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Newborn with Giant Non-Involuting Congenital Hemangioma: Mechanisms of Allodynia, Hyperalgesia and Treatment

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Abstract

In a newborn affected by a non involuting congenital hemangioma we measured allodynia through the application of a standard tactile stimulus and hyperalgesia through the regular administration of the Comfort scale which rates pain intensity. The baby presented signs of these pathological events over long periods of the disease. They may be attributed to the high amount of the nociceptive ligands in the hemangioma microenviroment and to the elevated concentration of TNF-alpha and IL-6 in the blood. For a long time, the pain was relieved by a combination of opioids, adjuvants and paracetamol, but also by thalidomide and unexpectedly by interferon alpha. A mechanism-based pain treatment needs to take into account the processes underlying pain and also the ongoing pathology.

Keywords

Pain Mechanisms, Allodynia, Hyperalgesia, Newborn, Treatment

1. Introduction

Tumors produce a series of algesic substances and mechanisms, differing based on the cancer stem cells and the various cytokines, chemokines, growth factors and immune cells crowding the microenviroment. Congenital hemangioma is a rare fetal tumor, whose nature and signaling pathways remain elusive. Recently, somatic missense mutations in codon 209 (Gln 209) in GNAQ and GNA11 have been found in this hemangioma variant [1]. A study has shown a marked VEGF-R1 up-regulation in this form, compared to the others [2]. Pain in these patients has been occasionally mentioned, but never investigated.

Noxious stimuli activate the nociceptive system, when the stimuli are repetitive and intense, they give rise to its sensitization. Allodynia and hyperalgesia are signs and symptoms which mirror such a hyperactive neural condition Allodynia is a painful response to a normally innocuous stimulus [3], while hyperalgesia is a pain response to a noxious stimulus, more prolonged and intense than expected [3]. Allodynia generally occurs in an area close to the site of the injury, rarely remote, always unaffected. By contrast, hyperalgesia occurs at or around the place of the lesion, primary or secondary hyperalgesia respectively. Primary hyperalgesia results from a peripheral sensitization, *i.e.* an increased nociceptor excitability [3] [4] [5], while secondary hyperalgesia and allodynia arise from a central sensitization, *i.e.* an amplification of neural signalling within the CNS [3] [4] [5]. To develop, this state requires sustained afferent peripheral input which causes heightened neuron membrane excitability, a strengthened synaptic efficacy and a reduced inhibition. The flow in the pain pathways ascending to the brain is thus enhanced and the nociceptive system undergoes an increased gain. These phenomena may take place in adults, but also in children [6] and newborns [7] [8]. In these subjects they have been assumed [6] [7] [8], having been investigated in few experimental and clinical settings [6] [8].

Molecular mechanisms engaged to activate the nociceptive system differ widely from those developed to sensitize it. Distinguishing signs and symptoms given by each of these conditions are, to some extent, attainable and very useful to plan a phenotype-based pain therapy [9]. However, while buffering brain activity changes may be feasible, reducing the nociceptor hyper-response is more challenging, since the key molecular pathways, responsible for the over-sensitivity, remain mainly undefined. Indeed, the multitude of stimuli able to activate and sensitize nociceptors [10] [11], the specific transducers [10] [12] and the second messenger cascade [5] [10] [12] are still under study. In this setting, the examination of the milieu in which these processes take place may yield a theoretical framework suggesting the mechanisms operating in generating pain.

An infant affected by a sometimes excruciating pain due to a giant non involuting congenital hemangioma (NICH) was referred to our Intensive Care Unit. To identify the mechanisms underlying pain, we proceeded to a detailed profiling over time of the different sensory signs and symptoms she presented, aiming to capture the changes occurring in sensitivity, in particular where and when they took place. We combined these observations with the ongoing clinical and laboratory findings to search for a plausible etiological association. Then established the treatment which in many instances proved curative for the pain and disease.

