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RESEARCH ARTICLE

AUTOIMMUNE/INFLAMMATORYSYNDROMEINDUCEDBYADJUVANTS (ASIA) –REVISION

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Abstract

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), also known as Shoenfeld□s syndrome, encompasses several autoimmune conditions andphenomena that are induced following the exposure to substances with adjuvant activity. The disease spectrum is heterogeneous in respect to clinical presentation as well as severity of the clinical manifestations. Some genetically predisposed individuals can develop generalized non-specific symptoms, autoantibody production, new onset, or worsening of disease presentation. In this review, we focus on the current knowledge presented in the literature on ASIA syndrome, increasing awareness about the basic concepts and highlight the amount of data accumulated in the last few years concerning the relationship between various adjuvants and autoimmunity.

Introduction:-

The explanationofthedevelopmentofanautoimmune / autoinflammatorydisease,alsoknown as Shoenfeld'ssyndrome, isextremelycomplexbecause it istheresultofaninteractionofseveralfactors, especiallyenvironmentalandgenetic. Proving a cause-and-effect link between a compoundand a clinicaldisorderisoneofthemostdifficultandcomplicatedissues in medicine andusually requires atleasttwoelements: statisticallysignificantreproducibleassociationandplausibleunderlying components[1]

In recentyears, as immune-mediateddiseasestransformedintooneofthemain causes ofmorbidityandmortalityworldwideandwithincreasingprevalenceandcharacteristics, in differentgeographical areas.[2]

The evolutionorworseningofanautoimmunedisease are alsoanamnesticsigns, butanysymptomswouldbe a consequenceofseveraldysfunctionsofanimmunologicalnature, triggeredbyexposuretoan adjuvant.[3]Geoepidemiologicalchanges are relatedtogeneticsusceptibility, in which a personmaybeabletodevelopanautoimmuneorautoinflammatorydisease (AI / AIFD) afterexposuretoanenvironmental factor.[4] A geneticpredispositionis, however, probablynecessary for thedevelopmentofanautoimmuneorautoinflammatorysyndrome, butthepresenceofanexternalenvironmentalfactororendogenous, referredto as the "exposoma", seemsessentialatthebeginningofanimmune response.[5]

Anexample, constant as anadjuvant in theliteratureis silicone. Widelyused in breastimplants, it canbehave as anadjuvantand cause ASIA syndrome in some women. It isworthmentioningthatinfections, toxinsandcertaindrugs, such as hyaluronicacid, wererelatedtotheoccurrenceofimmune-mediatedconditionsandtheirclinicalmanifestations[6]

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Withtheadventoftheincrease in the use ofadjuvantsubstances, thematerialsused in aesthetic medicine, theobjectiveofthisarticlewasto review theimportanceof ASIA, in aesthetic medicine, andtoelucidatetheassociationbetweenexposuretovariousadjuvantagentsandtheirpossibleclinicalmanifestations, duetothesignificantincrease in reported cases, afterthe use of silicone, botulinumtoxinandfillers.

ASIASyndrome

The ASIA syndromewasdescribedbytheFrenchmanGehardi et al, in 1998 [7], with a post-vaccinationetiologyand muscular impairment. However, thetermAdjuvant-InducedInflammatoryAutoimmuneSyndromewasonlyused in 2011, duetotheexpressiveandgrowingincrease in disorderscharacterizedbydysregulationoftheinnateandadaptiveimmune system afterexposuretotheadjuvant[8].

ASIA, consistsof a macrophagemyofasciitiswithcytopasmaticinclusionoftheadjuvant, whoseclinicalmanifestations include asthenia, chronic fatigue, myalgia, arthralgia, fever. Demyelinatingpolyradiculopathy, clinically similar to Guillain-Barré disease, withelectroneuromyographicchangeshasbeendescribed[9].

However, in thelastdecade, a series of case reportsassociatedwithseriousimmunological adverse events, includingautoimmunediseases, havebeenobservedwhenusingbotulinumtoxinandhyaluronicacid, used in aesthetic medicine [10].

Contrastingtheexistenceof ASIA Syndrome, Ameratunga et al. (2017) statethatthefactthatpatientswithdefinedautoimmunediseasesmaynotfitthe ASIA diagnosticcriteriarepresentsevidence for theirrelevanceofthe syndrome[11]. However, thedefinitionof ASIA wasdesignedtodescribealltheautoimmune processes inducedbyadjuvants, it isinherenttothedefinitionthatcertainexpressionsofspecificautoimmunediseasesfallunder.

