Vol. 14 - n. 1 - 2016
ISSN 2035-0678

RIVISTA ITALIANA di MEDICINA dell'ADOLESCENZA

Indexed in EMBASE/SCOPUS

Endo-Thal

Periodico quadrimestrale - Spedizione in abbonamento postale 45% - art. 2 comma 20/B legge 662/96 - Milano
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SCRIPTA MANENT EDIZIONI

Editoriale

Questo numero della Rivista Italiana di Medicina dell'Adolescenza è dedicato ad alcune problematiche auxo-endocrinologiche dell'età adolescenziale. In particolare, la terapia con ormone dell'accrescimento, l'insorgenza della pubertà precoce dopo trauma cranico, il coma mixedematoso e la valutazione della presumibile età cronologica di un minore, senza documenti, in conflitto con la legge.

Per "accertamento dell'età" si intende la procedura utilizzata per determinare l'età approssimativa di un individuo. Pur non riscontrandosi né nel contesto nazionale né in ambito comunitario un approccio uniforme nelle modalità operative, il termine "accertamento dell'età" tende ad essere più comunemente utilizzato per indicare l'uso di esami di tipo medico, volti a stimare l'età cronologica di un individuo attraverso una valutazione della sua età biologica (UNHCR, Field Handbook for the Implementation of UNHCR BID Guidelines, 2011,http:// www. refworld.org /docid /4e4a57d02.html, ultima cons. 30 ottobre 2013). L'accertamento dell'età dei minori, senza documenti in conflitto con la legge, è generalmente disposto dall'autorità giudiziaria o di pubblica sicurezza. Le metodiche usate oggi in Italia per determinare l'età biologica di un individuo si basano quasi sempre sulla valutazione dello stadio puberale e della maturazione scheletrica, effettuata con la radiografia mano-polso, refertata con il metodo di Greulich e Pyle (GP) o Tanner e Whitehouse (TW-2 o TW-3).

La questione dell'accertamento dell'età anagrafica tramite studio auxologico effettuato con esame radiografico è, come noto, una questione delicata e controversa. Uno studio condotto in Danimarca, su 159 soggetti provenienti da diverse aree geografiche, esaminati a più riprese da diversi operatori, ha evidenziato che utilizzando il metodo GP nel 95% dei casi esaminati la differenza nella determinazione dell'età era di circa un anno. Altri studi, utilizzando il metodo TW-2 hanno registrato differenze tra età scheletrica ed età ossea comprese in un range tra - 0,1 anni e +1,4 anni (con una tendenza alla sovrastima dell'età scheletrica); mentre con il metodo TW-3 queste differenze sono risultate in un range più contenuto. Ne deriva che gli esiti di un esame radiologico del polso, seppur statisticamente affidabili, sono suscettibili, nel caso individuale, di un margine di errore di varia ampiezza.

Queste considerazioni sono state riprese anche da Benso e Milani in un documento del 2013 (Alcune considerazioni sull'uso forense dell'età biologica. www.asgi.it/wp content/uploads /public/1_2013_ accertamento_ eta_mater). Gli Autori ci ricordano che "sino a oggi, non vi sono dati sufficienti che permettano di adattare queste metodiche alle etnie per le quali più frequentemente sono richieste stime dell'età anagrafica. Ciò non significa che i metodi per la valutazione dell'età scheletrica sono del tutto inutili. Il loro scopo originale non era la determinazione dell'età anagrafica in soggetti privi di documenti, ma la valutazione della differenza tra età anagrafica e biologica in diverse condizioni auxologiche, sia fisiologiche, per stimare il potenziale di crescita residuo, sia d'interesse clinico, per diagnosticare e monitorare malattie croniche, turbe nutrizionali, carenze ormonali, terapie sostitutive...." .

Il margine di errore è legato anche alla competenza dell'operatore. Uno studio condotto su 47 soggetti ha attestato una significativa variabilità intra-operatore (correlata all'esperienza di quest'ultimo), con tendenza alla sottostima dell'età. In sostanza, gli operatori più esperti hanno stimato l'età con una variabilità compresa tra -1,5 mesi e ± 7,6 mesi, mentre gli operatori meno esperti hanno manifestato una maggiore variabilità compresa tra 2,7 mesi e ± 10,3 mesi.

In conclusione, non esistono metodi scientifici capaci di determinare con esattezza l'età cronologica di una persona, soprattutto in età critica quale quella degli adolescenti. Un esame medico non può fornire che una stima dell'età cronologica di un individuo ed è, per sua natura, soggetto ad un margine di errore, quantificabile in un range la cui ampiezza è inevitabilmente determinata da vari fattori. Ne deriva che nessuna valutazione è precisa ed attendibile e di conseguenza un margine d'incertezza rimane sempre. È auspicabile che ulteriori ricerche e la combinazione di più metodi, non invasivi, possano migliorare questa valutazione. In tutti i casi, gli aspetti etici dovranno essere tenuti in dovuta considerazione nella preparazione delle linee guida per l'uso forense dell'accertamento dell'età biologica di un individuo.

Vincenzo De Sanctis

Vol. 14 - n. 1 - Gennaio-Aprile 2016

Rivista Italiana MEDICINA di dell'Adolescenza

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Registrazione Tribunale di Milano n. 404 del 23/06/2003

Stampa: Lalitotipo s.r.l.
Settimo Milanese (MI)

Abbonamento annuale (3 numeri) Euro 30,00.
Pagamento: conto corrente postale n. 1010097192 intestato a:
Edizioni Scripta Manent s.n.c., via Bassini 41, 20133 Milano

Sommario

An essential approach to the age assessment in undocumented minors in conflict with the law

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Summary

In forensic contexts, assigning an age to a living child of unknown identity may be necessary when the child is suspect in a crime, when penal codes differentiate law and punishment for children of different ages or if the child is a refugee. The age of criminal responsibility in the UK is the lowest in Europe with other European Union Member States setting the age of criminal responsibility between 14 and 16 years. In the absence of a known birth date, any assessment of age will be difficult. The age assessment should include a comprehensive physical description of the person including: physical development, bone maturity which is observed on radiographs as the development and fusion of the long bone growth centres (e.g. in the hand and wrists) and dental age estimation (including grading tooth development both clinically and on dental radiographs)
Currently there is no medical test or a group of tests that will absolutely and accurately let us know the exact chronological age of a human being. There will always be an uncertainty related to the estimate, and correctly expressing this uncertainty is just as important as the actual estimate.
More research is needed to define more precisely the best standard approach for age estimation based on a combination of different methods. Furthermore, professionals working with children should always strive to take ethical guidelines into consideration in making decisions of such minors.

Key words: *Undocumented minors, age assessment, current laws, European Countries*.

Un approccio alla valutazione dell'età di un minore, senza documenti, in conflitto con la legge

Riassunto

La valutazione della presumibile età cronologica (PEC) di un minore, senza documenti, in conflitto con la legge è un tema di rilevante attualità. L'età dell'imputabilità nel Regno Unito è la più bassa in Europa, mentre negli altri Paesi varia dai 14 ai 16 anni. Usualmente per la valutazione della PEC vengono presi in considerazione i seguenti parametri: esame fisico, valutazione della maturità ossea e dei denti. Nessuna valutazione è precisa ed attendibile e di conseguenza un margine d'incertezza rimane sempre. È auspicabile che ulteriori ricerche e la combinazione di più metodi possano migliorare questa valutazione nei minori. In tutti i casi, gli aspetti etici dovranno essere tenuti in considerazione nella preparazione delle linee guida.

Parole chiave: *Minori senza documenti, valutazione dell'età, legge, Comunità Europea*.

Introduction

The definition of "*children in conflict with the law*" varies depending on the domestic law. The definition which has been mainly adopted refers to anyone with a minimum age who comes into contact with the justice system as a result of having committed or being suspected or accused of committing an offence. A culpability action is an act which has been committed by an individual which is considered by society as wrong, damaging to other individuals or society as a whole or is otherwise unacceptable. Adults are presumed culpable for their criminal acts while young children are generally not found legally responsible for their wrongful acts. Adolescents fall on a continuum between these two poles (1-3). It is important to remember that culpability is only one factor rele-

vant to punishment. Punishment is generally taken to have several purposes, including retribution, deterrence, protection of society through incapacitation and rehabilitation (1).

Background

The rapid rise in adolescent crime in the late 1980s and early 1990s led to increased fears for public safety, and since 1992, many states have adopted additional procedures for transferring adolescents to adult criminal court (4).
In the USA in the late 1980s to early 1990s witnessed a rapid increase in juvenile homicide rates.
From 1984 to 1993, firearm homicides among juveniles increased over 200 percent, a much greater increase than that seen in other age groups (5).
This wave of juvenile violence received great public attention, generated considerable fear among the public, and led many state legislatures to take in consideration criminal responsibility, and, by implication, the imposition of adult punishment (1). In forensic contexts, assigning an age to a living child of unknown identity may be necessary when the child is suspected of a crime, when penal codes differentiate law and punishment for children of different ages or if the child is a refugee (6).

Table 1.
Age of law responsibility in European countries.

Country	Minumum age of criminal responsability
Austria	14
Belgium	18 (16 for serious offences)
Bulgaria	14
Czech Republic	15
Denmark	15
England and Wales	10
Estonia	14
Finland	15
France	13 (but educational measures can be imposed from the age of 10)
Germany	14
Greece	13 (but educational measures can be imposed from the age of 8)
Hungary	14
Iceland	15
Italy	14
Latvia	14
Lithuania	14
Luxembourg	18
Netherlands	12
Northern Ireland	12
Norway	15
Poland	13
Portugal	16
Romania	14
Russian Federation	14
Scotland	8
Slovakia	14/15
Spain	16 (14 in Catalonia)
Sweden	15
Turkey	12

Age of law responsibility in different counties

The age of criminal responsibility in the UK is the lowest in Europe with other European Union Member States setting the age of criminal responsibility between 14 and 16 (Table 1) .
This age limit for law responsibility is even lower in some non European countries (Table 2).
It has been reported in the UK through a study undertaken in 2007 that nearly 3,000 crimes committed in a single year were committed by children under the age of 10 years.
The figures show that 1,300 crimes and more than 60 sex offences were committed by suspects under 10 (7).

Table 2.
Age of criminal responsibility in non European countries (Minimum age at which children are subject to penal law in countries with 10 million or more children under 18 years old; Sources: CRC Country Reports (1992-1996); Juvenile Justice and Juvenile Delinquency in Central and Eastern Europe, 1995; United Nations, Implementation of UN Mandates on Juvenile Justice in ESCAP, 1994; Geert Cappelaere, Children's Rights Centre, University of Gent, Belgium).

Mexico	*6-12	Ukraine	10
Bangladesh	7	Turkey	11
India	7	Korea, Rep.	12
Myanmar	7	Morocco	12
Nigeria	7	Uganda	12
Pakistan	7	Algeria	13
South Africa	7	Uzbekistan	13
Sudan	7	China	14
Tanzania	7	Japan	14
Thailand	7	Russian Federation	14
United States	**7	Viet Nam	14
Indonesia	8	Egypt	15
Kenya	8	Argentina	16
Ethiopia	9	Brazil	****18
Iran	***9	Colombia	****18
Philippines	9	Peru	****18
Nepal	10		

*Legend: *Most states 11 or 12 years; age 11 for federal crimes;*
*** Age determined by state, minimum age is 7 in most states under common law;*
**** Age 9 for girls, 15 for boys; ***** Official age of criminal responsibility, from age 12 children's actions are subject to juvenile legal proceedings.*

Essential sources of law responsibility for minors in Italy

Italian criminal law is codified in the Codice Penale (Criminal Code), in special legislation, and, with regard to procedural rules, in the Codice di Procedura Penale (Code of Criminal Procedure). The Italian Criminal Code is divided into a general part, which contains the provisions that can be applied to all offences, and a specific part, which provides for single criminal offences. Criminal offences are divided into two main categories: crimes and misdemeanours. Another fundamental principle of Italian law is that neither a citizen nor a foreigner can plead ignorance of the law as an excuse for not complying with the law . In Italy, the minimum age of criminal responsibility is set at 14 years (Article 97 of the Criminal Code). Any minor who has not attained that age cannot be indicted for any type of illegal activity whatsoever; since it is presumed that the minor is incapable of understanding and intent. In certain circumstances, persons aged below 14 can be recognized as being socially dangerous and can therefore be subjected to security measures.

It must also be noted that persons aged between 14 and 18 years are not presumed to have the capacity of understanding and intent. In order to establish whether a minor aged between 14 and 18 years should be subjected to a penalty, the adjudicating body must, for each case and on the basis of the concrete evidence put before the court, ascertain whether the perpetrator of the crime had reached an adequate level of maturity and psychological development at the moment of the offence to understand the seriousness of the act (Article 98 of the Criminal Code). If the offender had attained the age of eighteen when the offence was committed, and is therefore considered an adult, it is presumed that he/she is capable of understanding and acting intentionally and is therefore criminally liable.

This presumption may be rebutted, however, if it is proved that the offender was unable to understand and act intentionally at the moment of the offence, due to infirmity (*Article 88 of the Criminal Code*) or other causes. If this is proved, the offender cannot be considered liable for the offence and therefore no penalty can be imposed on him/her, with the exception of those security measures that may be applied if the offender is recognized to be socially dangerous (8, 9).

Aim of present work

A forensic evaluator assessing adolescent culpability faces a complex task including age assessment in undocumented minors ,appreciation of wrongfulness, ability to conform to law, developmental course of aggression and impulsivity, psychosocial immaturity (including time sense, susceptibility to peer pressure, risk-taking, and ability to empathize), environmental circumstances, peer group norms, out-of-character action, incomplete personality development, mental illness, and reactive attitudes toward the offense (1).

In the present paper, the Authors set out state-of-the art for age estimation methods for specific case groups and define the minimum requirements for reference. In addition, issues relating to quality of assessment are discussed.

The age assessment

In the absence of a known birth date, any assessment of age will be difficult .The age assessment should include a comprehensive physical description of the person including: physical development, bone maturity which is observed on radiographs as the development and fusion of the long bone growth centres (e.g. in the hand and wrists) and dental age estimation (including grading tooth development both clinically and on dental radiographs) (10).

a. Physical description

The most appropriate approach is to use a holistic evaluation, incorporating narrative accounts, physical assessment of puberty and growth, and cognitive, behavioural and emotional assessments. This process consists in assessing height and weight, body mass index, as any visible signs of sexual maturity. There are clearly defined methods for rating puberty as described by *Marshall and Tanner* (13, 14). These give the ages of various stages of attainment of pubertal appearances, starting on average at 11 years in both males and females and going through to the final stages acquired two or three years later. Axillary hair growth, acne, facial hair growth and laryngeal prominence development should also be registered.

Any visible marks and comment on what weight will be attached to report, for example a general physical examination should be performed to describe any signs of a pathological condition which may interfere with the maturation rate because in circumstances of illness, undernutrition, extreme stress and disrupted socialisation, tools used to assess age are likely to be less reliable.

