Vincenzo Guidetti *and Elisa Salvi**

*Professor of Child and Adolescent Neuropsychiatry
** Phd in Child and Adolescent Psychiatry

What can be hidden behind an Headache?
- June 2007 admitted to Hospital at the age of 6 for RAP and Anorexia.
- September 2008 admitted to Hospital for Headache abruptly begun after summer holidays (once a week).
- September 2011: Frequency increased four / five times a week.
- Spring 2012: First observation in our Department.
Clinical Record (6 yo)

- Frequent abdominal pains apparently without cause.
- Loss of weight (<2kg)
- Anorexia
- Pallor
- All the blood exams and gastroscopy: regular
Headache with nausea and vomiting (seldom)

Location: unclear.

Accompanying symptoms: fear.

Lasting four hours per day, mainly in the early afternoon.

M. is often obliged to pick up her from the school.

Relieved from sleep.
How to collect datas from a Child?

- Often when You see a child with a passed history of headache data are unclear and need to be adapted to the child level:
- Children are NOT adult so it is necessary to remind that is compulsory to adapt the question to their level of Development!
Cortical Development of GM (in red high level in blue decrease. Gled 2004)
TAILOR QUESTIONING ACCORDING TO AGE!

HOW INFORMATION IS OBTAINED FROM CHILDREN AND HOW INFORMATION IS RECEIVED AND UNDERSTOOD BY CHILDREN IS UNDOUBTEDLY AFFECTED BY THEIR LEVEL OF COGNITIVE AND AFFECTIVE DEVELOPMENT.

THE VALIDITY OF INFORMATION OBTAINED FROM CHILDREN INCREASES WHEN ADULTS USE DEVELOPMENTALLY APPROPRIATE COMMUNICATION AND INTERVENTION APPROACHES.

Marcon & Labbè 1990
DIFFERENT COGNITIVE FACTORS NEED TO BE CONSIDERED WHEN WORKING WITH CHILDHOOD HEADACHE

- Illness causality
- Language development
- Perceptions of illness severity
- Conceptualization of time

Cognitive factors of headache
ILLNESS CAUSALITY

• According to Piagetian stages of cognitive development, explanations of illness move from incomprehension, to concrete and external (e.g. “from running and getting hot”) and finally to a more internal and physiological (e.g. “when people get nervous or do too much this causes their body to react with headache”) explanation.
LANGUAGE

THE DEVELOPMENTAL SEQUENCE OF WORD AND CONCEPT ACQUISITION HAS IMPLICATION FOR THE ACCURACY OF DIAGNOSIS AND FOR PSYCHOLOGICAL INTERVENTION: TREATMENT EXPLANATIONS MUST INCORPORATE LANGUAGE THAT CHILDREN UNDERSTAND

◆ THE CONCEPT “BECAUSE” IS NOT FULLY UNDERSTOOD UNTIL AGE EIGHT (Kuhn, Phelps 1976)

◆ DURING THE GRADE SCHOOL, CHILDREN HAVE DIFFICULTIES WITH CONNECTIVE WORDS AS “OR” AND “IF”, WITH THE LATTER THAT IT IS THE LAST CONNECTIVE CONCEPT TO BE GRASPED BY CHILDREN (Shine, Walsh 1971)
FOR RATING SEVERITY OR INTENSITY OF HEADACHE PAIN REMEMBER THAT CHILDREN UNDERSTAND THE CONCEPT OF “MORE” BEFORE “LESS”.

CHILDREN ACQUIRE PAIR ORIENTATIONAL TERMS ACCORDING TO THEIR SEMANTIC COMPLEXITY: CONCRETE TERMS (“BIG-SMALL”) ARE UNDERSTOOD BEFORE THE ABSTRACT ONES (“AHEAD-BEHIND”).

FOR YOUNGER CHILDREN THE USE OF FIGURES OR DRAWINGS IS MORE APPROPRIATE THAN DESCRIBING PAIN LOCATION VERBALLY.
OPEN-ENDED FORMAT ARE BETTER THAN SUPPLIED-RESPONSE FORMAT FOR ASSESSING ONGOING AND PAST PAIN EXPERIENCE FROM AGES FIVE TO TWELVE (Ross & Ross 1971).