2. Case Description

2.1. Clinical History

Female, 38 weeks post-conceptional age, body weight 2.700 Kg. Born with a giant cervico-facial hemangioma, the baby underwent multiple biopsies, on the

4th day after birth. Owing to a rapid expansion of the hemangioma, a 9-week course of vincristine (0.05 mg/kg /week, 101st-164th day) was prescribed, followed by a 16-week course of interferon alfa (1.000.000 U, 170th-282nd day). When discontinued, the infant manifested an improved general condition, and just over one month later was discharged from the hospital. Fifteen months afterwards, due to an enormous growth of the mass, she was treated with thalidomide (starting dosage: 0.5 mg/day; increase: 5 - 6 mg/weekly, upped dosage: 40 mg/day, 5th-133rd day). The therapy resulted in a slight reduction of the hemangioma, but also in a transient sensory and motor distal neuropathy. In the blood, TNF-alfa and IL-6 levels were very often high (66.4 pg/ml; 34.9 pg/ml, peak levels), slowly lowering during the thalidomide intake (14.3 pg/ml; 12.7 pg/ml, highest levels). She died at the age of 3 years as a consequence of a massive bleeding.

2.2. Measurement of Pain and Tactile Allodynia

Spontaneous pain intensity was measured by nurses, every six hours and as necessary, administering a version of the Comfort scale. This is a multidimensional observational scale composed of items grading behavioral and physiological pain indicators, whose psychometric properties have been widely proven [13]. The items weighting the respiratory rate dimension were removed, since the infant's breathing was irregularly supported by different respiratory devices. Scores range 8 - 40.

To quantify the allodinia, the response to light tactile stimuli was tested every morning at 9 a.m. before drug bolus administration. A clinically trained researcher gently stroked a cotton bud (Artsana, Italy; 0.38 gms = 3 mN ~) along about 1 cm, possibly in the same apparently healthy zone, 0.5 cm distant from the neoplasm borders, when the baby had been quiet and wakeful or irregularly sleeping for at least 10 minutes [14]. Besides the respiratory items, items assessing the allertness state were also removed, since some of them were *a priori* excluded by the instructions for the test administration. Score range: 7 - 35. The test was suspended when spontaneous pain was equal to or greater than 36.

2.3. Histology and Immunohistochemistry

H &E staining revealed numerous focal calcifications and extensive hypoxia and necrosis zones. 4 μm-thick serial sections of formalin-fixed and paraffin-embedded hemangioma sample were microweved at 500 W for 10 minutes, the endogenous peroxidase activity was then blocked with 3% hydrogenase peroxidase solution. The sections were incubated at room temperature for 1 hour with the following primary antibodies: monoclonal mouse anti-human CD34 class II clone QBEnd 10 (1:50; Dako, Golstrup, Denmark), monoclonal mouse anti-human CD31 (1:50; Dako, Golstrup, Denmark), polyclonal rabbit anti-human VEGF (A-20) (1:50; Santa Cruz Biotechnology, Inc, CA, USA), monoclonal mouse anti-human CD68, clone KP 1 (1:100; Dako, Golstrup, Denmark), polyclonal rabbit anti-human GLUT-1 (1:100; Dako, Golstrup, Denmark). The bound antibody was visua-

lized by the avidin-biotin peroxidase complex and fast red. Nuclear counterstaining was performed with Gill's haematoxylin no. 2 (Polysciences, Eppelheim, Germany). The primary antibodies were omitted in the negative controls. Intense staining for CD34, CD31 and VEGF A-20 was observed in the endothelial cells which were negative for GLUT-1 immunoreactivity. Numerous CD 68 and VEGF A-20 positive cells were identified in the stromal tissue. A Leica DMR-x microscope equipped with a Leica DC 500 digital camera (Leica Wetzlar Germany) was used.

2.4. Pain Phenotype and Treament

First stay in NICU: *Time course of spontaneous pain and allodynia*.