Geneticcorrelationand ASIA

Ofthemanygenetic loci involved in predispositiontoautoimmunity, themostprominent are thosethatcode for MHC class II molecules, which are responsible for presentingantigenstoimmunecells. Althoughtheexactmechanismthat links thesemoleculestoautoimmunityremainsundefined[12].

Anacceptedtheory relates totheaberrantpresentationofantigens for autoreactive T lymphocytes, resultingfromtheseallelicvariationsof MHC molecules, such as certain HLA DRB1 alleles. The geneticsusceptibilityassociatedwithautoimmunityresultsfromthetransportofcertain MHC alleles, as anevolutionarytoll, as thesegeneticcharacteristicscanprovide a survivaladvantage for thosewithanoveractiveimmune system, whichwouldbe more effective in fighting infections[13].

Triggers

The clinicalimportanceofthissyndromeisassociatedwiththeadjuvantterm, which denotes severalsubstancesthat lead totheactivationoftheinnateimmune system patternrecognition receptor (PRR), in ordertoincreasetheimmunologicalreactivityto antigens[14].

Some authorshavecorrelatedthissyndromewiththeadventof new aesthetic procedures withsubstances, such as liquidparaffin, silicone gel, acrylamides, hyaluronicacidandmethacrylatecompounds, whichhaveadjuvant properties[15].

Amongthesematerials, identified as foreignbodybehavior, were silicone (in 12.5% of cases), hyaluronicacid (HA) (in 29.2% ofindividuals) andpolyacrylamide (MAP) (in 37.5% of cases) [16].

The average time betweenexposuretoforeign material andtheonsetofclinicalsymptomswasonemonthandrangedfrom 2 weeksto 5 yearsaftertheonsetofthe syndrome.[16]

The twopolygenicautoimmunediseasesmostcommonlyreportedafterexposuretoforeign material were UCTD andSjogren'sdiseasewith a percentageof 19.4% and 2.6%, amongwell-definedwell-definedimmunediseases, respectively[16.]

Adjuvance - themechanismsofaction

The role ofadjuvants in thedevelopmentofautoimmunitywasconfirmedthroughexperimentsonmurine models, demonstratingtheabilityofvariousadjuvantstoinduceanincrease in theproductionofinflammatorycytokinesassociatedwiththeappearanceofautoantibodiesrelatedto lupus[17]

The adjuvanteffectiscarried out throughvariousmechanismsthataffecttheinnateandadaptiveimmune systems [18] Its actionistoincreaseinnateimmune responses bysimulatingevolutionarilyconservedmoleculesandthebindingtoToll-like receptors (TLRs) in addition, theyenhancetheactivitiesofdendriticcells (DCs), lymphocytes, macrophagesandactivatetheintracellularinflammatory system Nalp3 [19]

Thus, adjuvantsincreasethe local reactiontoantigens (for example, attheinfection site) and, subsequently, the release ofchemokinesandcytokinesfrom T-helperandmastcells[20].

The adjuvantmostused in medicine isaluminum. in vaccination, whichby molecular patternsassociatedwithdanger release, amongothers, uricacid, whichformcrystalsofmonosodiumurate. Thesecrystals are phagocytizedbytheresidentcellsanddisruptthefunctionsofthelysosomes. Thisresults in the release ofcathepsin B, whichcandirectlyorindirectlyactivatetheintracellularinflammatory system Nalp3, and caspase-1. In doingso, aluminumstimulatestheproductionandsecretionofcytokinessuch as IL-1β; IL-18 and IL-33.[21]Anotherimportantfunctionistoprovidephysicalprotectiontotheantigensandassist in thetranslocationoftheantigento regional lymph nodes. Thiswillallow for a greaterproductionandactivationof B and T cellsand a more robust response. The adjuvanteffectontheadaptiveimmune response isalsomediatedbytheactivationofthe Nalp3 inflammasome, whichcontributestotheinductionofadaptive T-2 (TH2) adaptive responses, such as interleukin-4 (IL-4) and IgE production.[21]