IN AN OPEN-ENDED FORMAT IS IMPORTANT TO KNOW THAT CHILDREN UNDERSTAND BEFORE THE “WH” QUESTIONS (where, what, which…) THAN THE “HOW” QUESTIONS (how, why, when…).
ACCURATELY MEASURING HEADACHE SEVERITY IS IMPORTANT BECAUSE THE PREDOMINANT OUTCOME MEASURE FOR DETERMINING TREATMENT SUCCESS.

THE FREQUENCY OF HEADACHE ATTACKS ARE USUALLY KEPT BY DIARIES, BUT THE 0-5 SCALE TO RATE INTENSITY OF PAIN MAY NOT MATCH THE CHILDREN’S PERCEPTIONS OF PAIN, MAINLY IN YOUNGER CHILDREN.
HOW CAN WE MANAGE THE SUBJECTIVITY OF THE SELF-EVALUATION OF THE INTENSITY OF PAIN?

NUMERICAL RATING SCALE (0 TO 10 scale) and VERBAL RESPONSE SCALE (none, mild, moderate, severe) SHOW A CLOSE RELATIONSHIP FOR RATING THE INTENSITY OF HEADACHE ATTACK (hershey et al., 2005), BUT THEY ARE NOT ADEQUATE FOR YOUNGER CHILDREN.
ESPECIALLY FOR YOUNGER CHILDREN, FACE SCALES SHOULD BE PREFERRED (Champion et al., 2001)
A mature understanding of time develops in late childhood, and is not until age twelve that children are able to estimate duration of an event, estimate time since or until an event’s occurrence, and estimate present time within twenty minutes (Marcon & Labbè 1990).

With headache children, for estimating time duration of head pain is useful to have a familiar concrete event (e.g., the length of a favorite television show) rather than time terms such as hour or minute.
Headache Characteristics

- Location: Parietal Left
- Throbbing
- Lasting four H.
- Photo and Phonophobia
- Nausea (seldom Vomiting)
- Anorexia
- Pain in the hips and back
- Need to lay
- Premonitory symptoms: sensation to be highly worry
Headache Characteristics II

- Often during the night
- Triggered by stressful event
- Avoidance behaviour (stop sports, dance etc)
- Difficulties to maintain the attention during studies
- Needs to lay in the bed, in dark for hours.
Familial History

- Mother: nothing relevant except GAD in the last six months
- Father: Recurrent Abdominal Pains (RAPs)
- Sister L. 16y.o.: Dishmenorrea
- No Familiality for M. / H in first and second degrees relatives
Personal History I

- Pregnancy: wellcomed and normal
- Delivery: 41 w. Normal
- Weight 2.700kg
- Need to be held all the time
- Bottle Feeding: highly voracious.
- Frequent Gas Colics.
- Frequent Startles in the bed.
- Dummy: up to 4 and half y.
- Dentition: >8 months
- Sphincterial Control: 2y 8m
- Sleep-wake R.: still unregular
Personal History II

- School Entrance: 3 yo. High Level of Separation Anxiety (SA)
- No Infectious Diseases
- 6y. admitted to H. for Abdominal Pain and Anorexia
- 7 y. Ad. To H. for Headache
- SA +++ at the entrance (changing 4 kindergardens)
- School Performances: poor
RED FLAGS I

- Inadequate history (description of headache and related features)
- Subject not co-operative (inability to do a complete neurological examination)
- Age < 5 years (relative red flag)
- Short or ultra-short paroxysms of headache (these are uncommon in children)
- Focal Neurological symptoms
- Neurological symptoms or signs of raised or low intracranial pressure (example: headaches worsened with postural change)
- Personality change
RED FLAGS II

- Deterioration of school work
- Occipital location of headache
- Headache worsened with coughing or physical activity
- Headache awakening the child up from sleep or consistently occurring first thing in the morning
- Associated symptoms in neck or back
- Pre-existing hydrocephalus/shunt
- Neurological signs
QUESTIONS

