective post-replication repair.
The incidence of the complementation groups varies geographically. In general, the most frequent complementation group is A, followed by XP-V and XP-C. All three account for about 90% of cases (7).
We report the case of a 30-year-old man with Xeroderma pigmentosum.

Case report
We present the case of a 30-year-old man who was diagnosed with XP at age 9. He presented with multiple brownish to blackish macules and papules on the face and upper limbs (fig. 1).

Fig. 1 - Multiple brownish macules of the face

This abnormal pigmentation initially appeared at 5 years of age and became more severe over time; moreover the patient referred a worse clinical during prolonged exposure to sunlight.
Other clinical signs included photophobia, keratitis and loss of eyelashes.
Eye examination revealed bilateral corneal opacities and conjunctival chemosis; fundus examination was normal. Routine blood, urine, and stool examination were within normal limits. He had 2 normal siblings, and there was no family history or other past medical history of note. The mother denied any consanguinity in the patient’s recent lineage. Thereafter, he underwent regular dermatology examinations and various skin biopsies. Pathologic evaluation led to the diagnosis of various cutaneous malignancies including 8 basal cell carcinomas, 1 cutaneous melanomas, 2 squamous cell carcinomas, and one melanoacanthoma (fig. 2).

Fig. 2 - Melanoacanthoma at 10 years of age

Annual neurological and ophthalmological examinations were performed and no abnormalities were identified. Currently, the patient performs a dermatological examination every 3 months while an ophthalmology examination and a neurological is carried out every year.

Discussion and Conclusions

Xeroderma pigmentosum is characterized clinically by erythema with scaling and diffuse hyperpigmentation or freckle-like lesions, especially in sun-exposed areas and usually onsets very early in life. Approximately half of XP patients present severe acute sunburn reactions after short sun exposure. Freckling of sun-exposed areas of the skin in children less than 2 years of age is unusual and it is indicated as a diagnostic marker for XP. Continued sun exposure of skin causes the appearance of poikiloderma, hypo- and hyper-pigmentation, atrophy and telangiectasia (1).

Clinically XP can be classified into 3 subgroups that include: 1) mild form with light brown freckles on the face alone; 2) moderate form with dark brown freckles with burning on the face, neck, ears, chest, hands, photophobia but without other associated skin and ocular changes and 3) severe form with extensive, dark brown freckles all over the body with cutaneous changes such as ulcers, keratoconjunctivitis, ectropion and skin malignancies. The lesions have a high risk of progression to cancers; the most frequent skin tumors in XP patients are basal cell carcinoma, squamous cell carcinoma and lentigo maligna melanoma. Keratoacanthomas and sarcomas (fibrosarcomas and angiosarcomas) have also been described.8

The mean age of onset of the neoplasms is 8 years of age in XP patients, in contrast of 60 years of age in the general population. The frequency of non-melanoma skin cancer is increased 10,000-fold and melanoma is increased 2,000-fold in XP patients under age 20 years compared to the general US population. 2/3 of xeroderma pigmentosum patients die before reaching adulthood because of tumoral progression (9, 10, 11). About 20-30% of patients with XP develop severe progressive neurologic deterioration characterized by ataxia, loss of reflexes, sensorineural hearing loss, dysphagia and decreased cognition (12).
The maximal form of neurological involvement has been defined the De Sanctis-Cacchione Syndrome. These children are characterized by retarded growth, spasticity and serious intelligence debility. Segmental demyelination, microcephaly, inner ear deafness and epilepsy may also be additional neurological signs of xeroderma pigmentosum patients (13). The incidence for central nervous system tumours (CNS) is also ten times higher than in the normal population. Astrocytomas, medulloblastomas, glioblastomas and malignant schwannomas are among the CNS tumors (12).

About 40% of xeroderma pigmentosum patients present same ophthalmological symptoms. Usually the light-exposed lids and the anterior sections of the eye are affected. Conjunctival inflammation, blepharitis, keratoconjunctivitis, ectropion, symblepharon, vascular pterygia, fibrovascular pannus formation and corneal ulcerations are some of the clinical findings which have been described in xeroderma pigmentosum with severe visual decline (14).

The incidence for tumors of the oral mucosa and internal organs is also elevated; more frequent occurrence of leukaemia is also characteristic of xeroderma pigmentosum patients.

The initial clinical diagnosis can be made on the basis of either the extreme sensitivity to UV or in the early appearance of lentiginosis on the face. The diagnosis can be confirmed definitively by employing robust cellular tests for defective DNA repair available in many countries (15).

Xeroderma pigmentosum must be distinguished from other so-called DNA-Repair Deficiency Syndromes as the Cockayne Syndrome (CS) and trichothiodystrophy (TTD)² and other rare disease characterized by pigmentation changes as Erythropoietic Protoporphyrria, (16) LEOPARD syndrome, (17) Carney complex (18) and Peutz-Jeghers syndrome (19).

Cockayne Syndrome is characterized by neurological symptoms (ataxia, mental retardation, inner-ear deafness), distinct facies (large, deepset eyes, prominent nose), progressive weight loss (cachexia), myopathy, microcephalus, dwarfism, calcifications of the basal ganglia, retinal pigment degeneration optic nerve atrophy and cataracts.

Trichothiodystrophy is characterized by limited intelligence, reduced fertility and by short and brittle hair due to sulphur deficient hairs (deficit of cystein-rich proteins in keratines).

Erythropoietic Protoporphyrria is easily screened through the finding of normal porphyrins and not every exposed skin site is affected in polymorphic light eruption.

The pigmented lesions of Carney complex and LEOPARD syndrome are not related to sun exposure and in Peutz-Jeghers syndrome the cutaneous pigmentation are perioral and acral.

A family history should also exclude these autosomal dominant lentiginoses.

In limited number of cases, however, diagnosis can be less clear because of pigmentation changes not appearing until adolescence. Solar urticaria can be excluded by the fact that the rash resolves within an hour of going indoors.

The prognosis of patients with XP includes a high morbidity and early mortality. Usually, two-thirds of XP patients die before reaching 30–40 years of age because of metastases, generally related to multiple SCCs with lymphatic and visceral expansion and less frequently, malignant melanoma (2).

Early diagnosis has an important role in the management of disease that includes avoidance of sunlight, minimizing UV and cigarette smoke exposure, early excision of skin lesions and genetic counseling.

Oral 13-cis retinoic acid has shown to reduce the incidence of epithelial new cancers in XP patients because of retinoids modulate keratinocyte differentiation (20).

Ophthalmic management includes UV-absorbing sunglasses with side shields, artificial tears, intermittent topical steroids, surveillance for ocular neoplasms, and management of complications. Eyelid and conjunctival cancers are the most commonly reported.

We underline the importance of a multidisciplinary approach for the management of patients with XP to prevent the serious complications that this disease can determine. Increased awareness and crucially early diagnosis, followed by rigorous protection from daylight and careful patient management, can dramatically improve the quality of life and life expectancy of affected individuals.
References


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