Althoughveryuseful, adjuvantscanbethe trigger for autoimmunityand trigger autoimmunediseases[22] The moststudiedadjuvantistetramethylpentadecane (TMPD) known as pristane, whichiscapableofinducing a lupus-like disease in a murine model ofsystemiclupuserythematosus (SLE) andthemostdescribed as a trigger for ASIA was silicone. [23]

In this model, similarlytohumandisease, theproductionofautoantibodiesanddamagetothe target organ (ie, kidneydisease) dependsonthesignalingpathwayofthe interferon receptor (IFN) -I.[23]

Immunizationofanimalswithpristaneacceleratedtheproductionof IFN-I bymonocytes via signalingbymeansof TLR-7 andtheadapterprotein MyD88 [24]Immunizationwithanotheradjuvant, squalene, inducesarthritis in ratsandtheproductionofautoantibodiesassociatedwith SLE in mice. Adjuvantaluminummaybecontained in immune complexes producedaftervaccination. [8]

Silicone oil

Silicone oilis a well-known granuloma inducerandcommerciallyused in themanufacturingprocessofmostsyringesavailableonthemarket. It dependsonthesiliconizationof its internal surface ofthecylinder, thisprocessfacilitatesthereductionofthe force toinitiatethemovementofthepistonand its subsequentsliding[25].

Thus, lubricatedsyringescan release dropletsof silicone oil, especiallywhenagitated, whichcan, throughinjectedsolutionscontaminatedwith silicone oil, cause health complications[26].

Theseparticleswillundergophagocytosis, withsubsequentformationof granuloma andmigrationthroughthe lymphatics.[5]Clinically, lymphandcutaneousnodulescanbeobserved, commonlydiagnosed as sarcoidosisduetodifficulties in the standard histopathological technique.[27]

It shouldalsobeemphasizedtheimportanceof silicone oil as a trigger for non-specificrheumaticdiseases, andmayalso trigger autoimmunediseasesorautoinflammatorydiseases. In thenearterm, theeffectof silicone oildepositionisthedevelopmentof ASIA syndrome[28], widelydescribed in manystudiesandincorporating immunomediatedconditions, alllinkedtoexposuretovariousagents, such as vaccinesand silicone implants[8].

The adjuvant role ofinfections

Severalmechanismsbywhichinfectiousagentscangenerateautoimmunityandorautoinflammatory responses havebeenestablished. Amongthemost common are molecular mycimetism, disseminationoftheepitope, polyclonalactivationandothers[29]

Epidemiologicalevidencesuggeststhatinfectiousexposure in earlychildhoodmay set thestage for theappearanceofanautoimmunedisease later in life[30]Thisnotionisconsistentwiththeobservationthatautoimmunity (ieautoantibodies) appearsyearsearlierof a developedautoimmunediseasebeingdiagnosed[31]

Other mechanismswithanadjuvanteffect, bywhichinfectionsmayberelatedtoautoimmunity, havebeenreported. Although common, theappearanceofanautoimmunedisease, having a bacterialcomponent as anadjuvant, andnotsowidespreadandapparentlynotalwaysspecifictotheagent. The adjuvanteffectof microbial particles, thatis, the non-antigenicactivationofinnateandregulatoryimmunity, as well as theexpressionofvariousregulatorycytokines, can determine whetheranautoimmune response remainslimitedandharmlessorprogressto a developed disease.[32]

Hyaluronicacid as anadjuvant

Nodulescanoccurduetoincorrectdistributionoffiller material, reactiontotheproduct (includinginflammation, hypersensitivityorgranulomatousreaction) orinfection[33]

Althoughthesefindingsclearlydemonstratethepotentialofcertainadjuvantstodirectlyinduceautoimmunity, the ASIA theoryrefersto a broaderinteractionthatinvolvestheexposureofindividualsgeneticallysusceptibletoadjuvants, alongwithadditionalenvironmentalfactorsthatcan trigger autoimmunity[34]

Calciumhydroxyapatitewasthefillerthatwasmostassociatedwithcomplications (2.6%) [35].