- What is Your Diagnosis?
- Which Informations You need more?
- Which Exams You should perform?
2. MNR w and w. contrast: n.t.n.
3. Neurological E.: normal
5. EEG: regular
Abdominal Migraine or Functional Abdominal Pain (RAP)?
The key clinical features of this group of disorders include:
- the episodic, reversible, and stereotyped nature of attacks.
- Children with childhood periodic syndromes are completely healthy between attacks and, in contrast, are extremely unwell during attacks. *Cuivillier 2008*
Cyclical Vomiting 1.3.1

- A. At least five attacks fulfilling criteria B and C.
- B. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting from 1 hour to 5 days.
- C. Vomiting during attacks occurs at least 4 times/hour for at least 1 hour.
- D. Sign-free between attacks.
- E. Not attributed to another disorder.
Benign Paroxysmal Vertigo of Childhood 1.3.3

- A. At least five attacks fulfilling criterion B.
- B. Multiple episodes of severe vertigo, occurring without warning and resolving spontaneously after minutes to hours.
- C. Normal neurologic examination; audiometric and vestibular functions between attacks.
- D. Normal electroencephalogram.
Benign Paroxismal Toricollis 1.3.5

A. Episodic attacks, in a young child, with all of the following characteristics and fulfilling criterion B:
   1. Tilt of the head to one side (not always the same side), with or without slight rotation
   2. Lasting minutes to days
   3. Remitting spontaneously and tending to recur monthly

B. During attacks, signs of one or more of the following:
   1. Pallor
   2. Irritability
   3. Malaise
   4. Vomiting
   5. Ataxia

C. Normal neurologic examination between attacks.

D. Not attributed to another disorder
A. At least five attacks fulfilling criteria B-D.

B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)

C. Abdominal pain has all of the following characteristics:
   1. Midline location, periumbilical or poorly localized
   2. Dull or “just sore” quality
   3. Moderate or severe intensity

D. During abdominal pain, at least two of the following:
   1. Anorexia
   2. Nausea
   3. Vomiting
   4. Pallor

E. Not attributed to another disorder.
Chronic Abdominal Pain in Children

- **Abdominal Migraine**: Functional abdominal pain with features of M. (paroxismal abdominal pain associated with Anorexia, Nausea, Vomiting or Pallor as well as maternal history of M. Headaches.

- **Functional Abdominal Pain**: A.P. without evidence of a pathological condition such as an anatomic, metabolic, infectious, inflammatory or neoplastic disorder.

- **American Academy of Pediatrics 2005**
Recurrent Abdominal Pains
American Ped. Gastroenterology Soc. 2011

- Clinical Clues
- Quadrant Pain
  - Early Morning P.; P. awakening at night
  - Early satiety, nausea, sour breath, belching

- Cause
  - The further the pain from the umbelicus, the greater the likelihood of organic D.
  - Peptic Origin
  - Peptic Origin
Recurrent Abdominal Pains
Causes II

- Crampy p. and/or bloating and/or intestinal gas related to meals, dairy products and food containing dairy products
- Respiratory symptoms, such as chronic cough, wheezing, laringitis
- Lactose Intollerance
- Giardiasis
- Gastroesophageal reflux
Recurrent Abdominal Pains: Causes III

- Infrequent stooling, incomplete evacuation, encopresis, mass in the left lower abdominal quadrant and hard stool in rectal vault, diet low in fiber and high in starches, abdominal distension

- Constipation
Recurrent Abdominal Pains
Causes IV

- Blood in stool
- Fever, weight loss, no increase in height, joint complaints and rash
- Self-induced purging behaviour with or without weight loss
- Peptic Origin or Inflammatory bowel Disease
- Inflammation or an infectious disease process
- Gastroesophageal reflux from an eating disorder
Weight loss, restrictive eating behaviour and fecal mass in left lower abdominal quadrant

Medication such as antibiotics for acne

Pain with specific physical activity and primarily muscle tenderness on examination

Constipation due to an eating disorder

Esophagitis

Muscle Strain
Recurrent Abdominal Pains Causes VI

- Cervical motion tenderness, adnexal tenderness, or adnexal mass on pelvic examination
- Episodic swelling on the throat or skin (extremities, face or genitalia)
- Pelvic Inflammatory disease, ovarian cyst, ectopic pregnancy
- Hereditary Angioedema
R AFP Phisiology

- Stress contributes to increased arousal in the central nervous system, releasing neuropeptides and neurotransmitters that, in turn, lead to dysregulation of the gastrointestinal system.