The newborn was admitted to NICU soon after birth. A few hours later she began to exhibit a high arousability towards nursing care and to display pain behaviors when innocuous tactile stimuli skimmed close to the hemangioma (comfort scale: 16; peak score) (**Figure 1(a)**). This response was interpreted as dynamic tactile allodynia, so the sensory test was introduced in the daily monitoring work-up and a continuous midazolam infusion (peak rate: 3 ɣ/kg/min) was started with benefit, alfentanil (5 ɣ/kg/h) being added after multiple biopsies. At the 45th day, the mass appeared to slightly increasing in size while the baby started to complain again (comfort scale: 22, maximmum rating) and to display a moderate pain to the cotton bud brushing (comfort scale: 21, highest score). At this point, midazolam was replaced by gabapentin (**Figure 1(b)**), which was rapidly titrated to 10 mg/kg/day, and by clonazepam (0.02 mg/kg/day, at 8 p.m.) (**Figure 1(c)**); an adequate analgesia, lasting many days, was rapidly achieved. As the hemangioma underwent a notable expansion, the baby began to show spontaneous severe pain and a heightened pain response to the allodynia testing (comfort scale: 32 and 30, maximum ratings). Gabapentin and clonazepam were successfully raised to 20 mg/ kg/ day and to 0.025 mg/kg/day (**Figure 1(b)** and **Figure 1(c)**), while methadone was prescribed (**Figure 1(d)**). During vincristine administration, the analgesic therapy initially proved adequate, but over time the infant began to show an increasing spontaneous pain at the hemangioma site and an enhancing painful response to allodynia assessment (comfort scale: 16 and 18, peak scores). Finally, the hypersensitivity extended beyond the mass site and an intense pain arose in large areas of the trunk skin at gentle touching. A further stepwise increment of gabapentin to 40 mg/kg/day, of clonazepam to 0.03 mg/kg/day and of methadone to 0.3 mg/kg/day efficaceously relieved pain. After vincristine discontinuation, interferon was started. Throughout its administration, severe flu-like symptoms swiftly developed, while the spontaneous pain and the pain elicited by cotton bud stroking eaxacerbated (comfort scale: 25 and 26, highest ratings). A supplementation of paracetamol was ineffective, whereas gabapentin (50 mg/kg/day) and methadone (0.23 mg/kg/day) definitevely attenuated pain. As a consequence, methadone was slowly withdrawn, and the adjuvant medications diminished. As interferon was discontinued, the baby appeared free from pain, therefore, after

further scaling down, gabapentin and clonazepam were supended and she was discharged to home.

Second stay in NICU: Time course of spontaneous pain and allodynia.

For 15 months, the baby was always painless, until the hemangioma underwent an enormous growth. On admission to hospital, she appeared to be in unbearable pain (Comfort scale: 39) (**Figure 2(a)**). A stepwise increase of gabapentin (50 mg/kg/day) (**Figure 2(b)**), clonazepam (0.04 mg /kg/day, at 8 p.m.) (**Figure 2(c)**) and methadone (0.3 mg/kg/day) (**Figure 2(d)**) quickly attenuated pain. During the thalidomide intake, despite the gradual reduction in adjuvant analgesics and opioid dosages, the pain intensity slowly subsided and allodynia vanished. As thalidomide was progressively withdrawn, the muscle weakness and pain, the baby had developed in the legs, decreased, fully disappearing one month after its discontinuation.

The last period at home

The infant was discharged with a treatment of gabapentin, which was efficaceous until the death. Throughout the whole duration of the disease, she received recurrent courses of codeine and/or paracetamol as established or when required.