Advantages and disadvantages

The main advantage of this method is that it is relatively simple and does not require any radiation exposure. However, anthropometric measurements do not take into consideration variations between ethnicity, race, nutritional intake and socioeconomic background. The evaluation of sexual maturity has the greatest margin of error and should be used for age determination only in conjunction with skeletal maturity and tooth development.

There are individuals who enter puberty at the age of nine and sometimes before that, while others only do so at the age of 15 or 16 without implication of a disease.

Thus, at the age of 14, it is possible to find a boy who is still prepubertal , another who is in the middle of puberty and another one

who has already reached adulthood. The same may occur with girls, at even an earlier age (15, 16).

b. X-ray hand bone age

Bone age is a way of describing the degree of maturation of child's bones. As a person grows from fetal life through childhood, puberty, and finishes growth as a young adult, the bones of the skeleton change in size and shape. These changes can be seen by X-ray. The "*bone age*" of a child is the average age at which children reach this stage of bone maturation. Skeletal maturity or bone age describes the degree of biological maturation. The technique for assessing skeletal maturity consists of visual inspection of the developing bones. Various areas of the skeleton have been used: the foot, the ankle, the hip, the elbow, the hand-wrist, and the cervical vertebrae (Table 3). The hand-wrist radiograph is commonly used for skeletal developmental assessment. Most investigators have found significant correlation among maturation stages derived from hand-wrist radiographs, changes in height during pubertal growth period and facial growth (17-19).

The most common method of skeletal maturity assessment uses a radiograph of the left hand and wrist to determine the different stages in bone maturation. There are two different techniques, namely the *Tanner and Whitehouse* II and III (TWII–III) and *Greulich and Pyle* (20-22).

Table 1.

Examples of five different long bones and the expected age where epiphyseal fusion occurs (From: Dabba JJ.Forensis 101. Epiphyseal fusion. www.jenjdanna.com).

	Estimated age of fusion	
Bone	**Proximal/ medial end**	**Distal/ lateral end**
Humerus (upper arm)	10-15 years	9-15 years
Radius (lower arm)	14-19 years	16-22 years
Femur (upper leg)	15,5-19,55 years	14.5-22 years
Tibia (lower leg)	15,5-22 years	14.5-19.5 years
Clavicle (collarbone)	19-30 years	19-20 years

Advantages and disadvantages

The *Greulich and Pyle* method is faster and easier to score and it is often the preferred method for a clinical application.

All bone age estimation methods have some errors. In other words if the same X-ray is assessed either by the same or different assessors the assigned bone age may vary (intra-observer and inter-observer error) (23, 24). A number of studies have investigated these effects and in summary have demonstrated an average intra-observer error of between 2 and 9 months and an average inter-observer error between 1 and 12 months. However, these were average errors and the error range in these studies was 0 to over 2 years. Combining both the intra- and inter-observer, variation differences of over 12 months frequently occur (25-30). Variation using computer software to define bone ages is less and varies between 0 and 6 months (31, 32).

Pubertal variation has a major impact on bone age estimation. Obesity tends to advance bone age maturation while malnutrition and conditions that reduce fat mass such as anorexia nervosa delay it. Any chronic illness during childhood may also delay bone age maturation. Severe neglect can also cause bone age delay while placing such children in a more caring environment can result in earlier puberty and an advanced bone age. Thus many factors need to be considered when trying to establish age based on bone age estimation alone (31-33).

c. The dental maturity for the assessment of chronological age

The last physiologic measure is dental maturity, which can be determined by the stage of tooth eruption or the stage of tooth formation. The latter is proposed as a more reliable criterion for determining dental maturation. Relationships between the calcification stages of individual teeth and skeletal maturity have been previously reported. Racial variations in the relationships have also been suggested (34, 35). There are several different types of dental examination that could be used to assess the age of persons in different age ranges. The *Demirjian and Nolla methods* are one of the most frequently used in estimating chronological age due to its simplicity, intra-examiner agreement, ease of standardization and ability to be reproduced, having been used and tested across a wide range of populations (36, 37).

Demirjian method

The Demirjian method is a system based on eight stages (from A to H) of dental maturity in the seven left permanent mandibular teeth, observable through orthopantomographs.

Each tooth was attributed a stage and converted in quantitative values by applying a specific table, the scores of the seven teeth are summed as a function of sex and the sum of dental maturity is obtained on a scale of 0 to 100. This total is converted in dental age using a table for converting the results of dental maturity. A proper Demirjian's evaluation of dental maturity involves dental panoramic X-rays and a complex assessment based on calcification stages for the seven left permanent mandibular teeth. In childhood (0-14 years) radiological examination of dental development includes all tooth types. In adolescence (14-21 years), the third molars are the only teeth undergoing maturation, this may decrease accuracy. In both cases, sex and race influence tooth development, so those factors have to be taken into account. This method has been widely used in different populations (38).

Nolla method

The Nolla method allows classification of dental development from stage one (1 - no sign of calcification with the presence of crept), to stage ten (10 - apical end completed). The orthopanto-

mograph of each tooth is assessed individually and compared with the stage of the Nolla table. The dental age calculated corresponds to the sum of the Nolla scores. This method requires very consistent discrimination by the observer in assessing dental maturity through radiography.

Advantages

Estimating age from the teeth has several advantages over skeletal ageing. The development of both the deciduous and permanent teeth can be studied from the embryonic period until early adult life. In addition, it is commonly observed that, for a given chronological age, dental age shows less variability than does skeletal age (39-41). For younger individuals, age estimation was more accurate due to the presence of many developing teeth, particularly the canines, premolars, as well as first and second molars; the intervals between morphological stages are shorter for individuals younger than 16 years of age and therefore, dental age estimation of these subjects is more accurate. Dental development is less affected than bone by adverse environmental circumstances such as nutrition and disturbances of endocrine function.

The reasons of less variability in dental age are not fully understood. A possible reason is that the development of all the deciduous dentition and part of the permanent dentition takes place before birth in a protected environment whereas skeletal growth and development, even though having a strong genetic basis, is exposed for an increasing length of time to external factors such as variations in nutrition, socio-economic status.

Disadvantages

- Demirjian method use orthopantomograms which are difficult to obtain in young children, due to both technical reasons, as well as legal and ethical considerations (42).
- Since simultaneous evaluation of seven left mandibular teeth are required, this cannot applied to children with lacking teeth due to an inborn or acquired defect (42).
- This method may not express, agenesis of teeth, distinctive retardation of dental development (excluding third molars), and systemic diseases and various developmental stages of the tooth (43).
- This method does not give maturity scores for stages 1-4 in case of 1st molar, central and lateral incisor; thus excluding the individuals below the age of 4-4.5 years (44).
- The accuracy of Demirjian method decreases in estimating the dental age in girls over 11 and boys over 13 years old. The fact that overestimation was more pronounced in grown-up children could perhaps be linked to the puberty and this result was in agreement with the studies *Bagherian et al.* (45).
- Examining crown and root growth and maturation radiographically can be varying due to different reasons such as: poor resolution of the radiographic images and biological variation among various populations studied (46,47)

Furthermore, there is strong concern over the dental and bone testing procedures conducted by dentists and physicians who are attempting to determine the age of young individuals for legal reasons (48). Inaccurate results would lead authorities to imprison some children with adult prisoners, which is unsafe and inappropriate for minors (49). For example, the *Australian Society of Forensic Odontology* gave evidence that wisdom teeth can start developing 'from mid-teens to early 20s'. For these reasons, the *International Organization for Forensic Odonto-Stomatology (IOFOS)* has published recommended procedures for quality assurance in forensic dental age estimation (50).

d. Other methods

The Iliac crest (Risser?s) test ,which requires an X-ray of the pelvic girdle, is thought to be a relatively reliable method for assessing age between the ages of 12 to 16 years. However, the impact of irradiation to the gonad has to be considered. Recent data from Denmark suggest that analysis of X-ray of the shoulder area yields the most accurate results regarding actual age (51). The use of non-ionizing radiation methods including magnetic resonance imaging (MRI) and ultrasound is attractive. Similar reservations, as X-ray evaluation, must apply due to considerable variation in the MRI-assessed rate of bone development during adolescence and age of attainment of maturity.

Further research is needed to validate the MRI approach to assessing age in normal populations before considering its use as a routine method for undocumented minors (32, 33).

Ethical aspects

Professionals working with children should always strive to take ethical guidelines into consideration in making decisions affecting these children. Even though the radiation dose from an X-ray of the hand is small (equivalent to 0.00017 mSv, i.e. 1-h exposure to background radiation in many cities) (52), clinicians have to consider whether or not the advantages outweigh the risks of inflicting radiation upon an individual.

This is because ionizing radiation is a consistently identified and potentially modifiable risk factor for meninigioma (brain tumour) (53, 54).

The use of multifactorial approaches for the assessment of chronological age

Most submissions to the inquiry openly acknowledge that there is no single reliable scientific method for determining a person's age. However, some go on to suggest that a '*multifactorial*' approach will provide more reliable assessment employing a combination of medical age assessment processes.

Conclusions

Age estimation presents a complex problem and requires considerable experience in recognizing significant changes and allowing for their variability with in any particular population. Age determination has great importance in many clinical decisions, being commonly used in pediatrics, legal medicine, forensic sciences, anthropology, odontopediatrics and orthodontics. Increased immigration and mixing of populations, due to the globalized economy resulting from the increased migratory flow, sets legal problems of various orders, with increasing importance of determining the chronological age of children, youths and young adults. So, estimating chronological age is important in assessing the legal adult age of people without documents for judicial purposes. In practice, age determination is extremely difficult to do with certainty, and no single approach to this can be relied on. Moreover, for young people aged 15–18 it is even less possible to be certain about age. There may also be difficulties in determining whether a young person, who might be as old as 23, could in fact be under the age of 18.

Therefore, there is a need both for identifying the best combination of methods and for finding the best approach for combining them and arriving at age estimates and associated uncertainties. Furthermore, there is also a need for a satisfactory way to scientifically determine the margin of error when combing methods, and there is a need for studies based on data from different methods that are acquired simultaneously from a single reference population.

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Aderenza e compliance al trattamento con ormone della crescita

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Adherence and compliance to GH treatment

Summary

Growth hormone (GH) is now being used since many years for the treatment of various growth disorders in childhood and adolescence. Its efficacy in promoting growth is influenced by several factors, among which adherence (A) and compliance (C) have been recognised as of primary importance for the growth response to treatment. Many studies on A/C to GH therapy have now been published, showing a wide range of A/C percentages (10% - 95%), possibly due to the different criteria in defining and evaluating A/C. All together, the different studies have demonstrated association between A/C and age, socio-economic condition, treatment duration and modalities (injection devices). A positive correlation has been shown between A/C and growth velocity, confirming the importance of A/C for the growth response to GH treatment. Different interventions have been suggested aiming at improving A/C, including share, between physician, patient and caregivers, of treatment modalities, decision to treat and choice of injection device, together with explanation and discussion of the rationale and aim of therapy. This review of the scientific literature on these issues reports the data available so far on this topic.

Key words: *Growth hormone, growth disorders, GH treatment, adherence, compliance*.

Riassunto

L'ormone della crescita (GH) è ormai da tempo utilizzato nel trattamento di diverse patologie dell'accrescimento sia in età pediatrica che adolescenziale. La sua efficacia è influenzata da numerosi fattori, tra i quali l'aderenza (A) / compliance (C) è stata riconosciuta di primaria importanza per la risposta accrescitiva alla terapia. Sono stati pubblicati molti studi sull'A/C al trattamento con GH, con una gamma di percentuali di A/C molto ampia (tra il 10 e il 95% circa), verosimilmente dovuta ai diversi criteri di definizione di A/C e ai diversi metodi di valutazione di A/C. Nell'insieme, gli studi pubblicati hanno dimostrato associazione tra A/C (o non-A/C) ed età, condizione socio-economica, durata del trattamento e modalità e dispositivi di iniezione. È stata dimostrata una correlazione positiva tra A/C e velocità di crescita sotto trattamento, che conferma l'importanza della A/C sulla risposta accrescitiva al GH. Sono stati suggeriti vari interventi per migliorare A/C, tra cui la condivisione, tra medico, paziente e suoi genitori, delle modalità di trattamento, della decisione di trattare e della scelta del dispositivo di iniezione, oltre alla comunicazione e discussione del razionale e delle finalità del trattamento. Questa revisione della letteratura discute i dati finora disponibili sull'argomento.

Parole chiave: *Ormone della crescita, disordini accrescitivi, trattamento con GH, aderenza, compliance*.

Introduzione

L'ormone della crescita (GH) è ormai in uso da più di 50 anni nel trattamento delle patologie della crescita, inizialmente come ormone estrattivo (da ipofisi umane) e, dagli anni '80 del secolo scorso, come ormone ricombinante umano (rhGH) (1).

La finalità principale della terapia con rhGH è quella di normalizzare la velocità di crescita dei piccoli pazienti nel minor tempo possibile e di far loro raggiungere un statura finale il più possibile adeguata al modello familiare, minimizzando rischi e costi del trattamento (2). Attualmente, oltre al deficit di GH, le indicazioni al trattamento in Europa comprendono il deficit accrescitivo secondario a s. di Turner (TS), s. di Prader-Willi (PWS), insufficienza renale cronica (CRF), deficit di gene SHOX (SHOX-D) e peso e/o lunghezza alla nascita piccoli per età gestazionale (SGA); in altri Paesi a queste indicazioni si aggiungono acondroplasia, s. di Noonan (NS) e bassa statura idiopatica (ISS).

Il successo della terapia con GH non è costante in tutte le condizioni, e diverse possono essere le ragioni di un insuccesso o di un successo solo parziale. È stato infatti dimostrato che la risposta accrescitiva al trattamento con GH è funzione delle modalità dello stesso: dose di GH e frequenza delle somministrazioni son

infatti direttamente proporzionali all'efficacia, e la risposta nel 1° anno di terapia (in termini di velocità di crescita e guadagno accrescitivo) dipende da diverse variabili, alcune direttamente proporzionali, come dose di GH e frequenza delle somministrazioni, e altre negativamente correlate (età all'inizio del trattamento, età ossea, velocità di crescita pre – trattamento).
Esiste inoltre una variabilità individuale di risposta da attribuire a diversi gradi di resistenza al GH e variabili genetiche individuali (3); tuttavia grande importanza è sempre stata attribuita la grado di aderenza / compliance del singolo paziente.

