Amyloidosis : Recent Trends and Updates in Diagnosis and Treatment

Protocol of Essay

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الداء النشواني: الاتجاهات الحديثة وتحديثات من التشخيص والعلاج

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Dalia El-Sayed Makled

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5-HT	5-hydroxytryptamine
AApoAI	Apolipoprotein A-I
AApoAII	Apolipoprotein A-II
ACD	Amyloidosis cutis dyschromia
AFA	Abdominal fat aspiration
AFib	Fibrinogen a α-chain
AGel	Gelsolin.
AL	Amyloid light chains
ALys	Lysozyme.
anti-SAP	Anti serum amyloid p
ASCT	Autologous bone marrow stem-cell transplantation
Aß2M	Amyloid beta-2 microglobulin
ATTR	Amyloid transports thyroxine and retinol
ß2-M	B2-microglobulin
CA	Cutaneous amyloidosis
CAA	Cerebral amyloid angiopathy
CKs	Cytokeratins
CO2	Carbon dioxide
CPHPC	Carboxy-pyrrolidin-hexanoyl-pyrrolidine-carboxylic acid
CREST	Calcinosis, raynaud phenomenon, esophageal motility disorders, sclerodactyly, and tangiectasia
CRP	C-reactive protein
DCs	Dendritic cells
DFLC	Difference between involved and uninvolved free light chain
DLQI	Dermatology life quality index.
DMSO	Dimethyl sulfoxide
EAC	External auditory canal
EBV	Epstein-barr virus.
EGCG	Epigallocatechin-3-gallate
ER	Endoplasmic reticulum
FAP	Familial amyloidotic polyneuropathy
FFPE	Formalin fixed, paraffin-embedded.
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FMF	Familial mediterranean fever
FPLCA	Familial primary localized cutaneous amyloidosis
GAGs	Glycosaminoglycans

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H&E	Hematoxylin and eosin
HDM	High-dose melphalan
HRQoL	Health-related quality of life
HSPG	Heparan sulphate proteoglycans
Ig	Immunoglobulin.
IHC	Immunohistochemical.
IL	Interleukin
IL31RA	Interleukin-31 receptor alpha
ISA	International society of amyloidosis
kPLCA	Keratinic primary localized cutaneous amyloidosis
LA	Lichen amyloidosis
LECT2	Leukocyte chemotactic factor 2
LMD/MS	Liquid chromatography/ tandem mass spectrometry
LSG	Labial salivary gland
MA	Macular amyloidosis
MCP-1	Monocyte chemotactic protein-1
MENDs	Microscopic epidermal necrotic debris
MMP-1	Metalloproteinases 1
MTZs	Microthermal zones
NA	Nodular amyloidosis
NAFL	Non-ablative fractional laser
NB-UVB	Narrowband ultraviolet B
Nd: YAG	Neodymium-doped yttrium aluminum garnet
NLPCA	Nodular localized primary cutaneous amyloidosis
NT-proBNP	N-terminal pro-brain natriuretic peptide
OSMR	Oncostatin m receptor
OSMRβ	Oncostatin m receptor-beta
PCA	Primary cutaneous amyloidosis
PLCA	Primary localized cutaneous amyloidosis
PUVA	Psoralens ultraviolet A
RNAi	RNA interference
ROS	Reactive oxygen species.
SAA	Serum amyloid a protein
SAP	Serum amyloid p component.
SCT	Stem-cell transplantation
SPF	Sun protection factor
SS	Sjögren's syndrome
ssNMR	Solid-state nuclear magnetic resonance
T_4	Thyroxin
TEM	Transmission electron microscopy

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TENS	Tanscutaneous electrical nerve stimulation
ThT	Thioflavin T
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
TTR	Transthyretin (transports thyroxine and retinol)
UV	Ultraviolet
UVB	Ultraviolet B

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Introduction

Amyloidosis is a generic term referring to abnormal extracellular deposition of heterogenic, misfolded, proteinaceous substances. They are composed of one of a family of biochemically unrelated proteins. These proteins are deposited in the form of insoluble oligomeric and polymeric protein fibrils in various tissues leading to architectural and functional changes of tissue ***(Kaltoft et al., 2013 and Bouaity et al., 2014).***

The description of the autopsy of a young man in 1639 by Nicolas Fonteyn, a Dutch physician and poet who lived in Amsterdam, was probably the first patient reported with systemic amyloidosis. The term ‘’Amyloid’’ was first used in 1838 by Schleiden, a German botanist, to describe the cellulose-like substance of plants ***(Touart and Sau, 1998).***

In 1854, Rudolph Virchow was one of the first to use the term amyloid for this amorphous and hyaline change in tissue because of an iodine-staining reaction similar to that of starch (amylon; Greek for origin). Although it is now known that amyloid has nothing to do with starch, the term amyloid is still used today ***(Hazenberg, 2013).***

While amyloidosis has been known since the 19th century, it is only within the last few decades that our understanding of it has matured. Although it is common in south east Asia including Japan and Taiwan, it is uncommon in Europe and North America ***(Quddus et al., 2014).*** The incidence of amyloidosis, although hard to calculate, is estimated to be 8 per million persons per year, in England, and accounting for 85% of all cases in developed countries ***(Gertz, 2014).***

Amyloidosis typically appears in middle-age and older individuals and even, occasionally, younger persons. The risk of developing the disease is greater in people who are 50 years and older **(*Terrier et al., 2008),*** have a chronic infection or inflammatory disease, have a family history of amyloidosis, have multiple myeloma (about 10% of patients with multiple myeloma also develop amyloidosis) and have a kidney disease that requires dialysis for several years ***(Steciuk et al., 2002).***