- Although many individuals may experience some type of abdominal distress under stressful situations, those with recurrent abdominal pain may react to the stress differently, or may have maladaptive coping mechanisms.

  (Weydert 2003, Cuvellier 2010).
Tension type Headache (48%), Migraine (43%) and Functional Abdominal Pain (11%) were the most common diagnoses with a high rate of co-occurrence; 18% had some form of Musculoskeletal Pain disease. Irrespective of pain location, chronic pain disorder with somatic and psychological factors was diagnosed frequently (43%).

55% of the children suffered from more than one distinct pain diagnosis.
Clinically significant Depression and General Anxiety scores were expressed by 24% and 19% of the patients, respectively. Girls over the age of 13 were more likely to seek tertiary treatment compared to boys.
Distribution of children with chronic pain by age and gender. Zernikow 2012
Recurrent Abdominal Pains (RAP)

- Abdominal pain diagnosis: 501 22.3%
- Functional Abdominal Pain: 253 11.2%
- Chronic pain disorder with somatic and psychological factors (Pain location abdomen): 204 9.1%
- Abdominal pain-related Functional Gastrointestinal Disorders other than functional abdominal pain: 27 1.3%
Drug therapy is often precluded by anorexia or vomiting, but simple oral analgesics can be tried, with or without metoclopramide or domperidone.

Analgesic or antiemetic suppositories are also useful.
Some authors successfully used both injected and nasal sumatriptan, but this treatment has not been subjected to a formal trial.
One report demonstrated the successful use of intravenous valproate to treat abdominal migraine attacks.
Only pizotifen has been subjected to a double-blind, placebo-controlled trial. The use of propranolol and cyproheptadine has received support.

Other authors obtained good results with clonidine and sodium valproate
If abortive therapy fails consistently, or episodes are frequent or severe, then daily prophylactic therapy to prevent subsequent episodes is recommended. 

Prophylactic agents to treat cyclic vomiting syndrome include antimigraine, antiepileptic, and prokinetic agents (e.g., erythromycin). A task force of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommended cyproheptadine or propranolol as first choice in children aged 5 years and younger children, the task force recommended amitriptyline or propranolol.

Prophylactic therapy is justified when episodes occur more frequently than once a month, are difficult to abort, or are particularly severe and disabling.
Could we consider this clinical case as an example of Daily Chronic Headache?
CHRONIC DAILY HEADACHE
THE DIAGNOSIS OF CHRONIC DAILY HEADACHE IS FUNCTION OF A QUANTITATIVE PARAMETER (AN ALMOST DAILY FREQUENCY OF THE CRISIS), INASMUCH AS WE DO NOT HAVE CLEAR QUALITATIVE PARAMETERS (A DEFINITE SYMPTOMATOLOGICAL CHARACTERIZATION OF THE CRISIS).
Basic : Headache around 15 / d / m.
- H Frequent but not Daily (37.5%)
- H. Daily but not Continuous (43.5%)
- H. Daily and Continuous (19.5%)

Mainly of Migrainous Type
CHRONIC DAILY HEADACHE: SILBERSTEIN’S CLASSIFICATION (1993)

PRIMARY VARIETIES
1. TRANSFORMED MIGRAINE
2. CHRONIC TENSION-TYPE HEADACHE
3. NEW DAILY PERSISTENT HEADACHE
4. HEMICRANIA CONTINUA

SECONDARY VARIETIES
• posttraumatic headache, cervical spine disorder, headache associated with vascular disorders, headache associated with nonvascular disorders, and others
**“TRANSFORMED” MIGRAINE**

1- History of episodic migraine (with or without aura).