Aderenza e Compliance

I concetti di "*Aderenza*"(A) e di "*Compliance*" (C) a una terapia differiscono leggermente dal punto di vista semantico (4), anche se sono spesso usati come sinonimi in Medicina.
A rigore, l'A consiste nell'esecuzione corretta della terapia nei modi e tempi della somministrazione, mentre il concetto di C implica anche un atteggiamento di condiscendenza, condivisione e allineamento al razionale della terapia stessa.
Più specificamente, l'A può essere definita come "*il grado con cui il comportamento di una persona, rispetto all'assunzione di una terapia, al seguire una dieta* e/o *attuare cambiamenti di stile di vita, rispetta le raccomandazioni concordate con un operatore di salute*"(5); la C invece può essere definita come "*il grado con cui il comportamento del paziente … coincide con la prescrizione clinica*"(6).
Altri Autori distinguono addirittura A e C da "*concordanza (Concordance)": "partecipazione del paziente al processo decisionale*" (7). Nel presente articolo saranno usati indifferentemente come termini sovrapponibili, dato che appartengono in questo contesto alla medesima problematica. Allo stesso modo, le definizioni di non-aderenza (non-A) (e non-compliance: non-C) possono variare: alcuni autori specificano cut-off fissi, come una A inferiore all'80 o al 95% (8), mentre altri considerano la non-A come "*quella sufficiente a interferire significativamente con il raggiungimento dell'obiettivo terapeutico*" (9).
La non-C in Medicina è stata identificata nel tempo come un importante problema di salute pubblica, che comporta anche un notevole carico finanziario sull'attuale sistema sanitario.
La ricerca in questo settore è stata quindi molto vasta, finalizzata alla comprensione, misurazione e risoluzione della non-C, e nell'insieme è stato osservato che da un terzo alla metà dei pazienti non rispettano i consigli e le prescrizioni mediche (10).
Mentre in passato però il ruolo del paziente era praticamente ritenuto secondario rispetto a quello del prescrittore/somministratore di terapia, nel corso del tempo il ruolo decisionale del paziente nella gestione del trattamento ha assunto un'importanza sempre maggiore, anche in seguito al prevalere della patologia cronica su quella acuta: in questo senso il coinvolgimento del paziente (e dei suoi genitori/tutori se in età pediatrica) è di fondamentale importanza, sia in termini di informazione rispetto alla terapia che di autonomia decisionale rispetto alla esecuzione o meno della stessa, alla scelta del tipo di trattamento e delle sue modalità.
L'A in Pediatria è particolare in quanto non è limitata al solo paziente, ma si estende ai genitori/tutori, e anche perché il bambino spesso non è consapevole dell'importanza e delle finalità della terapia ed è quindi riluttante ad assumerla (11).
Le ragioni di una non-A /non-C possono essere così sintetizzate:

- fastidio / scomodità; trattamenti a lungo termine (ad es. necessità di assunzioni multiple nella giornata per lunghi periodi: mesi – anni – a vita), specie se a somministrazione iniettiva: si pensi ad es. a una terapia insulinica nel diabete mellito di tipo I, con 4 iniezioni sottocutanee al giorno secondo le indicazioni correnti (12, 13),
- regimi terapeutici complessi (ad es. trattamenti multipli e misti, come in endocrinopatie multiple o in forme sindromiche con deficit multi – organo),
- età (ad es. tipicamente l'età adolescenziale, in cui è frequente la ribellione e/o il rifiuto della malattia e della sua terapia),
- dinamiche individuali e familiari (depressione, disagio sociale, problemi economici e organizzativi, ecc.),
- livello di comprensione dei benefici del trattamento e delle conseguenze della non-C da parte del paziente/famiglia.

È evidente da tutto ciò che i pazienti a cui viene somministrato l'ormone della crescita per mezzo di iniezioni sottocutanee quotidiane per molti anni consecutivi sono ad alto rischio di non-C, con conseguente fallimento o scarsa efficacia della terapia stessa.
Il trattamento con rhGH, come è noto, è molto costoso: il costo annuale per un bambino di 30 kg, ad esempio, varia da 15000 a 20000 dollari, e il costo annuale per far raggiungere ad adolescenti una statura finale ottimale può raggiungere i 50000 dollari (14). Pertanto una non-C può anche condurre a un notevole spreco economico oltre che incidere negativamente sulla risposta accrescitiva al trattamento.

Metodi per misurare A/C

A e C possono essere valutati con diversi metodi, ciascuno con vantaggi e svantaggi: non esistendo un metodo ideale, viene suggerito di usare più metodi combinati per ottimizzare l'affidabilità (8).
I metodi più frequentemente usati sono stati i seguenti:

a. piani terapeutici prescritti o rinnovati: incrociando le prescrizioni fatte dal Centro con le prescrizioni eseguite dal medico curante: questo vale laddove le prescrizioni vengano effettuate dal medico di territorio su indicazione del Centro, e non dove la prescrizione avvenga direttamente da parte del Centro attraverso la farmacia dell'ospedale.
   Utilizzato in vari studi (13, 15, 16), questo metodo ha il vantaggio di essere relativamente oggettivo, non invadente ed

economico, con dati semplici da ottenere (può servirsi ad esempio di questionari da inviare al medico curante) e possiede un buon grado di concordanza con altri metodi di misura di A (8, 17, 18). Ha tuttavia lo svantaggio di fornire solo una misura grossolana della A (8, 16);

b. questionari compilati dal paziente e/o genitori /tutori: presentano concordanza da moderata a forte con i metodi precedentemente esposti e hanno, come questi, il vantaggio di essere semplici ed economici (19). Principale svantaggio è la scarsa sensibilità per la non-A (spesso < 50%), che può essere attribuita a difficoltà di ricordare i particolari della somministrazione del farmaco e/o il timore di affrontare discussioni o di deludere i sanitari. Altro svantaggio è l'aspetto temporale: i pazienti ricordano meglio quanto accaduto negli ultimi giorni o sono più attenti alla terapia nei giorni che precedono il controllo;

c. un altro metodo, certamente più affidabile, è quello della fornitura diretta del farmaco da parte della farmacia del Centro di riferimento con l'obbligo di restituzione delle fiale utilizzate al Centro stesso al momento del successivo controllo: questo metodo e i suoi vantaggi / svantaggi verrà discusso successivamente a proposito dello studio di *Cutfield et al.* (20) sulla non-A al trattamento con GH.

d. sono stati anche proposti metodi basati sulla misurazione del GH nelle urine delle 12 ore precedenti il controllo, che correlano con la A: sono stati infatti osservati livelli di GH urinario più elevati in caso di A, che diminuivano significativamente anche solo dopo 2 dosi mancate.
Tuttavia queste metodiche hanno evidenti problemi di applicazione pratica (17), come pure il dosaggio dei livelli sierici di IGF-I. Questi ultimi sono infatti normalmente utilizzati dalla maggior parte dei clinici per valutare l'efficacia della terapia e controllarne la sicurezza, mentre non ne è chiaramente dimostrata l'affidabilità come indicatori di A (21), data anche la eterogeneità delle variabili che possono influenzarne i livelli (22-24).

Studi clinici su C/A

Diversi studi hanno valutato la prevalenza di non-A / non-C in pazienti pediatrici trattati con GH; la percentuale di non-A / non-C mostra un'ampia variabilità, dal 5 all'80%, certamente a causa dei diversi metodi di valutazione e della definizione di A/C.
Le principali caratteristiche degli studi sono riassunte in Tabella 1.

Tabella 1.
Principali studi su non-A / non-C al trattamento con rhGH (da ref. 25, modificata).

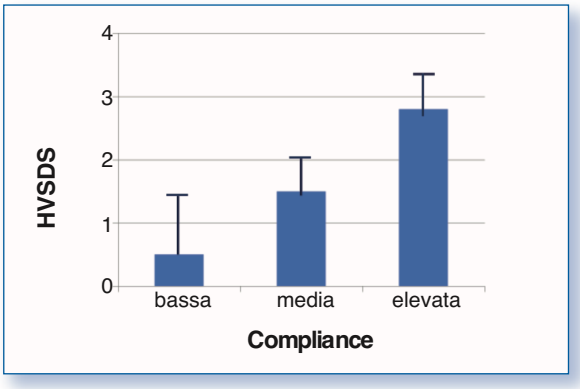
Referenza bibliografica	N° pazienti	Metodo	Definizione di non-A/C	% non-A/C
(26)	188	Questionario compilato da chi somministrava GH	>5 iniezioni perse dall'ultimo controllo >10 iniez. Perse dall'ultimo controllo	51 19
(27)	107	Colloquio con paziente genitori	≥ 3 iniezioni perse / mese	10
(28)	177	Questionario compilato da chi somministrava GH	Mancata compliance a tutti gli aspetti della terapia	16-42
(29)	29 (CRF)	Questionario compilato dal paziente e/o genitori	≥ 1 iniez. persa / mese ≥ 6 iniez. perse / mese	62 7
(30)	473	Questionario somministrato da infermiere a paziente e/o genitori	≥ 5 iniez. perse dall'ultimo controllo	6
(31)	17 (CRF)	Colloquio con i genitori	<1 iniezione persa / sett. ≥ 1 iniez. persa /sett.	35-82 6-9
(32)	631	Non definito	≥ 3 iniez. perse / mese ≥ 15 iniez. Perse / mese	15-24 6-13
(33)	50	Conto delle fiale	Non specificamente definita	5-8
(13)	6487	Rinnovo prescrizioni	Non rinnovo prescrizione nel 1° anno di terapia	5-10
(16)	75	Prescrizioni rilasciate	>1 iniez. persa / sett. >2 iniez. perse / sett.	39 23
(34)	882	Questionario compilato da paziente / genitori	non-C occasionale non-C e scetticismo	64-77
(20)	175	N° fiale richieste / mese N° fiale restituite / mese	>1 iniezione persa / sett 1 iniezione persa / sett.	34 66

Come si evince dalla Tabella 1 la maggior parte degli studi basa la percentuale di non-A/C sulla somministrazione di questionari autocompilati o addirittura sul colloquio con il paziente e /o genitori / tutori in occasione della visita di controllo, con tutti i limiti di affidabilità già esposti. Lo studio che utilizza una metodologia più precisa (incroci tra numero di fiale necessarie per il trattamento prescritte e numero di fiale utilizzate ritirate al momento del controllo) è quello di *Cutfield et al.*, condotto in Nuova Zelanda su 175 pazienti con bassa statura di diversa eziologia (GHD, TS, ISS, SGA, PWS) (20). Più in particolare, la C è stata valutata con due modalità:

- numero di fiale di GH richieste per mese per paziente (GHreq, basate su autoreferenza verbale da parte di chi assisteva il paziente),
- numero di fiale restituite (GHret)
  entrambe espresse come percentuale del numero di fiale prescritte per ciascun paziente. Una C soddisfacente era definita come l'85% o più di A al trattamento prescritto, equivalente alla perdita media di una iniezione / settimana. I pazienti (N° 175) vennero divisi in 3 gruppi:
  - C elevata (≤ 1 dose persa / settimana)
  - C media (>1 and <3 dosi perse / settimana),
  - C bassa (≥ 3 dosi perse / settimana).

La percentuale globale di non-C risultò del 66% (73/110) sulla base di GHret e addirittura del 34% (59/172) sulla base di GHreq. Calcolando la perdita di efficacia in base al tasso di non-C, gli autori osservarono che, sui 6-8-mesi di osservazione della velocità di crescita, la perdita di >1 dose per settimana si traduceva in una diminuita efficacia del trattamento in termini di velocità di crescita, direttamente proporzionale al numero di dosi perse (Figura 1).

Figura 1.
SDS di velocità di crescita (HVSDS, media ± SD) su 6-8 mesi in base al livello di compliance al trattamento con GH (Cutfield WS et al. 2011) (v. testo).



Gli Autori conclusero che lo studio indicava che la non-C è molto frequente in Nuova Zelanda nonostante un contesto in cui esiste un contatto regolare con gli operatori sanitari e in cui non c'è alcuna restrizione finanziaria personale alla disponibilità di GH; questo si ripercuote anche sull'efficacia, visto che i pazienti che perdevano più di una dose / settimana mostravano una crescita significativamente ridotta rispetto a quelli con buona C.

Inoltre lo studio mostrava che il metodo di valutazione della C basato sul numero di fiale restituite ("*GHret*") è più efficace e obiettivo nel valutare la C rispetto a quello dell'autodichiarazione da parte delle famiglie del numero di fiale usate (GHreq), anche se GHret potrebbe sottovalutare la C a causa di possibili fiale rotte, perse o semplicemente non restituite, in quanto la restituzione non era un presupposto necessario per ricevere il rinnovo della fornitura del farmaco. Il metodo "*GHreq*" non differirebbe inoltre dai metodi usati per valutare la C in precedenti studi, basati su questionari compilati dai pazienti (16, 26, 30, 32, 34): infatti i genitori potrebbero non voler ammettere di aver perso o dimenticato somministrazioni per imbarazzo o timore di essere rimproverati dai sanitari.

Un sistema alternativo potrebbe essere l'uso di dispositivi elettronici con la memorizzazione della dose di farmaco somministrata, che fornirebbero una valutazione più affidabile della C del paziente. Il limite di questi dispositivi è soprattutto nel costo e nella maggiore complessità di utilizzo.

In un recente studio multicentrico su 217 pazienti trattati con GH per diverse cause (GHD, TS, SGA, ecc.) in Turchia (35) gli Autori hanno suddiviso i pazienti, in base alla percentuale di A, in 4 gruppi: A eccellente (0% di dosi perse), A buona (fino a 5%), A discreta (5-10%) e A scarsa (>10%). La percentuale di aderenza diminuiva con il passare dei mesi di trattamento: i pazienti con A eccellente / buona mostravano velocità di crescita significativamente superiore a quelli con A discreta / scarsa, così come i livelli di IGF-I correlavano direttamente con la percentuale di A.

Un altro studio recente sull'A al trattamento con GH è stato effettuato su pazienti pediatrici con Insufficienza Renale Cronica (CRF), nell'ambito di un ampio studio collaborativo tra 55 Centri di Nefrologia Pediatrica del Nord America (Chronic Kidney Disease in Children – CkiD – study)(36). L'A al trattamento con GH era valutata insieme a quella di altri farmaci (Vitamina D, chelanti del fosforo, eritropoietina, alcali, ferro) e correlata alla risposta accrescitiva. La definizione di non-A era dicotomica: i pazienti riferivano a ogni visita di controllo se avevano perso almeno una dose / settimana di qualsiasi dei farmaci prescritti: la non-A era definita come la perdita di almeno 1 dose per ciascun farmaco considerato. Questa definizione quindi, oltre ad essere autoriferita (con le limitazioni già discusse più sopra) non teneva conto della severità della non-A (se cioè veniva persa una o 2 o 3 o più dosi, per cui il paziente che perdeva una sola dose era assimilato a quelli che ne perdevano di più). Mentre non veniva trovata alcuna correlazione tra non-A alle altre terapie diverse dal GH, i pazienti aderenti al trattamento con GH mostravano guadagno staturale maggiore rispetto a quelli non aderenti, in cui non veniva osservato alcun guadagno accrescitivo. In particolare, i pazienti aderenti al GH mostravano un incremento annuo

medio di 0.18 SDS in altezza rispetto a nessun cambiamento per i non-aderenti; inoltre, tra i pazienti aderenti, quelli con altezza <3° percentile mostravano un incremento medio annuo di 0.33 SDS in altezza. Questi risultati sono comunque molto significativi se si tiene presente che nella CRF il ritardo accrescitivo è di natura multifattoriale (37) e che non vi è carenza di GH ma una forma di resistenza all'ormone stesso (38), per cui la risposta accrescitiva al GH non è sempre ottimale e necessita di dosi più elevate che nel deficit di GH "*classico*".