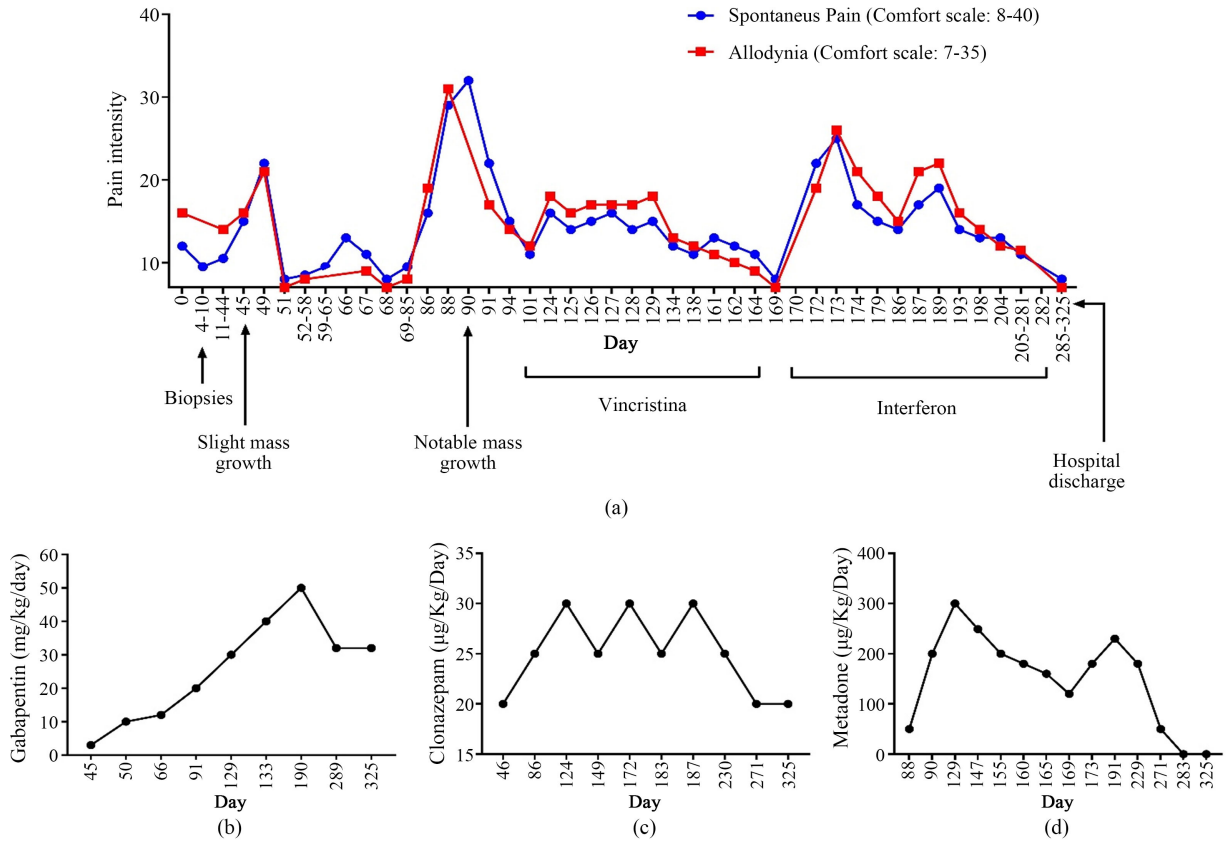

Figure 1. (a) Time course of spontaneous pain and of pain evoked by the allodynia testing. Pain intensity is reported as peak pain intensity per day or period. Salient clinical features, including therapy for disease, are also shown. Allodynia testing was suspended during the post-operative time after biopsies and when spontaneous pain intensity was ≥36. (b), (c), (d). Dosages of gabapentin (b), clonazepam (c) and methadone (d) over time. Peak dosage and the day it was reached are specified.