2- The patients may start out in their teens or twenties with episodic migraine and later develop CDH, with features of both migraine and tension-type headache.

3- It is often difficult to distinguish between headache sub-types.

4- These patients have frequently a family history of migraine, menstrual aggravation, identifiable trigger factors, and unilateral headache.
1- The patients may have a history of Episodic Tension-type headache or may begin de novo and meet IHS criteria for Chronic tension-type headache.

2- The headaches are more often diffuse and bilateral, frequently involving the posterior aspect of the head and neck, and may have some migrainous features.

3- The major difference with “transformed migraine” is the absence of a clear history of episodic migraine.
NEW DAILY PERSISTENT HEADACHE

1- Patients may refer fairly rapid-onset. Some remember the exact day or time when the headache started.

2- Head pain is continuous.

3- Absence of a clear history of episodic migraine or tension-type headache.

4- It is best described as a Chronic Tension-type headache with some migraineous features.

5- The patients are generally younger than those with “transformed migraine”.
HEMICRANIA CONTINUA

1- Indomethacin-responsive headache disorder.

2- Continuous but fluctuating, moderately severe, unilateral headache that can alternate sides.

3- Phono-photophobia, nausea, and tearing.

4- It cannot be triggered by neck movements, but tender spots can occur in the neck.

5- It may be occasionally associated with autonomic dis. (ptosis, mydriasis, sweating).
ADULT CDH PATIENTS FREQUENTLY REFER THE ONSET OF HEADACHE DURING THEIR INFANCY OR ADOLESCENCE (Solomon, Lipton, Newman 1992; Silberstein 1993).

Studies on Clinical and Prognostic Features of CDH lack of common DIAGNOSTIC CRITERIA.

At present, a clear differentiation with adult characteristics is not achieved.

The application of the Silberstein’s model in the youngest age does not give us an exhaustive diagnostic framework, opening the hypothesis of specific symptomatological expression of CDH in children and adolescents.
PREVALENCE of CDH in Ch. and Ad. ranges from 0.2 to 0.9 /1.4 % (Sillanpaa et al., 1991; Abu-Arefeh et al 1994, Wang 2006).

In adults, the prevalence is around 2% (Silberstein, 1993).

CLINICAL FEATURES

In the developmental age, frequent and severe migraine attacks overlap daily crises of tension-type headache. The onset clinical features are very similar to the subsequent (chronic) trend. In adults, it is more typical the tendency of migraine to change over time, taking tension features with almost daily crises.
In adults, analgesic overuse is frequently called in question as a factor involved in the chronic evolution of headaches.

In developmental age, the association of CDH and analgesic abuse is a field requiring a different framing, in terms more preventive than etiologic. Even if Cuivillier (2008) found 20% of Ad. Abusers.

Prospective studies may help the recognition of prognostic factors involved in adult CDH, and not completely framed in CDH related to analgesic overuse (“rebound headache”).
Eighty-six consecutive CDH patients were taken into account (60F, 26M; m.a.12.3yrs; s.d.+2.1yrs; range 7-18yrs). The sample has been selected among 571 patients (233F, 338M; m.a. +11.4yrs; s.d.2.9yrs; range 4-18yrs) first referred to our Headache Center.

One hundred patients (60F, 40M; m.a 10.7; s.d.+2.6aa; range 4-18), randomly selected from the whole sample constituted the control group: 64 subjects had migraine, 36 subjects had tension-type headache.
PREVALENCE OF PRIMARY HEADACHES IN THE WHOLE SAMPLE (N=571)

- CDH: 50%
- MIGRAINE: 15%
- ETTH: 35%
PREVALENCE OF THE SUB-TYPES OF CHRONIC DAILY HEADACHE

86 (15%) SUBJECTS HAD CDH (60F, 26M; m.a. 12.3yrs; s.d. ±2yrs; range 7-18yrs)
Prevalence of Psyc. Comorbidities

- MIGRAINE
  - MULTIPLES: 20%
  - SINGLES: 48%
  - ABSENCE: 32%

- EPISODIC TENSION-TYPE
  - MULTIPLES: 5%
  - SINGLES: 18%
  - ABSENCE: 77%

- CDH
  - MULTIPLES: 70%
  - SINGLES: 20%
  - ABSENCE: 10%
PREVALENCE OF PSYCHIATRIC DISORDERS IN CDH SAMPLE

Multiple disorders are presented.