Metodi per migliorare C/A

Possibili strategie per migliorare la A al trattamento con GH comprendono: riduzione della frequenza di somministrazione con formulazioni di GH a lunga durata di azione, attualmente ancora in fase di studio; uso di dispositivi di iniezione automatici o di aghi sempre più fin per ridurre il dolore o il timore del dolore e, sempre per questa finalità, utilizzo di dispositivi senza ago (needle-free). I dispositivi di somministrazione differiscono tra loro per alcune caratteristiche importanti che possono facilitarne l'uso e rendere meno fastidiosa l'iniezione. Queste caratteristiche comprendono: passaggi nella preparazione dell'iniezione, modalità di ricostituzione del farmaco (polvere + liquido o preparato già liquido), dispositivi "*usa e getta*" monodose o multidose, dispositivi needle-free, modalità di conservazione (in frigorifero o stabili a temperatura ambente) e dispositivi di iniezione elettronici con possibilità di memorizzazione delle dosi somministrate collegabili on-line al PC o altri dispositivi elettronici del medico/infermiere, che permetterebbero un più efficace controllo dell'A al trattamento. A questo proposito diversi studi hanno sottolineato l'utilità di dispositivi sempre più perfezionati nel migliorare l'accettabilità del trattamento da parte dei pazienti (12, 27, 39-46). Questi studi (per lo più sostenuti da Aziende Farmaceutiche del settore, e pertanto con un possibile bias di oggettività, ma non per questo meno meritevoli di attenzione) sottolineano di volta in volta i vantaggi di formulazioni liquide rispetto a quelle da miscelare e/o che non necessitano di refrigerazione rispetto a quelle da conservare in frigorifero, o di dispositivi di somministrazione automatici rispetto a manuali, elettronici rispetto a meccanici o senz'ago rispetto a quelli con ago.
Sebbene non vi siano dati nell'ambito del trattamento con GH, per trattamenti con altri farmaci è stato osservato un miglioramento dell'A con calendari cartacei giornalieri (47) o incentivi economici (48), o fornendo maggiore supporto e informazione ai pazienti e alle loro famiglie sui benefici della terapia e sulle conseguenze della non-C (49).
Questo aspetto è sottolineato in uno studio olandese condotto su 69 genitori di bambini in trattamento con GH, che attraverso un questionario valutava le opinioni dei genitori circa il trattamento dei loro figli, con particolare attenzione alle loro percezioni sulla comunicazione e il supporto da parte dei sanitari (50). Il 48% dei genitori riferiva mancanza di libertà di scelta del dispositivo di somministrazione del GH che più si adattasse al loro figlio; la quasi totalità riteneva che i loro figli e loro stessi avrebbero tratto vantaggio dall'autosomministrazione, dopo adeguato addestramento; il 37% riferiva che i loro figli vivevano con ansia la terapia con GH, e l'83% avrebbe apprezzato un supporto psicologico per superare tale ansia.
Allo stesso modo la metà circa dei genitori avrebbe auspicato supporto psicologico per superare l'aumento della riluttanza alla terapia da parte dei figli che si presentava con l'età puberale.
In sostanza, quindi, gli autori sottolineavano come la comprensione delle finalità e delle implicazioni del trattamento con GH veniva percepito dai genitori come presupposto per ottenere una migliore A alla terapia e che i loro dati suggerivano la necessità del coinvolgimento dei genitori nel processo decisionale nella scelta del dispositivo, fondamentale per migliorare l'accettazione del trattamento e ridurre i problemi emotivi dei loro figli.
Tuttavia proprio uno dei più recenti studi sull'A in 103 pazienti trattati con rhGH ha al contrario rilevato come proprio la autosomministrazione sembri essere un predittore negativo di A al trattamento, insieme all'età puberale (46); l'A in questi pazienti era inoltre inferiore a quella di 97 soggetti pediatrici in trattamento con L-Tiroxina, sottolineando l'importanza della via di somministrazione (iniettiva per il GH e orale per la L-Tiroxina) come fattore che influenza A/C, come già detto più sopra.
Resta comunque valida la raccomandazione del massimo coinvolgimento del paziente e dei suoi famigliari nella decisione di iniziare il trattamento e nella scelta del dispositivo: come accennato più sopra, in questo caso ai concetti di A e C (obiettivi da perseguire che concorrono all'efficacia del trattamento) si aggiunge quello di "*concordanza*": quest'ultima infatti riguarda più strettamente il rapporto tra il paziente e il clinico e si basa sulla convinzione che le due figure debbano "*lavorare insieme*", in accordo con la moderna visione della condivisione dell'informazione con i paziente e della sua responsabilizzazione per una decisione terapeutica informata e consapevole (51).

Caso Clinico

DF giunge all'osservazione presso il nostro Ambulatorio Auxoendocrinologico per rallentamento della crescita.
Anamnesi familiare negativa per patologie di rilievo; statura materna 168 cm (≥ 75° percentile); statura paterna 170 cm (≥ 10° percentile);statura media genitoriale corretta per genere: 163 cm (=50° percentile);
Anamnesi fisiologica: secondogenita; ritardo intrauterino di accrescimento (IUGR); nata alla 38° settimana da parto con taglio cesareo con peso 2020 g (< 3° percentile) e lunghezza 43 cm (< 3° percentile); Apgar 10 – 10; allattamento al seno materno; postnatalità nella norma.
Anamnesi patologica remota: nulla di rilevante.

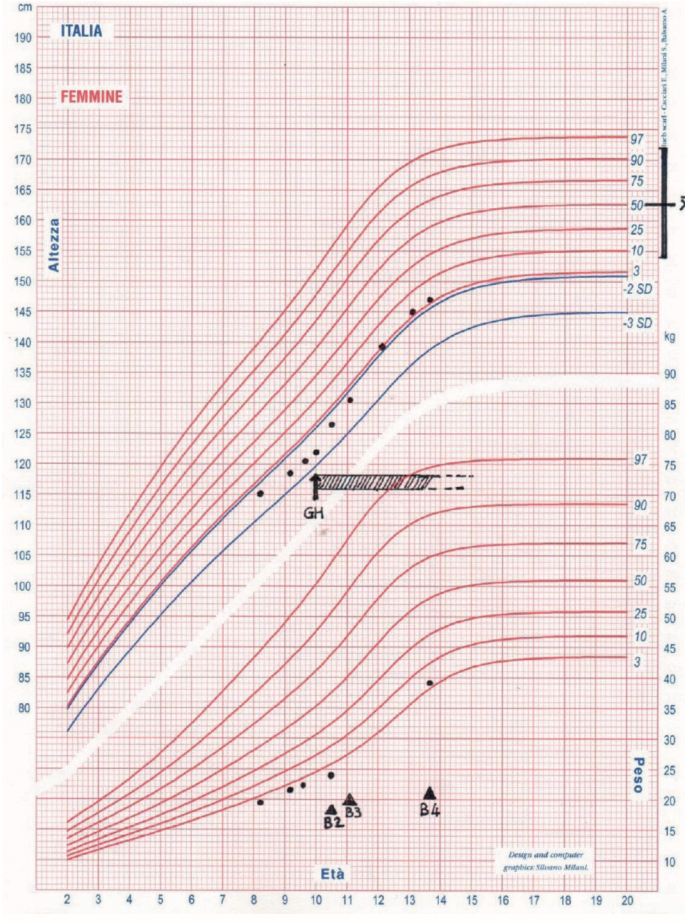
Anamnesi mirata: scarso accrescimento per cui eseguiti esami di screening da parte del Curante per scarsa crescita, risultati negativi.

Alla prima visita: età 8.3 anni; altezza (Ht) 115.2 cm (-2.49 SDS); peso 19.5 kg (< 3° percentile); condizioni generali buone; obiettività nella norma; impubere; età ossea (TW3): 7.8 "*anni*".

Controllo a 9.2 anni: Ht 118.5 cm (-2.54 SDS); peso kg 21.1 (< 3° perc.); velocità di crescita (HV) 3.9 cm/anno (-2.2 SDS); test di stimolo per GH (clonidina): picco di GH dopo stimolo nella norma (>10 ng/ml).

Successivo controllo: età 9.7 anni; Ht 120.5 cm (-2.61 SDS); peso 22.2 kg; HV: 3.9 cm/anno (-1.96 SDS). Impubere. Viene consigliato trattamento con GH in base ai criteri della nota AIFA 39. Inizia trattamento con GH all'età di 10 anni, previa esecuzione di OGTT, IGF-I e RMN ipotalamo - ipofisi, tutti risultati nella norma. Dose 6.6 mg/settimana (0.3 mg/kg/settimana).

Figura 2.



1° controllo dopo inizio terapia: età 10.6 anni; Ht 126.8 (-2.29 SDS); peso 24 kg; stadi puberali (Tanner) B2 PH1; HV: 7.3 cm/anno (+1.75 SDS).

2° controllo sotto trattamento: età 11.1 anni; Ht 130.6 cm (-2.15 SDS); peso 25.5 kg; HV 7.8 cm/anno (+1.24 SDS); stadi puberali B3 PH1; condizioni buone, obiettività nella norma.

3° controllo sotto trattamento: età 12.1 anni; Ht 139.3 cm (-1.76 SDS); peso 32.0 kg; HV 9.0 cm/anno (+0.61 SDS); stadi puberali B3 PH3; condizioni buone, obiettività nella norma.

4° controllo sotto trattamento: età 13.2 anni; Ht 145.0 cm (-1.66 SDS); peso 38.6 kg; HV 5.7 cm/ anno (-1.71 SDS); stadi puberali B3 PH3; condizioni buone, obiettività nella norma.

5° controllo sotto trattamento: età 13,7 anni; Ht 147.0 cm (-1.82 SDS); peso 39.1 kg; HV: 4.4 cm/anno (-0.08 SDS); stadi puberali B4 PH4; condizioni buone, obiettività nella norma.

La paziente non ha mai presentato o deposto effetti indesiderati; la bimba si è detta soddisfatta della crescita che l'ha portata a valori di statura più adeguati a quelli delle sue coetanee. I valori di glicemia, fT4, TSH e IGF-I si sono sempre mantenuti nella norma; non è ancora comparso menarca e, data la crescita tuttora > 2 cm /anno, la paziente proseguirà il trattamento fino a crescita < 2 cm/anno e saldatura delle cartilagini di accrescimento (Figura 2).

Commento: la paziente è stata portata alla nostra attenzione in età già piuttosto avanzata e quando ancora il trattamento con GH dei bambini nati SGA non era previsto dalle regole europee e italiane; è stata posta in terapia con GH non appena entrata in vigore la normativa sul trattamento; la crescita sotto GH è stata certamente influenzata dall'esordio puberale fisiologico della paziente, ma il trattamento è iniziato prima che comparissero i primi segni puberali, per cui nei primi 6 mesi di terapia la risposta accrescitiva è da attribuirsi alla sola terapia con GH.

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Dichiarazione di conflitto d'interesse: "*La pubblicazione di questo articolo ha ricevuto assistenza editoriale e redazionale da Airon Communication s.r.l. e un supporto non condizionato da Novo Nordisk S.p.A*"

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Linear Growth and Nutritional Parameters in Adolescents with Severe Atopic Dermatitis

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Summary

Introduction: Atopic dermatitis (AD) is a chronic inflammatory condition affecting local immunity and skin hydration. Severe AD may affect growth and weight gain in infants and children but its effects on growth and nutrition in adolescents are not yet well known.

Main objectives of study: To measure the effect of AD on linear growth and to evaluate some nutritional parameters in adolescents with severe AD.

Methods: We studied linear growth and body mass index (BMI) in 18 adolescents with severe AD (Scoring Atopic Dermatitis - SCORAD index > 41) seen at the Pediatric Allergy and Immunology Clinic of Hamad General Hospital of Doha (Qatar) between June 2014-2015 with severe AD. Anthropometric data was collected and serum total protein, albumin, 25OHD, zinc and IgE concentrations were measured.

Results: The height standard deviation score (Ht-SDS) was <-2 in 1/18 (5.5%) and < -1 in 27.8 % of them. Their BMI was 16.7 ± 3.6 Kg/m^2. In 16.7 % of adolescents with AD the BMI < 14 Kg/m^2 (BMI-SDS < -2). Hypoalbuminemia (serum albumin concentration < 4 g/dl) and hypoproteinemia (serum total protein concentration < 64 g/dl) were found in 22.2% and 11.1 %, respectively. SCORAD was higher in adolescents with hypoalbuminemia and low BMI compared to those with normoalbuminemia and BMI (67.9 ±22.1 vs 58.3±22.5; p = 0.045). Vitamin D deficiency and zinc deficiency (< 9.95 μmol/L) were diagnosed in 31% of patients and 33.3% of patients, respectively. Anthropometric data (Ht-SDS, BMI) and nutritional parameters (serum albumin, zinc and 25OHD concentrations) did not correlate significantly with the severity of the disease (SCORAD index).

Conclusions: Adolescents with severe AD had high prevalence of hypoalbuminemia, zinc and vitamin D deficiency. Albumin loss may lead to malnutrition and low BMI in these patients. Therefore, it is mandatory to closely monitor linear growth and nutritional parameters in patients with severe AD, and to treat early any nutritional deficiency.

Key words: *Atopic dermatitis, Adolescents, Growth, BMI, Zinc, Vitamin D*.

Accrescimento e parametri nutrizionali in adolescenti con severa dermatite atopica

Riassunto

Gli Autori hanno valutato gli effetti sulla crescita ed alcuni parametri nutrizionali in 18 giovani adolescenti (11.8 ± 1.7 anni) con dermatite atopica severa (Scoring Atopic Dermatitis - SCORAD index > 51). La statura espressa in SDS (Ht-SDS) è risultata <-2 in 1/18 (5.5%) ragazzi and < -1 in 27.8 %. Nel 22.2% è stata diagnosticata una ipoalbuminemia ed in un terzo dei pazienti un deficit di vitamina D e zinco. Pertanto, un'attenta valutazione dell'accrescimento e dello stato nutizionale è necessario nei soggetti con dermatite atopica allo scopo di diagnosticare e trattare precocemente il deficit nutrizionale.

Parole chiave: *Dermatite atopica, Adolescenti, Accrescimento, BMI, Zinco, Vitamina D*.

Introduction

Atopic dermatitis (AD) is an intensely itchy, chronic eczematous disorder stemming from complex genetic and environmental factors that contribute to an excessive immune response to allergens coupled with epidermal barrier dysfunction (1). The terms '*atopic eczema*' and '*atopic dermatitis*' are synonymous. Research on AD has focused mainly on infancy and early childhood, with few surveys in adolescents (1).