Late reactionsto HA-basedfillers are estimatedtooccur in approximately 0.02% oftreatments 36 The twomost common polygenicautoimmunediseasesafterexposuretoforeign material were UCTD andSjogren'sdiseasewith a percentageof 19, 4% and 2.6%, amongimmunediseases, respectively.[35]

Diagnosis

Shoenfeld[37], (2011) suggestedcriteriathat ASIA diagnosis, whichcan help [38], recognition. For thediagnosisof ASIA: atleastthepresenceoftwo major criteriaorone major criterionandtwominorones as canbeseenbelow:

Major criteria:

• Exposuretoanexternalstimulus (infection, vaccine, silicone, adjuvant) beforeclinicalmanifestations.
• Appearanceofoneoftheclinicalmanifestationsbelow:
- Musclepain, myositisormuscleweakness;
- Joint painand / orarthritis;
- Chronic fatigue, non-restfulsleeporsleepdisorders;
- Neurologicalmanifestations (lossofstrength, lackof balance, musclespasms)
- Cognitiveimpairment, memoryloss
- Fever, drymouth;
• Removaloftheinitiatingagentinducesimprovement.
• Typicalbiopsyoftheorgansinvolved.

Minor criteria:

Appearanceofautoantibodiesdirectedagainstthesuspectedadjuvant.
• Other clinicalmanifestations (eg, irritablebowelsyndrome).
• Specific HLA (eg HLA DRB1, HLA DQB1).
• Emergenceofanautoimmunedisease (egmultiplesclerosis, systemicsclerosis).

Laboratoryfindingsamong ASIA syndrome cases

The patientshadelevatedacutephaseproteinsandcreatinekinase (CK). His groupalsoconfirmedthetheorythattherarityofthecomplicationwasduetogeneticsusceptibility, sinceonlypatientswith HLA profile DRB1.[39]

BasedonthefindingsofWatad, et al (2019), the status oftheautoantibody profile, 54.4% ofpatientshad a positive autoantibody test. Specifically, 48.2% were ANA positive, 7.0% were positive rheumatoidfactor (RF), 6.0% were positive for anti-SSA, 3.8% positive for anti-TPO, 3.4% positive for anti -dsDNA, 2.2% for centromere, 2.0% for anti-Sm, 1.8% for anti-RNP, 1.0% for anti-Scl70 and, finally, 1.0% for anti-SSB. Stratifying for thediseasesubtype, 55.4% ofpatientswithwell-definedimmunediseaseand 16.7% ofthosewithundefinedautoimmune / autoinflammatorydiseasewere positive for atleastone autoantibody.[10]

Treatment

Pharmacological

Amongpatientswith ASIA syndrome in general, 2.4% and 10.2% weretreatedwithbiologicalagentsanddisease-modifyingantirheumaticdrugs (DMARDs), respectively, while 13.6% hydroxychloroquineand 34.0% prednisoneorotherglucocorticoids[10].

Non-pharmacological

Explantationoftheforeignbody, implanted, significantly improves symptoms.[34]

Considerations

In thelastdecade, ASIA syndrome, definedby a hyperimmune response, hasbeendescribed in geneticallysusceptiblepeople, afterexposuretoenvironmentalfactorsthatact as adjuvants.

In addition, littleisdiscussedaboutthelubricationofsyringeductswith silicone, whichislittleknownamonginjectorsandbasedonstudiesbyBacker, et al (2016), ASIA syndromeis more likelyto trigger RheumatoidArthritis, SjögrenandRaynaud, in patients in contactwithadjuvants[40]

AccordingtoYamaguchi'sdiagnosticcriteria, thepresenceoffever, arthralgia, adenopathy, splenomegaly, rashandleukocytosis in theabsenceof ANA andrheumatoidfactorallowsusto diagnose ASIA [41].

The time betweenadjuvantimplantationandtheonsetofsymptomsis variable[42], butclassicallyintermittent high fever, arthralgia, pink spots, cervical lymphadenopathyandferritinandelevated CRP are ofinteresttothe case confirmation[43] The treatmentsusedoften lead toremovaloftheadjuvant material.

Theseenigmatic, syndromicandrecentclinicalfindingsshouldawaken in the medical injectorstheconstantupdatingofpossiblecomplicationscausedbyhypersensitivity, in patientsafterthe use ofaestheticsubstances.

This review demonstratesthat, exposuretocomponentsthatcompriseanadjuvanteffect, canovercomegeneticbarriersandco-exposureto triggers, startingautoimmunediseases.

Thus, thereported data allowustohave a broadviewofthisnewlydefinedpathogenesisandcanfacilitatethesearch for preventiveandinterventionistactions.

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