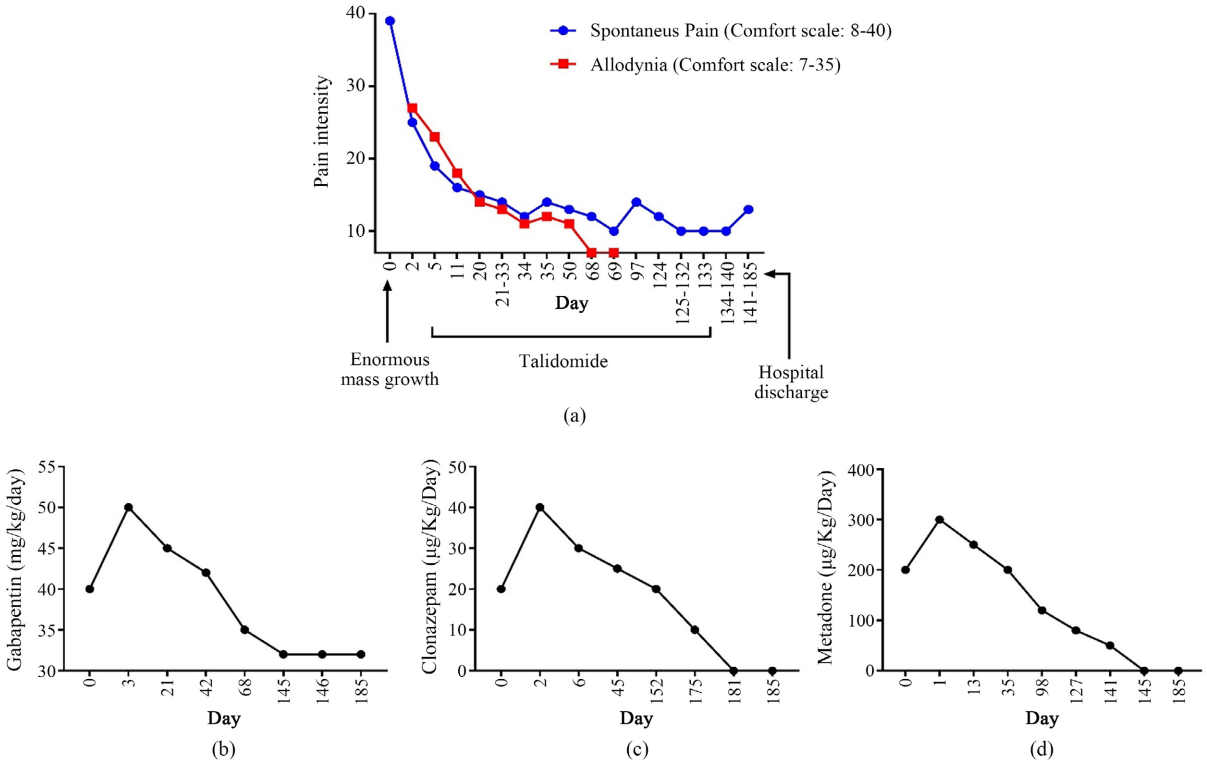

Figure 2. (a) Time course of spontaneous pain and of pain evoked by the allodynia testing. Pain intensity is reported as peak pain intensity per day or period. Thalidomide administration is also shown.Allodynia testing was suspended when spontaneous pain intensity was ≥36. (b), (c), (d). Dosages of gabapentin (b), clonazepam (c) and methadone (d) over time. Peak dosage and the day it was reached are specified.

3. Discussion

Allodynia to touch and hyperalgesia were the main traits of pain over time. A peripheral and central sensitization, due both to an intense neural outflow and humoral input, must be taken into account. These changes responded to pharmacological interventions.

Immunohistochemestry highlighted in the hemangioma tissue a series of biochemical stimuli, able to activate and sensitize nociceptors. Indeed M1 macrophages (CD 68 positive cells) secrete numerous inflammatory cytokines and mediators into the microenvironment [15], exciting sensory neurons. The up-regulation of VEGF, generating a continuous remodelling of the extracellular matrix, promotes the coupling of the molecules, stored there, with receptors [16]. The large pannel of ligands present in the tissue and their high promiscuity in binding common transducers [4] [5] increase nociceptor sensitivity and responsiveness, and hence the action potential. A high persistent flow along the nociceptive paths results in an enhanced post-synaptic N-methyl-D-aspartate (NMDA) and α – amino-3-hydroxy-5-methyl – 4-isoxazolepropionic acid (AMPA) receptor activity, as well as a reduced gabaergic and glycinergic inhibition, and an activation of microglia and astrocytes which likewise modulate synapses functions [3] [5]. A gain of the NMDA and AMPA signaling, following tissue injury and inflammation, has been proven also in neonatal rats. Indeed, the sc injection of an

inflammatory agent at the first post-natal week significantly increases the frequency of miniature excitatory post-synaptic currents (EPSCs), without altering the miniature inhibitory post-synaptic currents (IPSCs) [17]. Regarding glial cells, during early post-natal life, unless potently stimulated, as in the case of an excitoxic NMDA dose administration or bacterial endotoxin intraspinal injection, they develop a weak immune response after an insult [18].