According to recent data, recurrence rate is around 2.4%, and high persistence rates of disease symptoms are seen among adolescents, especially those with positive personal or parental

atopic background, high socioeconomic status, and female gender, and high-risk occupations (2). Some infants and children with the severe form of AD suffer from growth failure, hypoalbuminemia, anemia and edema. In addition, delayed puberty and skeletal maturation is described in older children and adolescents with AD. These manifestations are attributed in part to extensive loss of protein through the skin.

The administration of steroids can result in rapid healing of the skin, conservation of albumin and correction of the anemia. However, the negative effect of steroids on linear growth still poses a risk on the growing child (3-5).

The effect of severe AD on growth and nutritional parameters in adolescents have not been fully studied before. We report our experience in 18 adolescents with severe AD.

Patients and Methods

We studied linear growth in all adolescents with severe AD who attended for the first time to the Pediatric Allergy/Immunology Clinic at Hamad Medical Center (HMC) in Doha (Qatar) during the period from June 2014 to June 2015. Their AD severity was measured according to Scoring Atopic Dermatitis (SCORAD) score. We measured their weight, height, body mass index (BMI) and recorded their height Z scores (Ht-SDS) using WHO growth charts. Their laboratory tests included complete and differential blood count (CBC), renal and hepatic functions, serum IgE, IgG, IgA, IgM, serum zinc (Zn) and vitamin D (25-OHD) concentrations. Exclusion criteria included those adolescents with chronic disease other than AD, such as: asthma, food intolerance, or allergic rhinitis and associated psychological problems which could influence growth. The proposal of the study was approved by the Ethics committee of HMC.

Results

Eighteen adolescents (8 males and 10 females) aged 11.8 ± 1.7 years (Age range: 11- 16 years) with severe AD (SCORAD > 51) were studied. Patients had normal renal and hepatic functions. Anthropometric and laboratory data are presented in Table 1.

The Ht-SDS was < -2 in 1/18 (5.5 %) and < -1 in 27.8 % of them. Their BMI was 16.7 ± 3.6 Kg/m^2. In 16.7 % of adolescents the BMI < 14 Kg/m^2 (BMI-SDS < -2). Hypoalbuminemia (serum albumin concentration < 4 g/dl) and hypoproteinemia (serum total protein concentration < 64 g/dl) were found in 22.2% and 11.1 %, respectively. Vitamin D deficiency (25-OH vitamin D < 20 ng/ml) was found in 31% of the studied patients (4/13) and 25-OHD insufficiency (25-OH vitamin D between 2-20 ng/ml) was found in the remaining patients (9/13). Zinc deficiency (<9.95 μmol/L) was diagnosed in 33.3% of patients. None of the patients had anemia (hemoglobin concentration < 12 g/L).

SCORAD was higher in adolescents with hypoalbuminemia and low BMI compared to those with normoalbuminemia and BMI (67.9 ± 22.1 vs 58.3 ± 22.5; p = 0.045) but did not correlate with any of the auxological parameters (Ht-SDS and BMI) nor with albumin, total protein and zinc concentrations.

Discussion

Atopic dermatitis (eczema) is amongst the most common disorders of the skin in young people around the world. "*Atopic*" means that there is typically a genetic tendency toward allergic disease. AD is a chronic or recurrent inflammatory skin disease that usually begins in the first few years of life and is often the initial indication that a child may later develop asthma and/or allergic rhinitis (hay fever). Acute eczema/dermatitis is characterised by oedema, erythema, vesiculation, exudation and crusting. Microscopy shows collections of serum in the stratum corneum, moderate to marked spongiosis, intraepidermal vesiculation, moderate to marked sub-epidermal oedema in the papillary dermis and lymphocytes in the upper dermis. Chronic eczema /dermatitis is characterised by lichenification (1, 2). Studies on the natural history of atopic dermatitis document up to 60% spontaneous clearing by puberty (1, 2). Cutaneous symptoms of nutritional disorders can be the result of poor nutrient intake/anorexia, zinc deficiency and nutritional deficiencies. The severity of dermatitis in individual cases can be measured and monitored in several ways. We used the SCORAD index to classify the AD as severe. In our adolescents, the BMI was low and Ht-SDS was below -1 and -2 in 27.8 % and 5.5 %, respectively.

Table 1.
Anthropometric and lab data of Adolescents with Severe AD.

	Age	BMI	HtSDS	Alb	Protein	25OHD	Total IgE	AEC	Hb	Zinc
	yr	Kg/m^2		g/L	g/L	ng/ml	kU/L	cells/mcL	g/dl	μmol/L
Mean	10.3	16.7	-0.3	43.8	74.9	13.9	3713.2	876.0	12.9	8.7
SD	2.1	3.6	1.1	4.5	6.2	6.6	8308.8	829.6	0.8	1.6

Legend: BMI = body mass index; Alb = serum albumin; Protein = serum total protein ;
AEC = Absolute eosinophilic count; 25OHD = 25 hydroxy vitamin D; Hb = hemoglobin; Zinc = serum zinc level.

Unfortunately, the difference in patients' standing height versus midparental scores were not available. We recommend serial growth measurements in all children and adolescents with severe AD in order to detect early changes on growth pattern.

These patients had a high prevalence of hypoalbuminemia and hypoproteinemia (22.2 % and 11.1 %, respectively) due to loss of albumin and globulins through the diseased skin. Albumin loss may lead to malnutrition and explain in part their low BMI. In support to our findings, *Baum et al*. reported high prevalence of delayed growth and skeletal maturation in children with AD (6). Furthermore, hypoproteinemia can be a life-threatening condition owing to hypovolemic shock as a result of hypoproteinemia and vascular infarction as a result of thrombocythemia (7).

One third of our patients had high prevalence of Zn deficiency which may contribute to their impairment of growth. Zinc is the intrinsic metal component or activating cofactor for more than 70 important enzyme systems, including carbonic anhydrase, alkaline phosphatases, dehydrogenases and carboxypeptidases. It is involved in the regulation of nucleoproteins and the activity of various inflammatory cells and plays a role in growth, tissue repair and wound healing, carbohydrate tolerance and synthesis of testicular hormones.

Therefore, in patients with severe AD, Zn deficiency may negatively affect linear growth and pubertal development and deteriorates and increases the risk and severity of their skin inflammation and infection (8-11).

Linear bone growth is adversely affected in children with chronic inflammatory disorders. Atopic dermatitis is one of the chronic inflammatory conditions which is associated with the release of many inflammatory cytokines in the circulation. In the chronic phase of AD activation of Th-1 lymphocytes which produce mainly IFN-γ, TNF-α, IL-8 and IL-12. These cytokines can impair the GH-IGF-I axis at several levels.

First, cytokines, in particular IL-1β, have been shown to decrease GH secretion in vivo. Second, infusion of IL-1β and TNF-α induces profound anorexia susceptible to decrease circulating IGF-I. Third, IL-1β and TNF-α, can stimulate secretion of stress hormones as glucocorticoids and these hormones can, in turn, induce a state of GH resistance. In addition, a direct effect of cytokines on hepatocyte IGF-I gene expression has been suggested. However, the role of high inflammatory cytokines and mediators on growth, in such children has not been studied so far (12-20).

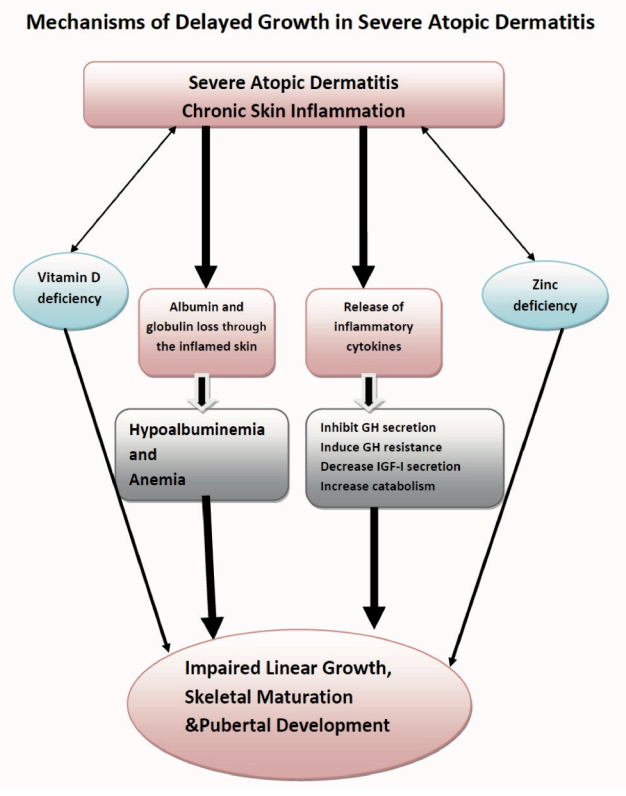
Treatment with steroids, which inhibits inflammation and release of these markers, results in dramatic improvement of dermatitis and rapid correction of hypoalbuminaemia, oedema and anaemia in severe AD (12-20). In order to verify these assumptions it is necessary to research the interaction of these inflammatory markers on linear growth, growth factors and skeleton in children and adolescents suffering from atopic disorders (Figure 1).

This study showed high prevalence of vitamin D deficiency and/or insufficiency in adolescent patients with AD. Given the potential for vitamin D to suppress inflammatory responses, enhance antimicrobial peptide activity, and promote the integrity of the permeability barrier, correction of VDD and supplementation can provide a possible therapeutic intervention in this disease. Some data suggest that vitamin D deficiency may be related to the severity of AD and advocate the need for studies evaluating the use of vitamin D as a potential treatment in patients with this disease. A double-blind randomized controlled trial utilized a regimen of 1,000 IU/day of vitamin D for one month during the winter in children with winter-related AD (5 subjects received supplementation versus placebo in 6 subjects). Baseline changes in global assessments of skin showed that the vitamin D treatment group had a significant improvement in baseline score compared to placebo (21-23).

In conclusion, severe AD in adolescents may adversely affect their linear growth and weight gain through different mechanisms. Loss of albumin through the inflamed skin, low zinc and vitamin D status must be compensated by proper medical treatment of inflammatory cutaneous condition and by appropriate nutritional support.

The judicious use of steroids and other drugs to inhibit severe inflammation and decrease inflammatory mediators may improve growth in these patients.

Figure 1.
Possible mechanisms of delayed growth in patients with atopic dermatitis.



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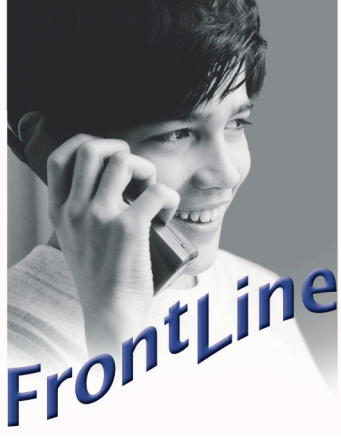

La terapia 'appropriata' ...un personal trainer o un tapis roulant?

Solveig Cogliani

Magistrato del TAR - Lazio.

Il tema dell'autonomia prescrittiva è strettamente connesso all'esatta individuazione del concetto di appropriatezza terapeutica. È di questi mesi il vivace dibattito sul nuovo decreto che dovrebbe garantire 'l'appropriatezza' delle prestazioni sanitarie, in un'ottica di razionalizzazione e contenimento della spesa, per ottenere risparmi nel settore, anche attraverso lo stop ad esami e visite inutili, ovvero "*inappropriate*". Per tali esami, infatti, è stato stimato un costo ogni anno di circa 13 mld per il Servizio Sanitario Nazionale. Peraltro, le Regioni saranno chiamate a garantire un'applicazione omogenea dei nuovi criteri di appropriatezza su tutto il territorio.

Non può sfuggire come si tratti di un tema molto complesso, in cui ogni approccio non può che seguire un metodo sistemico, integrato da aspetti etici, economici [1] e giuridici, tenendo in considerazione esigenze diverse:

- la necessità di garantire a tutti le cure, contenendo gli sprechi e l'imprescindibile libertà del medico di scegliere la cura più adeguata al singolo paziente,
- i principi di libera concorrenza,
- la specificità dei farmaci biotecnologici.

In tale contesto, la problematica dell'autonomia prescrittiva è questione che attiene alla prescrizione dei farmaci biotecnologici, quanto alle indagini diagnostiche, e per affrontarla non può che sottolinearsi che il centro di ogni discorso non può che essere e deve rimanere l'uomo. Ed, in quest'ottica, anche la lettura dell'art. 32 della Costituzione, deve avvenire alla luce degli altri diritti e doveri scolpiti nella Carta costituzionale, quali l'obbligo di adempiere ai doveri di solidarietà, quello di rispettare la dignità della persona, di assicurare il pari trattamento a tutti gli individui, e soprattutto, il fondamentale obbligo di rispettare la libertà individuale che si esplica anche nell'inviolabile diritto di scelta della cura da intraprendere.

Da tale affermazione ne discendono necessariamente altre due:

- da un lato, il medico, nella sua scienza e coscienza, dovrà sentirsi libero di prescrivere al paziente le cure che egli ritenga maggiormente idonee a raggiungere un beneficio;
- dall'altro, le procedure di acquisizione dei farmaci dovranno consentire una approvvigionamento adeguato alle indicazioni '*date*' e '*rilevate*' dai medici curanti.

I limiti dell'autonomia prescrittiva: il quesito

Per fare un esempio, traendolo dalla medicina dello sport, si può pensare alla formula di Karvonen: essa è utilizzata per misurare il parametro di intensità nell'esercizio cardiovascolare e per pianificare l'allenamento sportivo sulla base della frequenza cardiaca (ritmo cardiaco). Perché? Perché essa costituisce – a differenza di altre formule approssimative - il metodo più accurato per misurare la percentuale della frequenza cardiaca massima individuale, perché nello stabilirne i valori tiene conto di parametri soggettivi.

Ed il punto del quesito oggetto della presente indagine è tutto qui, ovvero nell'individuazione della cura. Se è vero che il Sistema Sanitario Nazionale ha subito varie modifiche che hanno visto il passaggio e la trasformazione da un sistema fondato sulla visione universalistica ed egualitaria all'emersione dei c.d. livelli essenziali di assistenza e all'emergere della necessità di ripianamento dei disavanzi, non si può prescindere dai principi fondamentali del nostro ordinamento, che sono impressi dalla Carta costituzionale e dal ricordare che il concetto di appropriatezza terapeutica risulta già puntualmente disciplinato dalla legge dello Stato: al centro di tale contesto normativo rimane certamente l'individuo.