Frequencies

Sleep Dis.  Adjust. Dis.  School Ph.  Tic  Stuttering

60  60  35  17  9
IN 2008
WE INTERVIEWED 46 OF 81, ACCORDING TO ICHD-II CRITERIA.
(33F, 13M; M.A.21.8, SD=2.72)
To 2008:
- We found an overall improvement in 87.0% (40/46)
- A worsening in 6.5% (3/46)
- A unchanging in 6.5% (3/46)

• Nineteen patients were headache-free (41.3%).
• Eleven patients had frequent episodic tension-type headache (23.9%).
• Nine patients infrequent episodic tension-type headache (19.5%).
• Six patients (13%) chronic tension-type headache; of this one present secondary headache.
• One patient had migraine without aura (2.2%).

No patients with medication overuse
COMPARING FOUR AND TEN YEARS

- Headache-free
- Improvement
- Unchanging
- Worsening

After 4 years
After 10 years
Factors Precipitating CDH
Sheshia & Guidetti 2010

- Infection
  - Minor head injury
  - Stressor etc

- Primary Episodic Headache
  - Factors precipitating or contributing to transformation and maintenance of CDH
    - Genetic
    - Stressors, including maltreatment/abuse
    - Lifestyle/environment/medication overuse, head injury etc
    - Gender (post-pubertal female)
    - Anxiety, depression
    - Other psychiatric disorders

- Psychiatric Co-morbidity: Especially anxiety and depression

- CDH
  - Other pain syndromes?
  - Sleep disorders?
  - Obesity?
What We need to know more?
Why Headache frequency is changed?

Drug Abuse?

Changing in the Life Style?

- None, Parents do not like to give drugs except in a very “special” cases.

- Parents refer, as a minor problem in the g.life, the death of the GM, living with them, some months earlier.
GM died during family holidays,
The g., back at home, didn’t find her anymore.
She lived with them since the g. was 5 yo
Question II

- Are there Associated Disorders?

- Recurrent Abdominal Pains (RAP)

- NB: Headache and RAP are the most frequent Somatic Complaints in Children (Egger, Costello 1999)
Question III

- What about Psychiatric Comorbidities?
Time relationship between Headache onset: School Attendance before and Mourning, after.

Family Psychiatric Comorbidity: F. with Multiple Somatizations and M. with GAD
Focus our Attention!

- Headache and Migraine could be the expression of relevant psychological problems!
- Evaluate how headache frequency influences QoL
METHOD I

- One Preliminary Talk with Parents
- Four Talks with the G.:
  - Three Free Talks
  - One Tests Administration
Parent’s Talk

- High Level of worries for her school performancies
- They stress the difficulty of falling asleep and maintain the sleep. The G. asks very often to sleep with them.
- They think that their daughter is only “a little bit shy” (underevaluate separation anxiety)
- They refer to the death of GM as non-relevant event. “she was old “(68y.)!
After some difficulties to leave her mother, the G. become cooperative.

She expressed immediately the fear that her P. could die as happened with the GM.

She is very worried for her school performances and relationships (particularly with one of the two Teachers).

She is very worried for her health.
Drawing Herself
Drawing a Tree
Tests Results : SAFA

- SAFA, self-administered Scale analyzing:
  - Anxiety (A), Depression (D), Obsessive/Compulsive (O),
  - Psychogenic Eating Disorders (PED, Somatizations (S), Phobias.(Ph)

- Normal Level: D, PED, Ph.
- High Level: A, O, S
Tests Results : CY-bocs

- Analyze the deppness of OCD.