High levels of TNF-alpha and IL-6 were found in the blood of the baby. This condition gives rise to a systemic inflammatory response (SIRS), leading to peripheral and central neural hyperactivity. Indeed, the inflammatory material infiltrating peripheral perfused tissues results in the production by the resident immune cells of further proinflammatory cytokines [19] which may sensitize and/or activate the nociceptive terminals. The inflammatory cells and molecules entering the brain, given the high hemato-encephalic barrier permeability [4], give rise to the production by brain endothelial cells of pro-inflammatory compounds (COX2, PGE2 cytokines) [20] and a robust glia cell activation [4] [20]. Some studies have also shown a direct and distinct action of TNF-alpha and IL-6 on synaptic neurons. Indeed, if exogenously supplied, TNF-alpha enhances NMDA and AMPA induced currents [4] [21], while IL-6 cytokine markedly reduces GABA and glycine activity [4] [21].

The magnitude of allodynia and hyperalgesia is greatly enhanced in newborns and infants, due to the structural and functional frame of the Central Nervous System at this age. In fact, during early life, the A-beta myelinated fibers extend into superficial laminae I of the spinal cord, thus promoting the coupling between the nociceptive and mechanical systems; this interaction is the mechanism underlying allodynia occurrence [7]. Furthermore, in the early post-natal period, the NMDA system is constitutively up-regulated and the descending and local inhibitory pathways down regulated, the resulting hyperexcitability is the physiological substrate for hyperalgesia to take place [22].

Given this background, the primary target of the analgesic drug regimen was to contrast the neuroplastic changes due to the excessive and longlasting nociceptive activity. Gabapentin and clonazepam were therefore administered and their dosages incremented each time additional stimuli excited the nociceptive fibers, both of these drugs reducing the neural hyperactivity [23] [24] [25]. Gabapentin was initiated as the mass began to enlarge, the stretching of the tissues adding further nociceptive stimuli [26] to the stimuli already at play, thus potentiating the afferent discharge. During vincristine administration, the dosage was increased, owing to the spread of mechanical hypersensitivity, resulting from an enhanced, still elusive, gain in neural excitability [27]. During early interferon alpha intake, gabapentin dosage was augmented since this drug, generating a severe flu-like syndrome in our infant, heightened the inflammatory condition and thus the nociceptive afference. Methadone was also given since this opioid reduces the NMDA receptor up-regulation [28]. To combat the nociception, medications exerting contemporaneously an antinociceptive and antiangiogenetic action were casually or deliberately administered. Indeed, paracetamol, given to

reduce pain, while exercising an analgesic effect through the inhibition of cyclo-oxigenase, contrasts angiogenesis through the same pathways [29]. Thalidomide, prescribed to treat hemangioma, by inhibiting VEGF and bFGF-2 [30], produces an anti-angiogenic action and at the same time, by reducing the synthesis of TNF-alpha and other proinflammatory cytokines [30], diminishes the inflammatory effect and the neuroimmune response. In virtue of this action, thalidomide has been found to attenuate mechanical allodynia [31] [32] as well as prevent and in part reverse hyperalgesia [31] [32]. Consistently, in the present case, during its administration, the blood concentration of TNF-alpha and Il-6 and the allodynia signs markedly reduced. The decrease of pain and allodynia during late interferon administration, notwithstanding the scaling down of opioid and adjuvants, and the absence of pain after interferon discontinuation are hard to interpret. Plausibly, its anti-angiogenic and immune action ultimately resulted in a marked attenuation of the mechanisms underlying nociceptive activity. Furthermore, recent studies have found that interferon inhibits excitatory synaptic trasmission by suppressing glutamate release [33] and diminishes nociception by activating opioid receptors [34].

The findings here reported must be taken with caution for two main reasons. Post-natally, the cutaneous sensitivity rapidly reduces, the size of the receptive field decreases, and the mechanical threshold gradually increases [22]. Thus, the response to tactile stimulations, *i.e.* the cotton brushing we applied to our baby to test allodynia, rapidly changes over time.The ambiguity of infant pain behaviors and the lack of anchor points to refer to, may make the hyperalgesia diagnosis non-objective.

4. Conclusion

Pain arises from pathological events which activate specific sensory signals that the nervous system may strongly enhance. A translational approach from the basic research may suggest the mechanisms operating in amplifying the nociceptive signal and the disease processes generating a nociceptive activity. Their targetting by drugs allows a mechanism-based pain therapy which is, clearly, the best "physiologic" treatment we can offer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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