Così per tornare all'approccio iniziale, ogni paziente è diverso, per così dire, ha una frequenza cardiaca differente, con la conseguenza che l'allenamento (ovvero la terapia) più appropriato non potrà essere un generico percorso sul tapirulan, eguale per tutti, ma dovrà consistere in un *training* personalizzato, individuato dal medico curante. Tali considerazioni, peraltro non prescindono dal dato economico, in quanto, sia il concetto di appropriatezza terapeutica, ne contiene in sé il significato, sia – in effetti – la terapia '*migliore*' o meglio più appropriata, sarà per l'appunto anche quella in grado di avere efficacia nel minor tempo possibile, di ridurre il tempo di ricovero ospedaliero, di ridurre al massimo gli sprechi con indubbie ripercussioni positive anche sul contenimento della spesa sanitaria globale.

Conclusioni

Quale autonomia prescrittiva? Non può essere che "*Tutta*", ovvero tutta quella necessaria a consentire la scelta del farmaco più

appropriato alla luce del concetto di appropriatezza terapeutica (di cui all'Accordo collettivo nazionale reso esecutivo dal d.P.R. n. 270 del 2000, ed alla luce delle responsabilità già previste dall'ordinamento, cfr. il d.l. n. 323 del 1996, come conv. In l. n. 425 del 1996) e del principio di autonomia prescrittiva nella scelta del presidio diagnostico-terapeutico da applicare di cui all'art. 12 del codice deontologico.

Per prescrizione appropriata si intende, infatti: quella che risulti tale da garantire (per quantità, qualità e modalità di somministrazione della cura) – un miglioramento delle condizioni del paziente, sicché da essa è già espulso ogni comportamento prescrittivo che induca il paziente ad un consumo di farmaci incongruo o inadeguato. Afferma il richiamato Accordo che è onere del medico "*lo sviluppo e la diffusione del corretto uso del farmaco nell'ambito della quotidiana attività assistenziale*".

In tale contesto, dunque, l'efficacia dell'intervento, che concreta il concetto di appropriatezza, consiste nel comportamento del medico che deve sempre finalizzare la prescrizione al fine di ottimizzare il rapporto mezzi (farmaci-indagini) al risultato ovvero al miglioramento della salute del paziente in modo da raggiungere il massimo risultato con il minimo impiego di principio attivo. La funzione del medico prescrittore è già dunque, secondo la normativa vigente, quella di rendere possibile l'assunzione di un onere a carico dell'amministrazione sanitaria, essa è necessariamente connessa al concetto di '*appropriatezza terapeutica*', come precisato, in quanto il medico nell'adempiere al proprio compito:

- è tenuto ad assicurare "*l'appropriatezza nell'utilizzo delle risorse messe a disposizione dalla Azienda per l'erogazione dei livelli essenziali ed appropriata assistenza*",
- ricerca "*la sistematica riduzione degli sprechi nell'uso delle risorse disponibili mediante adozione di principi di qualità e di medicina basata sulle evidenze scientifiche*",
- effettua le sue prescrizioni, secondo "*scienza e coscienza*".

Il medico è sì coinvolto, dunque, negli aspetti gestionali, essendo tenuto ad un corretto uso del farmaco, ma la scelta terapeutica rientra nella sua esclusiva sfera volitiva e, dunque, nella sua esclusiva responsabilità innanzitutto etica e deontologica. Non si tratta di un'illimitata discrezionalità del medico, perché la giurisprudenza ha evidenziato che il medico ha l'obbligo di attenersi ai criteri dettati in sede nazionale e che il suo comportamento può essere sindacato in relazione alle scelte compiute dalla generalità degli altri medici, salvo comunque la possibilità per il medico prescrittore di poter provare la particolarità della patologia trattata.

Nota

Sul punto, con specifico riferimento alle procedure di evidenza pubblica per le forniture, non possono che assumere rilievo le indicazioni contenute nella nuova direttiva appalti 24/2014/UE riguardo al concetto di economicamente vantaggioso, laddove il considerando n. 90 rivaluta come criterio di selezione delle offerte quello della "*qualità*".

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Myxoedema coma: A report in an adolescent with aplastic anemia and iron overload

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Summary

We report a 14 year old girl who developed myxedema coma, a rare life-threatening condition that has not been reported before in patients with aplastic anemia and iron overload. Treatment consisted of L-thyroxine, supportive measures and appropriate management of infection. In addition, the patient was treated with glucocorticoids in stress doses. After 17 days of hospitalization she was discharged in stable condition on L-thyroxine (75 µg daily) and intensive iron chelation therapy. After 35 days, the FT4 and TSH levels were in the normal range.

Key words: Myxedema coma, Aplastic anemia, Iron overload, Treatment.

Coma mixedematoso in una adolescente con anemia aplastica ed emosiderosi

Riassunto

Viene descritto un caso clinico di coma mixedematoso in una ragazza di 14 anni in terapia trasfusionale e chelante dall'età di 4 anni. Gli autori descrivono gli aspetti diagnostici e terapeutici ed il decorso clinico. La ragazza è stata dimessa dopo 17 giorni di ricovero ospedaliero in condizioni stabili ed in trattamento con L-tiroxina e terapia chelante intensiva. La funzionalità tiroidea è rientrata nella normalità dopo 35 giorni.

Parole chiave: Coma mixedematoso, Anemia aplastica, Emosiderosi, Terapia.

Introduction

Aplastic anemia (AA) is a rare disorder characterized by hypocellular bone marrow in the absence of an abnormal infiltrate resulting in progressive pancytopenia. The incidence is 2-3/million inhabitants/year, in Europe, but higher in East Asia. Acquired aplastic anemia may develop at any age. The age distribution of the disease shows two peaks, one between 10 and 25 years, and a second among the over 60 year-olds. There is no sex predilection (1, 2). The severity of the disease is graded according to the blood count parameters and bone marrow findings (Table 1). Survival in severe aplastic anemia (SAA) has markedly improved in the past 2 decades because of advances in hematopoietic stem cell transplantation, immunosuppressive and biologic drugs, and supportive care with red cell (leukocyte-depleted blood products) and platelet transfusions (4-8). Immunosuppressive therapy, including cyclosporin and antithymocyte globulin, is used in patients for whom bone marrow transplantation is not an option, with response rates of 60–80% (6-8). However, supportive care with red blood cell transfusions is also essential in many patients. Iron overload can, therefore, become a significant problem in regularly transfused patients, leading to organ damage, particularly in the liver, endocrine glands and heart (1, 2, 6). Iron chelation therapy is recommended in case regular transfusions become a persistent requirement when serum ferritin levels exceed 1,000 ng/ml (1, 2, 6). We report a 14 years old girl who developed myxedema coma, a rare life-threatening condition, that has not been reported before in patients with AA and iron overload.

Case history

A 14 year-old girl was admitted last November to the Department of Pediatrics for weakness, altered mental status and abdominal pain of one-day duration. A diagnosis of non severe (moderate) aplastic anemia (NSAA) was made at the age of 4 years and since

Table 1.
Classification of aplastic anemia based on severity of pancytopenia (from Ref. 1 and 8; modified).

Severe aplastic anemia (SAA)	Very severe aplastic anemia (VSAA)	Non severe (moderate) aplastic anemia (NSAA)
• Bone marrow cellularity < 25% • Two of three peripheral blood criteria: - Absolute neutrophil count (ANC) < 500/µL - Platelet count < 20,000/µL - Corrected reticulocyte count <1%	Same as SAA with absolute neutrophil count (ANC) < 200/µL	• Bone marrow cellularity < 25% • Peripheral blood cytopenias do not fulfil criteria for SAA

Table 2.
Diagnostic criteria for myxedema coma (Six criteria and points assigned).

GCS	0-10 = 4 points 11-13 = 3 points 14 = 2 points, 5 = 0 points
TSH	> 30 = 2 points 15-30 = 1 point
T4 below normal	1 point
Hypothermia (temperature < 96 F)	1 point
Bradycardic (HR < 60)	1 point
Precipitating illness present	1 point
Scoring	Myxedema coma ≥ 7 likely = 5-7 unlikely < 5

From: *Chiong and Mariash et al.: Development of an objective tool for the diagnosis of myxoedema coma. Endocrinology Review. Indianapolis: Indiana University School of Medicine; 2011. p. 24-6; GCS – Glasgow coma scale, TSH – Thyroid-stimulating hormone, HR – Heart rate*

than she received regular scheduled blood transfusions and chelation therapy with deferioxamine (40 mg/kg of body weight). On examination she was pale, hypothermic (temperature 34.5 °C) and bradycardic (48 beats/min) with fine crackles at base of left lung, pretibial edema, delayed relaxation phase of the Achilles tendon. Abdomen was soft with hepatomegaly and no masses. Pupils were equally round and reactive to light. Fundoscopic exam was normal. Tympanic membranes were clear. Oropharynx was clear. There was no goiter or surgical scar of thyroidectomy. She was short with no signs of pubertal development (Tanner stage breast 1 and pubic hair 1). The blood pressure was 90/60 mmHg. The peripheries were very cold to touch, with a capillary refill of more than 4 seconds. The Glasgow Coma Scale (GCS) score in conjunction with designed diagnostic scoring system for myxedema coma followed by the Indiana University School of Medicine, Indianapolis was 9 (a score ≥ 7 is considered to be highly suggestive/diagnostic of myxedema coma) (Tabele 2) (9). One year before hospital admission her TSH value was 6.7 mU/L (normal: 0.5-4.0 mU/L). TSH and free T4 were ordered. Further testing included a chest radiograph that showed mild cardiomegaly and left lower lobe pneumonia. Urine, throat and blood cultures were also obtained. Sinus bradycardia, low voltage complexes, prolongation of the QT interval and nonspecific ST-T changes in electrocardiogram were recorded. An echocardiogram documented normal left ventricular ejection fraction with the presence of mild pericardial effusion. Additionally, complete blood count, serum electrolytes, glucose, cardiac enzymes, C-reactive protein, and liver function tests were ordered. Clinical, biochemical and hormonal profiles are reported in Table 3. Arterial blood gas testing revealed hypercapnia ($PaCO_2$ 48 mm Hg) and a pH of 7.35. Serum ferritin level was high (2570 ng/ml; normal values: < 250 ng/ml). The hypothermia was treated with passive rewarming using ordinary blankets and a warm room. Broad-spectrum of antibiotics and hydrocortisone IV were started. Given the lack of imminent life threatening conditions, the patients was treated with L-thyroxine (initial dose 4 µg/kg/ body weight) through a nasogastric tube followed by 100 µg daily orally. Thyroid function was checked frequently (every 3 days). Hyponatremia and hypoglycemia were corrected with saline and free water restriction, and intravenous dextrose. The patient's body temperature progressively increased to 36 °C over a period of about 36 hours. Over the next 4 days the biochemical parameters returned to normal values and after 17 days of hospitalization she was discharged in stable condition on L-thyroxine (75 µg daily) and intensive iron chelation therapy. After 35 days, the FT4 and TSH levels were in the normal range. Thyroid ultrasound showed reduced volume of gland and inhomogeneity of the parenchyma.

Discussion

Myxedema coma is a syndrome that results from the intense reduction of the thyroid hormone synthesis. Patients rarely present with coma, thus a more accurate term may be myxedema crisis. It is characterized by an altered mental status, defective thermoregulation, and other symptoms related to slowing of function in multiple organs. Therefore, the diagnosis should be considered in any patient with coma or depressed mental status who also has hypothermia, hyponatremia, and/or hypercapnia. Myxedema coma is difficult to distinguish from sepsis, and since infection is often the precipitating event in a patient with preexisting hypothyroidism, generally the patients must receive empiric antibiotics until sepsis is ruled out (10, 11). In our patient the physical examination findings combined with clinical history strongly suggested a myxedema crisis. The following illnesses were included in the differential diagnosis: sepsis, myxedema coma, toxic ingestion and Addisonian crisis. The results of FT4 and TSH confirmed the diagnosis. Treatment consisted of L-thyroxine, supportive measures and appropriate management of infection. In addition, the patient was treated with glucocorticoids in stress doses (Table 4). The ideal mode of therapy and doses of thyroid hormone therapy in myxedema coma remain controversial due to the rarity of the condition and lack of clinical trials.

Three different regimens have been suggested (12):

1. intravenous or oral T4,
2. intravenous T3 or
3. a combination of T4 and T3. Giving T4 intravenously has been advocated because absorption via the oral route is variable and unpredictable (13). However, one study showed that the clinical response obtained by oral T4 occurred promptly even in a case of myxoedema ileus (14).

Table 3.
Clinical, laboratory findings and management of myxedema crisis in our patient.

Clinical and laboratory findings	Results
Age	14.2 years
Sex	Female
Clinical findings	
Height: cm (percentile)	143 - < 3rd centile
Weight: kg (percentile)	39 - < 1st centile
Tanner stage (Breast-Pubic hair)	1 - 1
Body temperature (°C and °F)	34.5 (93.9)
Blood pressure (mmHg)	95/60
Glasgow Coma Score	9/15
Myxoedema Coma Score*	9
Heart rate (beats/min)	48
Respiratory rate (breaths/min)	10
Pulse oximetry on ambient air	95%
Etiology of myxedema	Hemosiderosis and infection
Hormonal assay	
FT3 (normal:2.6–7.0 pmol/L)	2.0
FT4 (normal: 10-22 pmol/L)	<5.9
TSH (normal: 0.5-4.0 mU/L)	57.7
PRL (normal: 5-20 ng/mL)	8.8
Thyroglobulin antibodies (normal:< 4 IU/mL)	< 4
Thyroid peroxidase antibodies (normal:<9 IU/mL)	< 9
Cortisol level (normal:5-25 μg/dL)	12.5 μg/dL
Culture	
Throat	Negative
Blood	Negative
Urine	Negative
Chest X-ray	Pneumonia
Laboratory findings	
Hemoglobin (normal: 11.3-14.1 gm/dL)	7.6
White blood cells (5-13 x 109/L)	3.330
Serum glucose (normal: 65-99 mg/dL)	94
Serum creatinine (normal 0.3 - 1.1 mg/dL)	1.2
Calcium (normal: 8.4-10.2 mg/dL)	8.8
Sodium (normal: 135-146 mmol/L)	128
Potassium (normal: 3.4- 4.4 mmol/L)	4.5
C-Reactive Protein Test (normal: 0-10 mg/dL)	13.6
Creatine kinase MB (normal: < 7.6 μg/L)	5
Alanine transaminase [ALT] (normal: ≤ 40 U/L)	62
Specific myxedema measures	
Intravenous glucose	+
Hyponatremia correction	+
Oral thyroxine	+
Hydrocortisone	+
Duration of hospital stay	17 days

The *American Thyroid Association* recommends combination therapy with T4 and T3 (15). T4 given IV has a long half-life, so it can be administered once-daily. Liothyronine (T3) has a short half-life and must be administered every 8 hours. Because of concerns about abrupt onset and fluctuating concentrations in tissues, coadministration of T3 with T4 is recommended. Furthermore, the rate of conversion of T4 to the active hormone T3 can be reduced in these patients.T3 has a quicker onset of action than T4, as increases in body temperature and oxygen consumption has been reported to be faster with T3 therapy compared to T4. T3 therapy is given in adults as bolus of 5-20 μg intravenously and to be continued at a dosage of 2.5-10 μg every 8 hours depending on the patient's age and coexistent cardiac risk factors (16, 17). Our patient, due to lack of imminent life threatening conditions and because of severe hemosiderosis was treated with L-thyroxine (initial dose 4 μg/kg/body weight) through a nasogastric tube followed by 100 μg daily orally. She gradually improved and after 17 days of hospitalization was discharged in stable condition on L-thyroxine (75 μg daily) and intensive iron chelation therapy.