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Amyloidosis ranges from being localized ‘’ affecting only one tissue or organ’’ to systemic types. Furthermore, each of these, is subclassified into primary and secondary types ***(Bhat et al., 2010).***

However, despite the morphologic similarity in different clinical settings, amyloid is heterogeneous with respect to the nature of the amyloid fibrils. Therefore, classification of amyloidosis has been controversial and difficult for a long time ***(Steciuk et al., 2002).***

Although localized cutaneous amyloidosis, in general, is not life threatening condition, it usually presents with itchy, hyperkeratotic papules and plaques. Skin becomes hyperpigmented, lichenified or, in rare variant, may develop waxy nodules that ulcerate and bleed. These disfiguring skin conditions, in addition to itching, may lead to psychosocial and emotional effects that may have a significant impact on quality of life ***(Fang et al., 2015).***

However, secondary localized cutaneous amyloidosis type is commonly associated with several skin tumors, both benign and malignant, such as squamous cell carcinoma. Which, increased the mortality rates in cases with localized cutaneous amyloidosis ***(Touart and Sau, 1998).***

In contrast to localized amyloidosis, systemic amyloidosis leads to serious life threatening conditions such as: nephritic syndrome, renal failure, liver cell failure, cardiomyopathy, dyspnoea, syncope secondary to orthostatic hypotension, alternating bouts of constipation and diarrhea, splenomegaly, adrenal dysfunction, paresthesiae, peripheral neuropathy and bleeding tendency. These diseases are caused by the progressive deposition of amyloid materials in organs such as: Kidneys, liver, heart, gastrointestinal tract, adrenal glands, nerves and skin ***(Hazenberg, 2013).***

Amyloidosis is a tissue-based diagnosis. Biopsy of classical mucocutaneous lesions is the procedure of first choice ***(Westermark, 1995).*** However, in the absence of evocative cutaneous lesions, biopsies can be done elsewhere. Abdominal subcutaneous fat, rectal, gingival or renal biopsies are thought to be useful ***(Steciuk et al., 2002).***

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The available treatments depend on, the amyloidosis type and the organs affected, as well as on the patient's age, condition and personal preference, and the prognosis of amyloidosis and its life expectancy are adversely affected by this factors, too ***(Wechalekar et al., 2013).***

While the average survival rate in familial amyloidosis is up to 15 years, the average survival rate is about 12-18 months in primary systemic and myeloma-associated amyloidosis without treatment and only about 6 months for patients with severely impaired heart function. The main cause of death is being cardiac and renal failure, and is linked to degree of plasma cell clonality and marrow infiltration ***(Perfetti et al., 1999).*** Staging systems and prognostic markers have predominantly focused on cardiac markers ***(Kumar et al., 2012).***

Therapy of primary cutaneous amyloidosis (PCA) is not standardized and many treatment modalities have been used with variable success ***(Maurelli et al., 2015).*** Despite the presence of various therapeutic modalities for primary cutaneous amyloidosis (PCA), none is considered curative or satisfactory ***(Bandhlish et al., 2012),*** and since the disease runs a chronic course, therapeutic management remains challenging ***(Kalkan et al., 2014).***

The treatment of the disease is inadequate, even if there are several alternatives for treatment, either, conventional or novel treatments, these include: topical and systemic treatments ***(Love et al., 2008).*** But As more data on the pathophysiology of primary localized cutaneous amyloidosis (PLCA) becomes available, new and more targeted treatments can be used for this condition ***(Yew and Tey, 2014).***

The precursor-product concept is the current basis of treatment, thereby aiming to decrease the levels of precursor proteins in serum to normal or undetectable values. Future clinical research will be directed at stopping amyloid deposition and increasing amyloid clearance ***(Hazenberg, 2013).***

There are various therapeutic modalities for PCA have been proposed for cutaneous amyloidosis that improves the cosmetic appearance of the lesions; Among these modalities, ultraviolet light therapy Such as ultraviolet (UV) A1 phototherapy ***(Maurelli et al., 2015)***, narrowband ultraviolet B (NB-UVB) phototherapy and

photochemotherapy ***(Lee et al., 2014).*** And physical therapeutic options such as: surgical excision, cryotherapy, dermabrasion ***(Wong, 1990)***, curettage, electro curettage and electrodessication ***(Aoki and Kawana, 2009).***

Unfortunately, however, the recurrence rate in certain types of cutaneous amyloidosis is high; thus, the need for new approaches for treatment options ***(Norisugi et al., 2014).***

There are many successful laser treatments include: carbon dioxide laser ***(Esmat et al., 2015)***, pulsed dye laser ***(Sawamura et al., 2005)***, frequency-doubled Q-switched yttrium aluminum garnet (Nd: YAG) laser ***(Liu, 2000),*** Recently, fractional ablative 2,940nm Erbium: yttrium aluminum garnet (YAG) laser ***(Anitha and Mysore, 2012)*** And non-ablative fractional 1,550nm Yttrium/Erbium fiber laser (NAFL) used ,too ***(Panchaprateep et al., 2015).***

In addition, this technology shows a clinical outcome equivalent to ablative fractional laser with a more favorable safety profile, especially in darker skin type ***(Lee et al., 2014).***

In general, there are no preventive measures for amyloidosis. However, the secondary forms of amyloidosis could be prevented by treating the underlying diseases. In addition, genetic counseling can be beneficial in prevention of familial amyloidosis.