- All the Values higher than normal!
Treatment

- Cognitive Psychotherapy once a week for the G. x six months.
- Parents psychotherapy: once every 15 days x six months
- No Drug Preventative Treatment.
- Paracetamol if necessary
Six Months Follow-up

- Migraine Frequency: one x month
- Separation Anxiety: reduced: she fall asleep almost immediately, sleep in another room,
- No headache during the night.
- Worries on health: reduced
- Twice a week: Dance
- Saturday dedicated to plays with friends
- School Performances. Clearly improved
The G. presents some typical aspects of Neonatal Hyperactivity:
- Need to be held all the time.
- Voracious Bottle Feeding
- Multiple Startles in the bed
- Gas Colics
- Alteration in S/W cycle
- This encompass with Temperament type B:
  - (Temperament describes how a child approaches and reacts to the world).

Amplifiers!!!
Amplifiers are children with a reduced ability to encompass with internal stimuly (gas colics)
And environmental (startles).
They represent around 20% of healthy neonates (Temperament B Type)
All kind of stressfull events induce amplified answers: as school achievement!
They are particularly prone to psychiatric comorbidity (Anxiety, Depression)
(Guidetti et al 1984, 2011)
“The interactions found between child and maternal factors highlight the complexity of pain behavior even in infancy”

Individually-based reactivity level (temperament is the behavioral indicator of it) predicts behavior in early infancy.

In late infancy, pain behavior is more strongly related to the patterns of maternal responsivity to pain cues.

(Sweet, McGrath, Symons, Pain 1999)
Highly reactive infants were found to be more likely to display anxious symptoms in mid childhood (7 years).

Notably, the odds of reporting anxious-depressive symptoms in childhood were doubled in those with high reactive and avoidant temperament styles.

Andrew J. Lewis and Craig A. Olsson *Early Life Stress and Child Temperament Style as Predictors of Childhood Anxiety and Depressive Symptoms: Findings from the Longitudinal Study of Australian Children*, Depression Research and Treatment Aug 2011
This can explain the “basic equipment “of the G., genetically influenced.

But the Story even stress the relevance of Epigenetic Factors!
Epigenetics encompasses changes to the DNA structure without changing the genetic code, resulting in chromatin remodeling and consequently affecting transcriptional potential and expression of genes. Epigenetic marks can be dynamic but can also be stably inherited through cell divisions. Therefore, epigenetic processes enable cell and developmental stage specific regulation of gene expression, but also play an important role in programming lasting responses to environmental cues.

Epigenetic mechanisms may underlie a part of migraine pathophysiology (and even the chronification of migraine) and therefore might provide a novel promising avenue for improving pharmacotherapy.

Else Eising et al. Epigenetic mechanisms in migraine: a promising avenue?

*BMC Medicine 2013, 11:26*
The first study that assessed the effect of stress on the epigenome showed that low maternal care, a model for early life stress, could lastingly affect the behavior and stress responsiveness of rat offspring throughout their lifespan through increased DNA methylation at the brain-specific promoter of the glucocorticoid receptor gene *Nr4a3*, the main receptor for glucocorticoid stress hormones.

Other studies have linked stress during early life as well as during adulthood to a wide variety of long-lasting epigenetic alterations at stress effector genes (for example, *Bdnf*, *Gr* and *Crh*), affecting structural and functional aspects of the brain such as stress reactivity and synaptic plasticity.

Hunter RG: *Epigenetic effects of stress and corticosteroids in the brain.*

*Front Cell Neurosci* 2012, 6:18
A conceptual diagram of the ABC model of the emergence of gender differences in depression in adolescence. (Depressogenic Vulnerability represents the collection of all the vulnerabilities, all of which are hypothesized to interact with negative events to yield gender differences in depression.)


The ABCs of Depression: Integrating Affective, Biological, and Cognitive Models to Explain the Emergence of the Gender Difference in Depression
GENETIC

↓ 5-HT INNERVATION

TEMPERAMENT

HYPERREACTIVITY

PERSONALITY TRAITS

MITOCONDRIAL ENERGY RESERVE

BRAIN ENERGY DEMAND

BIOCHEMICAL SHIFTS

SPREADING DEPRESSION

TRIGEMINOVASCULAR ACTIVATION

MIGRAINE ATTACK

ENVIRONMENT
Thank You for Your Attention!

ご清聴ありがとうございます