The prognosis for patients with myxedema coma is difficult to define because of the small number of cases reported in the literature. One study reported a mortality rate of about 30 percent, while another suggests the mortality rate may be as high as 60 percent. Factors associated with a poor prognosis include advanced age, bradycardia and persistent hypothermia (18, 19).

Interestingly, *Dutta et al*. recently reported from their series of 23 consecutive patients with myxedema coma that L-thyroxine treatment defaulters had more severe manifestations compared with de novo subjects. Moreover, these authors identified various predictors of mortality including hypotension, bradycardia at presentation, need for mechanical ventilation, hypothermia unresponsive to treatment, sepsis, intake of sedative drugs, lower Glasgow Coma Score (GCS), high APACHE II score and high Sequential Organ Failure Assessment (SOFA) score. The latter SOFA score had the best predicted value (20).

In conclusion, a high index of suspicions is needed among clinicians in order to rapidly recognize this condition for making an early diagnosis. Treatment should be commenced on clinical grounds while waiting for laboratory results. It is also vital that these patients receive intensive care level treatment with close monitoring of their cardiovascular parameters and level of consciousness. It is also essential to check periodically the endocrine function of these patients to identify and treat the condition precipitating the coma. Follow-up care after discharge is necessary to ensure adherence with thyroid hormone replacement.

Table 4.

Medical care of myxedema coma (From: Wall CR. Myxedema coma: diagnosis and treatment. Am Fam Physician. 2000; 62:2485-90; modified).

Airway management	Maintenance of adequate airway is crucial, since most patients have depressed mental status along with respiratory failure. The diaphragmatic weakness induced by hypothy roidism is reversed by thyroid hormone replacement. Mechanical ventilation may be necessary.
Supportive measures	Treat hypothermia with passive rewarming using ordinary blankets and a warm room. The use of a rectal probe helps to determine the true core temperature and to monitor rewarming. If mechanical ventilation is prolonged, total parenteral nutrition may be required.
Infection	Infection should always be considered and empiric broad-spectrum of antibiotics be considered until appropriate cultures are proven negative.
Thyroid hormone replacement	The ideal mode of therapy and doses of thyroid hormone therapy in myxedema coma remain controversial due to the rarity of the condition and lack of clinical trials. At present, oral and intravenous T4 and T3 are used. Remember that starting IV levothyroxine without treating adrenal insufficiency can precipitate an adrenal crisis.
Glucocorticoid therapy	Patients with primary hypothyroidism may have concomitant primary adrenal insufficiency. Furthermore, there is a potential risk of precipitating acute adrenal insufficiency caused by the accelerated metabolism of cortisol that follows T4 therapy. Intravenous hydrocortisone is preferred at a rate of 50mg every 6 hours.
Severe hyponatremia	The hyponatremia is a result of decreased free water clearance due to elevated levels of antidiuretic hormone and/or diminished blood flow to the kidneys. Correct severe hyponatremia with saline and free water restriction.
Hypoglycemia	Hypoglycemia may be a result of the down-regulation of metabolism seen in hypothyroidism; it may also indicate the possibility of adrenal insufficiency. Correct hypoglycemia with intravenous dextrose.
Hypotension	Bradycardia, low cardiac output and overall blood volume deficit frequently exacerbate the hypotension. Is usually corrected with thyroid hormone therapy. Infusion of dextrose saline solutions and vasopressors if required.

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Precocious puberty in a girl following severe traumatic brain injury (TBI) in early childhood: A simple coincidence or a possible consequence?

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Summary

True precocious puberty (PP) is rare following external head trauma. We describe the long term follow-up of a girl who developed PP at the age of 7.6 years, after three years of severe head trauma. Severe brain injury may be associated with hypothalamic-pituitary dysfunction including PP; however, the mechanism is not yet well-understood. The current case report highlights the importance of close monitoring of patients following significant head trauma. Children exhibiting signs of early puberty need prompt evaluation by the appropriate Paediatric medical subspecialist.
The diagnosis should include detailed anamnesis and clinical examination, measurement of pituitary and sex hormones, assessment of bone age and imaging of the hypothalamic-pituitary area and gonads. Therapy with a gonadotropin-releasing hormone agonist (GnRH) may be indicated, in selected cases.

Key words: Central precocious puberty, Severe traumatic brain injury, Follow-up.

Pubertà precoce centrale in una bambina prepubere successiva a severo trauma cranico: Una semplice coincidenza o una possible conseguenza?

Riassunto

La comparsa di una pubertà precoce centrale in seguito ad un trauma cranico è un evento di rara osservazione. Gli Autori riportano la personale esperienza in una bambina di 7 anni e 6 mesi. Viene sottolineata l'importanza della anamnesi, dei tests diagnostici e neuroradiologici. Inoltre viene ribadita l'indicazione ad effettuare un attento monitoraggio clinico, auxologico ed endocrino nei bambini che hanno subito un trauma cranico severo.

Parole chiave: Pubertà precoce centrale, Trauma cranico severo, Follow-up.

Introduction

Precocious puberty (PP) in girls is defined as the development of secondary sexual characteristics before the age of 8 years [1, 2]. Its incidence constitutes 1:5000 - 1:10 000 and occurs more frequently in girls than in boys [1, 2].

There are two types of PP, central and peripheral. Central precocious puberty arises from the early maturation of hypothalamic-pituitary axis.

Peripheral precocious puberty arises from premature secretion of sex steroids from gonads or other sites, or due to exogenous exposure. PP can be either isosexual or heterosexual, complete or partial, and intermittent (un-sustained), or progressive.

True PP is usually progressive and reflects the normal sequence of pubertal hormonal maturation occurring at a noticeably earlier age. Early gonadotropin maturation stimulates the gonads to secrete sex steroids which promote the development of somatic sexual characteristics. In addition sex steroids accelerate skeletal maturation and induce a growth spurt that influences final adult height [1, 2]. Therefore, early recognition of PP is important for two main reasons: to diagnose the underlying aetiology and to slow the accelerated skeletal maturation to prevent its negative effect on final adult height.

In girls, true PP accounts for > 80% of the cases of central PP. The most frequently detected brain abnormalities associated with true PP include hypothalamic hamartomas, optic gliomas, astrocytomas, pineal tumours, post-infectious encephalitis, hydrocephalus, neurofibromatosis and previous CNS injury [3-7].

True PP is rare following external head trauma. We describe the long-term follow-up of a girl who developed central PP within three years of severe exogenous head trauma.

Case report

An 8.8 yr girl was admitted to our Paediatric Endocrinology service for assessment of early puberty starting one year before referral (Tanner stage B2 at the age of 7.6 years). She was born following a normal pregnancy with a birth weight of 3.16 kg and length of 52 cm as the first child of non-consanguineous parents. At the age of 4.7 yr she was admitted to the Paediatric Intensive Care for severe head trauma [Glasgow Coma Score (GCS) < 8] secondary to an accidental fall. Magnetic resonance imaging (MRI) demonstrated mild cerebral edema and absence of focal hypothalamic injury.

On physical examination, her height (Ht) was 127 cm (23° percentile), weight was 31.2 kg (72° percentile), body mass index (BMI) was 19.3 kg/m^2 and head circumference was at 25th per-

centile. Breast and pubic hair were at Tanner stage 3. No goitre was present. Blood pressure was 105/55 mmHg. Her psychomotor development was normal. Her blood cell count, renal and liver function tests and the levels of plasma glucose and electrolytes were in the normal range.

Serum thyroid stimulating hormone (TSH), basal follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were within normal limits (FSH: from 6 to < 11 years = < 0.1-4.3 IU/liter; LH: from 6 to < 11 years = <0.1-5.0 IU/liter). After provocation test with intravenous GnRH 2.5 μg/Kg, serum LH and FSH rose to peak levels of 17.2 IU/liter and 6.4 IU/liter (IMMULITE 1000 DPC, Los Angeles, CA), respectively. Basal 17 ß estradiol was 249.5 pmol/liter (normal values from 6 to < 11 years = < 73.4-216.53 pmol/liter). Basal levels of cortisol (19.5 μg/dL), prolactin (13 ng/ml), IGF-1 (185 ng/ml), dehydroepiandrosterone sulphate (DHEAS) (30 μg/dl); and 17 hydroxiprogesterone (0.95 ng/ml) were in the normal range for sex and Tanners' pubertal staging [8, 9].

Bone age as determined by Tanner Whitehouse RUS-method III was 10.8 yr. Pelvic ultrasound showed a bulky uterus (4.2 cm in length with endometrial thickness of 5.7 mm) and her ovaries were 2.5 and 2.8 ml in volume with two large follicles (0.9 cm and 1 cm). Brain MRI showed a normal pituitary gland with a mild upper convexity compatible with the activation of the hypothalamic-pituitary gonadal axis.

Clonidine stimulation test was performed to exclude partial growth hormone deficiency (GHD). This was done because of the reported high prevalence of GHD after TBI (up to 42%) [10, 11]. Basal GH was 1.1 ng/ml and the peak was normal (16.2 ng/ml). Her parents refused treatment with LH-RH analogue.

The patient was regularly followed up every 4 months. The pace of her pubertal development was normal and she had her first menstrual period at the age of 9.10 yr (the age of menarche in the mother was 12 years). At that time her height was 144.6 cm (86° percentile), weight was 43.2 kg (91° percentile) and bone age was 12.6 yr. Pubertal assessment according to Tanner staging was B5 and PH4. In the following 3 years menstrual cycles were regular. The patient's final height is 152 cm (4° percentile), (mother's Ht: 160 cm - 31th percentile; father's Ht: 170 cm - 20th percentile).

Discussion

There is a considerable risk of developing pituitary dysfunction after TBI in children, adolescents and adults. Road-traffic accident, falls, sport injuries, child abuse and shaking injury are the most common etiological factors for paediatric TBI [12-15].

The commonest post-TBI chronic endocrinopathies include hypothalamic-pituitary dysfunctions and diabetes insipidus. Studies have reported that anterior pituitary hormone abnormalities may improve, remain stable, or deteriorate in the first 12-36 months following head injury [16, 17].

The precise mechanism by which exogenous head trauma causes PP remains unknown. However, the clinical features of these children are consistent with the hypothesis that extra-hypothalamic areas which restrain pituitary gonadotropin secretion before puberty, when damaged by the trauma (as demonstrated by MRI), can result in early activation of hypothalamic-pituitary-gonadal axis pubertal axis. Direct mechanical injury and/or hypoxic insult to the hypothalamus, pituitary stalk or pituitary gland secondary to haemorrhage, edema, and increased intracranial pressure are incriminated [12, 16, 17].

CPP is rare following external head trauma. Our patient was admitted to the outpatient pediatric endocrine clinic at the age of 8.8 years for assessment of early puberty, starting one year before referral. There was no family history for precocious puberty. The biochemical criteria for diagnostic confirmation of CPP vary in the literature but are mostly based on the LH response during a standard GnRH test [18]. In our patient, LH response to GnRH stimulation (> 5 IU/liter) in accordance with the recent consensus guidelines established the diagnosis of central PP following her severe TBI reported in early childhood [18-20].

At the first examination the BMI was in the normal range and the MRI showed normal anatomy of the hypothalamic-pituitary region. The progression of pubertal changes with precocity varies. Some children show a normal tempo of sexual maturation from the time that puberty is initiated, whereas others show a staccato pattern of maturation that progress to a more gradual pubertal development. Others who begin early puberty show steady progression but often at a tempo that is much slower than with normal puberty. Although the average interval from normal breast development to menarche is 2 to 2.5 years, about 20% of girls do not menstruate for 4 or more years after the first signs of puberty [1, 2, 21].

In our girl, the interval between Tanner stage B 2 to menarche was normal (2.5 years).

Previous studies on the biochemical evaluation of girls with CPP post-TBI are not well detailed. Only a few case reports or small case series have highlighted a link between TBI and hypothalamic-pituitary hormone abnormalities. In a recent systematic review, 25 patients were reported [23]. The youngest patient was 2.1 yr old and one-third were below 6 years at their first endocrine evaluation. The time interval from the occurrence of TBI and the age at first endocrine assessment ranged between 3 months and 3 years [22, 23]. The follow up of these patients was not regular. Some had a fast progressive puberty, one had menarche at the age of 7.5 yr and some were treated with LH-RH analogues. A delay in referring the patient for endocrine evaluation was reported by some authors [23].

In conclusion, CPP is rare following external head trauma. Although some Authors believe that the rate of precocious puberty after TBI is unlikely to exceed that of the normal population, others believe that the occurrence of CPP after TBI, is not a simple coincidence but a possible consequence of TBI [23]. The majority of patients who develop CPP after TBI had severe

injury as assessed by Glasgow Coma Scale or by significant structural damage (skull fractures, intracranial haemorrhage or cerebral injury) detected by CT or MRI [23].

Children exhibiting signs of early puberty need prompt evaluation by an expert paediatric specialist. The diagnosis should include detailed history and clinical examination, measurement of pituitary and sex hormones, assessment of bone age and imaging of the hypothalamus-pituitary area and gonads. Close long-term clinical follow-up of children after severe TBI is required to evaluate their rate of growth and pubertal development. Therapy with a gonadotropin-releasing hormone agonist may be indicated, in selected cases.

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International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A)

Potential diagnostic and therapeutic use of Continuous Glucose Monitoring Systems (CGMS) in Thalassemia Major: A short presentation of personal experience

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Abstract

The prevalence of diabetes insulin dependent (DM) and impaired glucose tolerance (IGT) in adolescents and young adults with TM conventionally treated with desferioxamine (DFO) varies in different series (up to 10.5 % and 24 %, respectively). The most accurate method with which to evaluate altered glucose metabolism in patients with TM is still controversial. It has been demonstrated recently that the continuous glucose monitoring system (CGMS) is a useful and valid tool in defining glucose metabolism in children and adults affected by TM with early glucose derangements. CGMS is also an useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment of glucose homeostasis in TM patients and response to therapy. The Authors report their experience for the diagnosis and treatment of glucose abnormalities in thalassemia.

Key words: Thalassemia major, Glucose abnormalities, Continuous Glucose Monitoring System (CGMS).

Introduction

Glucose tolerance abnormalities and diabetes mellitus are common complications in thalassemia patients. Pancreatic iron loading in thalassemia major (TM) patients begins after the first decade of life and the incidence increases with age. While glucose intolerance occurs at an earlier stage during adolescence, diabetes frequently occurs at later stages and is usually secondary to iron overload and subsequent chronic liver disease (1-4). Up to 25% of patients with TM may have isolated impaired fasting plasma glucose (IFG) a condition considered as a pre-diabetic state. However; it is not known how many TM patients with IFG may progress over the years to diabetes (1,2). The prevalence of diabetes insulin dependent (DM) and impaired glucose tolerance (IGT) in adolescents and young adults with TM conventionally treated with desferioxamine (DFO) varies in different series (up to 10.5 % and 24 %, respectively) (1-4). In general, 51% of TM patients have impaired insulin secretion, 32% have increased insulin secretion and 19% have delayed insulin secretion (4) These conditions are believed to precede the clinical expression of diabetes mellitus. Elevated serum ferritin concentrations and hepatitis C infection have long been considered as important factors associated with the development of abnormal glucose tolerance in TM patients (1-4). Zinc deficiency might lead to an exacerbation of the inability of the pancreas to secrete sufficient amounts of insulin in response to oral glucose load in TM patients (5, 6). A family history of diabetes does not seem to be not a significant predictor for future diabetes risk (5-7). The considerable variation in the occurrence of glycemic abnormalities can be partially explained by the marked differences in the cohort's genetic background, transfusion regimens, degree of chelation, screening method used and also relates to the ages of patients being studied, with lower rates in younger patients.

Diagnostic value of CGMS in patients with TM

The most accurate method with which to evaluate altered glucose metabolism in patients with TM is still controversial. Even if the annual oral glucose tolerance test (OGTT) by the age of 10 years is the recommended method, a diagnosis of 'normal' glucose tolerance during OGTT does not exclude abnormal postprandial glucose levels at home (1, 2, 8). There is now evidence that the OGTT method, evaluating fasting and 2-h post load glucose, may miss episodes of hyperglycaemia (8-10). Furthermore, the credibility of Hb A1c has been questioned because the hemoglobin composition of patients' erythrocytes are considerably modified, due to regular and frequent transfusions. The results may be falsely increased or decreased depending on the proximity to transfusion, shortened erythrocyte lifespan and the assay used (11-15).
It has been demonstrated recently that the continuous glucose monitoring system (CGMS) is a useful and valid tool in defining glucose metabolism in children and adults affected by TM with early glucose derangements (10–15). Indeed, the CGMS allows monitoring of glycaemic profiles throughout a period of 72 h for a total of 288 glycaemic registrations per day. It identifies glycaemic excursions and constitutes a valid device to understand the 24-h glycaemic trend and profiles. *Rimondi et al*. investigated the value of using CGMS in six TM patients with abnormal glucose homeostasis after an oral glucose tolerance test (OGTT) (10). Two-hour OGTT glucose values and CGMS fluctuations were classified as normal if < 7.8 mmol/l, impaired if 7.8 to 11.1 mmol/l, diabetic if > 11.1 mmol/l. The TM patients spent from 1 to 23% of the time with a blood glucose level from 7.8 to 11.1 mmol/l. In five patients the CGMS confirmed the impaired glucose tolerance diagnosis and in one patient the CGMS excluded the diagnosis of diabetes. A case report in Oman studied the use of CGM as a follow-up tool in a TM patient with abnormal glucose homeostasis (16). Both studies suggest that CGM is a useful method to detect glucose levels in these patients. Similarly, we studied 16 adolescents with TM (19.75 ± 3 years) using OGTT and CGMS for 3 days. Using OGTT 25% had IFG, 12.5% had IGT and one of them had diabetes. Using CGMS the maximum BG (3h postprandial) 25% had diabetes and 56% had IGT. Serum ferritin concentrations were correlated significantly with the fasting BG and the 2-h blood glucose levels in the OGTT as well as with the average BG recorded by CGM (17). *Albaker et al*. showed that using CGMS detected diabetes state in 2 thalassemic patients who had HbA1C in the impaired glucose range. Furthermore, the study showed a direct relationship between the time of the first transfusionand the CGM results (18).

Therapeutic (monitoring) value of CGMS in patients with TM

CGMS is a useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment of glucose homeostasis in TM patients and response to therapy (8, 10, 16, 18).
CGMS was useful in documenting a poor glycemic control in a 27-year-old woman, with prolonged periods of hyper- and hypoglycemia. Her blood sugar levels showed suboptimal control (erratic, unexplainable blood glucose readings throughout the day that ranged between 120 and 300 mg/dL [6.6–16.7 mmol/L]),with significant hyperglycemia in the morning.
Based on these results, her insulin regimen was adjusted and the blood glucose levels were greatly improved throughout and the patient was able to meet her target blood glucose range (72–140 mg/dL [4–7.8 mmol/L]) in 70% of the time (8).

Personal experience

Patient 1
A 15 year old male with TM presented with nocturia. His FBG was 5.6 mmol/L and OGTT showed a BG level at 2hrs of 8.5 mmol/l. His CGMS showed a diabetic range of BG after dinner and overnight. Based on this tracing, a basal insulin (Glargine) was prescribed at night. A satisfactory response was recorded by CGMS (Figure 1).

Patient 2
A 14 year old girl with TM with no symptoms related to glycemic abnormalities. Her FBG was 4.9 mmol/L and an OGTT showed a BG level at 2 hrs of 6.9 mmol/L (IGT). CGMS tracing showed prolonged persistent hyperglycemia after lunch suggesting a need for prandial insulin to cover her carbohydrate load. Insulin aspart before lunch properly controlled her glycemia (Figure 2).

Patient 3
A 13 year old boy with TM had a normal FBG

Figure 1.
CGMS before and after insulin glargine (each day different color of curve).

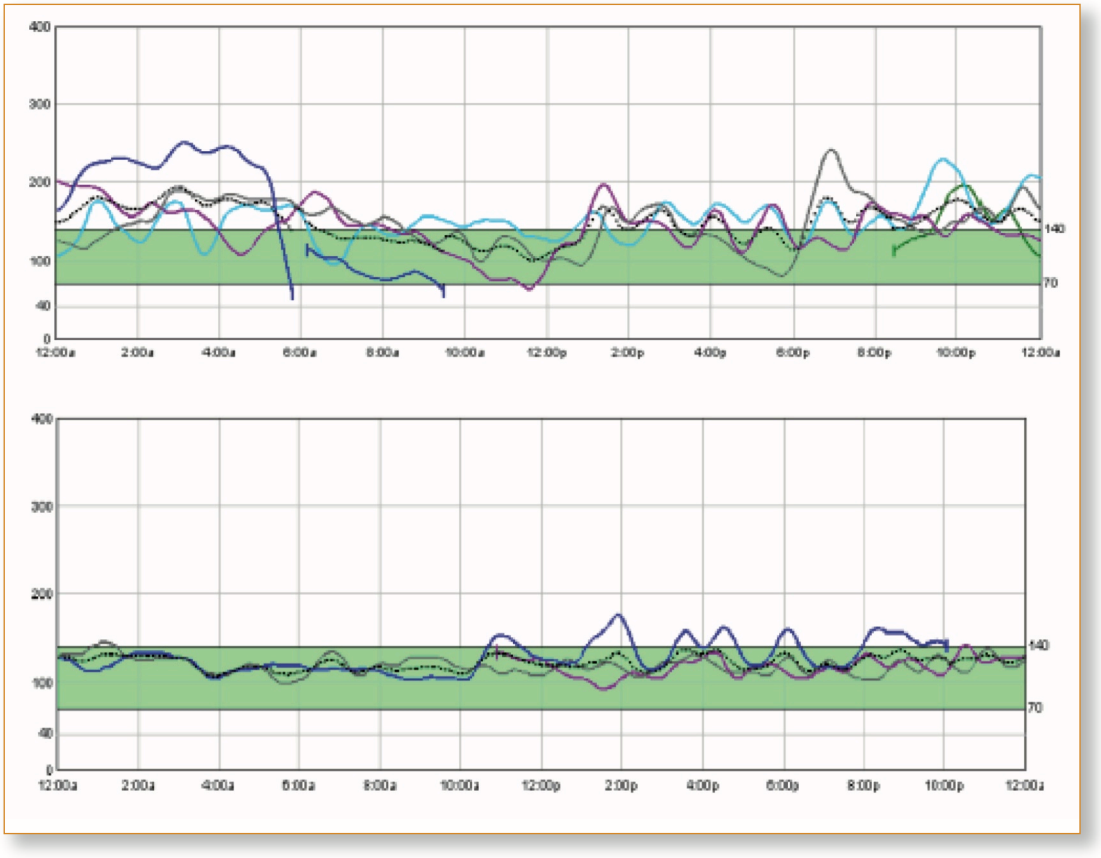


Figure 2.
CGMS before and after insulin aspart (each day different color of curve).

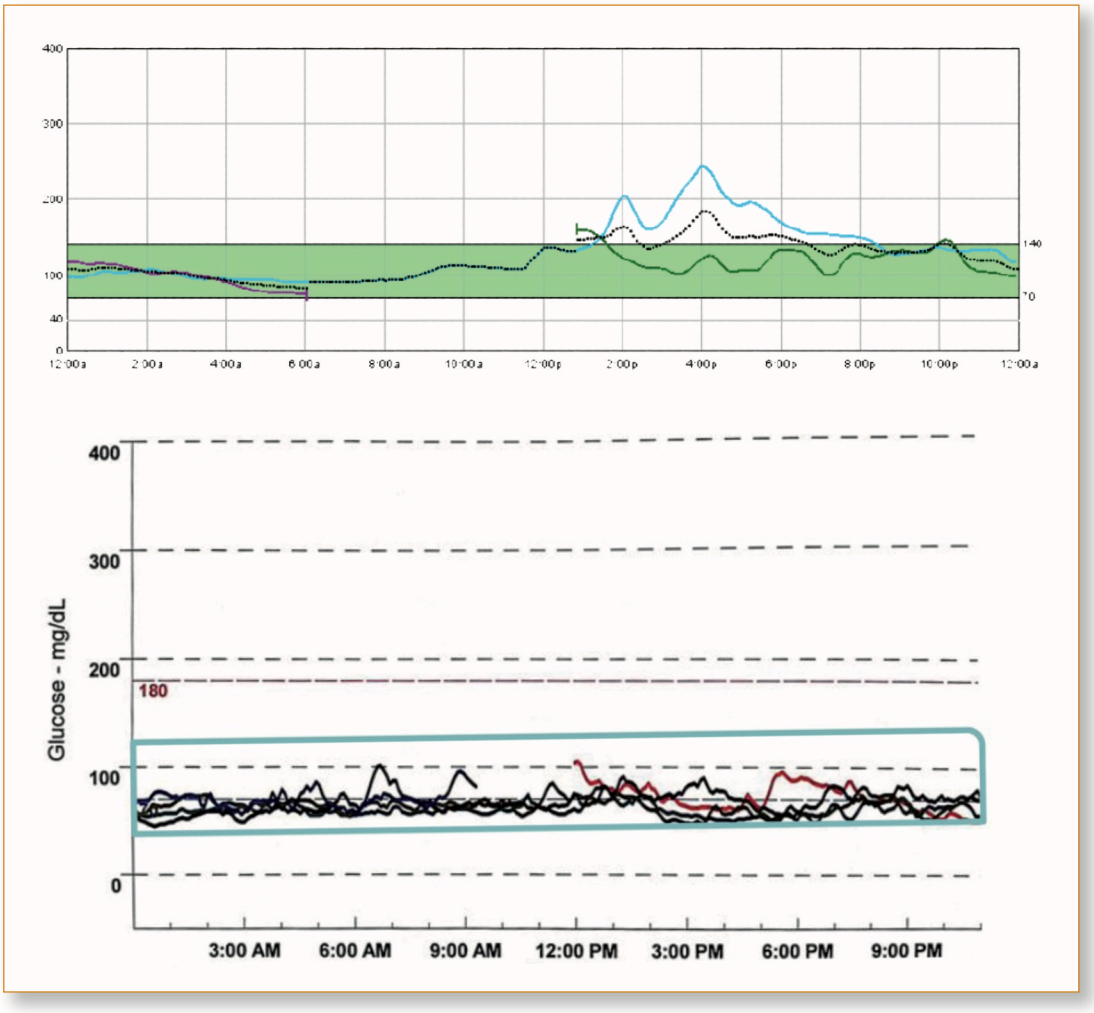
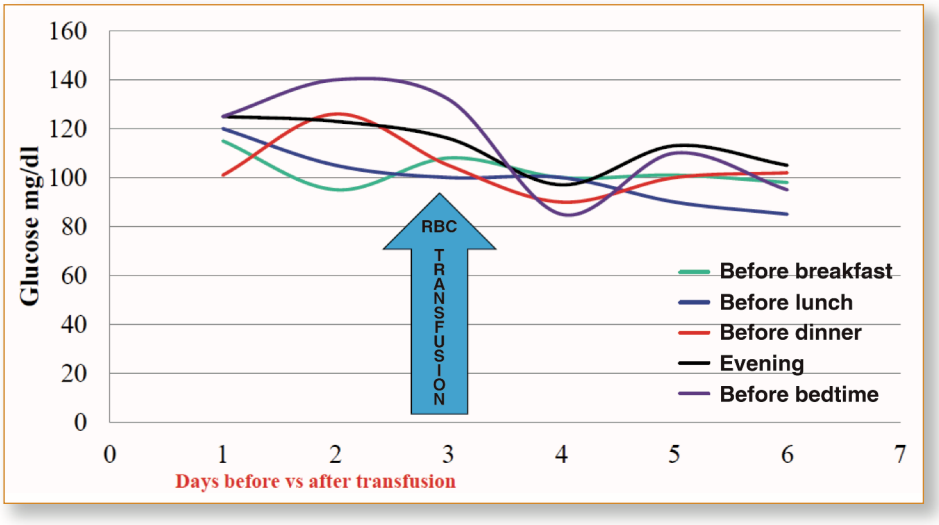


Figure 3.
Effect of transfusion (packed blood red cell; blue arrow) on blood glucose using CGMS.



(4.5 mmol/L) and OGTT (2h BG =7.6 mmo/l). Applying CGMS monitoring showed IGT state. Furthermore, the effect of packed red cell transfusion showed marked reduction of his BG before meals and overnight. This is the first case to document the rapid beneficial effect of blood transfusion on glycemia in a thalassemic patient (Figure 3).

Conclusions

Advances in TM care have led to improved survival and quality of life in patients with TM; however, many chronic endocrine diseases have emerged as a result of potential endocrine complications by routine screening and a high index of suspicion is imperative for patients with TM to receive timely treatment.Our results demonstrate that the CGMS is a useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment of glucose homeostasis in TM patients. Proper and early iron chelation or the use of intensive iron chelation in those with high iron load the new oral chelators have been shown to decrease or reverse these glycemic abnormalities.In addition, optimization of insulin therapy with the help of CGMS appears to be clinically useful and cost-effective approach.

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Declaration of Interest:
The authors report no conflicts of interest.

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