Impaired Function, Ethics & Social Justice: Steroid Patterns amongst ‘Apathetic’ Refugee Children in Sweden

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Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda
Presentation: A “New Illness”; an Exploration of Steroid Patterns in ”Apathetic Refugee Children”


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History of the Epidemic

- 2002, change of practice in Immigration Board
- From 2003, an overwhelming number of cases of refugee children that were in a stuporous state, non-responsive to communication, often unable to eat or drink and sometimes incontinent
- 2004: More than 400 known cases
The government’s task force

- The minister of foreign affairs nominated a special co-ordinator with the task of explaining the phenomenon
- The explanations advanced were
  - Factitious disorder, possibly intoxication
  - Neglect
  - Malingering
Clinical characteristics of the condition

- In most cases there are reports or allegations of severe persecution or human rights abuse in the country of origin (Lindberg, Sundelin 2005)
- “The child is totally passive, immobile, lacks tonus, withdrawn, mute, unable to eat and drink, incontinent and not reacting to physical stimuli or pain. Periods of panicky refusal and/or anxiety can proceed or intervene with the stuporous state. Secondary symptoms may appear, such as tachycardia, rise in temperature, weight gain, oedema, profuse sweating, reactivation (?) of latent viral infection, skin ulcers and muscular atrophy.” (Bodegard Acta Paediatrica, Volume 94, Issue 12 December 2005, pages 1706 - 1707)
The present study

• Initiated in order to study steroid metabolites in so-called "apathetic refugee children"

• **Hypothesis:** If stress-related a) low cortisol and

• b) increased, possibly neuroactive precursors to cortisol are increased

• Data collection from 2005-2007, patients close to lab facilities, only clear cut cases,

• total n = 11 (cases) plus 2 siblings

• Mean age: 14.00 (s.d. 2.3) for 7 girls, and 14.75 (s.d. 2.2) for 4 boys

• Variables
  – Trauma history (interview data from parents)
  – Symptom score
  – Days with gastric tube
  – Days to turning point (first sign of recovery such as movements)
Chemical analysis

- Steroids of the pathway of steroid biosynthesis were analyzed with high-sensitivity Liquid Chromatography tandem Mass Spectrometry (LC-MC)
Whole group (n=13) Mean(s.d.)

<table>
<thead>
<tr>
<th></th>
<th>Whole group (n=13)</th>
<th>Girls (n=9)</th>
<th>Boys (n=4)</th>
<th>Siblings (n=2)</th>
<th>Cases (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>1.54 (2.28)</td>
<td>0.44 (0.36)</td>
<td>4.01 (2.93)*</td>
<td>0.87 (0.73)</td>
<td>1.66 (2.46)</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.085 (0.070)</td>
<td>0.05 (0.03)</td>
<td>0.16 (0.09)*</td>
<td>0.035 (0.00)</td>
<td>0.09 (0.07)</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>1.76 (0.87)</td>
<td>1.83 (0.94)</td>
<td>1.61 (0.78)</td>
<td>1.35 (0.43)</td>
<td>1.84 (0.92)</td>
</tr>
<tr>
<td>17-OH-Pregnenolone</td>
<td>3.28 (1.79)</td>
<td>3.39 (1.68)</td>
<td>3.05 (2.26)</td>
<td>3.73 (1.62)</td>
<td>3.20 (1.88)</td>
</tr>
<tr>
<td>Allopregnenolone</td>
<td>0.08 (0.07)</td>
<td>0.10 (0.07)</td>
<td>0.04 (0.02)</td>
<td>0.055 (0.007)</td>
<td>0.088 (0.070)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.46 (0.98)</td>
<td>0.63 (1.16)</td>
<td>0.10 (0.03)</td>
<td>0.065 (0.007)</td>
<td>0.54 (1.06)</td>
</tr>
<tr>
<td>OH-Progesterone</td>
<td>0.51 (0.30)</td>
<td>0.45 (0.25)</td>
<td>0.64 (0.40)</td>
<td>0.37 (0.19)</td>
<td>0.53 (0.32)</td>
</tr>
<tr>
<td>11-Deoxycortisol</td>
<td>0.70 (0.48)</td>
<td>0.64 (0.37)</td>
<td>0.90 (0.59)</td>
<td>0.87 (0.73)</td>
<td>0.67 (0.46)</td>
</tr>
<tr>
<td>11-Deoxycorti-costerone</td>
<td>0.95 (0.59)</td>
<td>0.82 (0.49)</td>
<td>1.25 (0.76)</td>
<td>0.66 (0.40)</td>
<td>1.00 (0.61)</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>7.03 (5.17)</td>
<td>5.94 (4.43)</td>
<td>9.48 (6.57)</td>
<td>10.34 (3.49)</td>
<td>6.43 (5.32)</td>
</tr>
</tbody>
</table>
Whole group (n=13) | Girls (n=9) | Boys (n=4) | Siblings (n=2) | Cases (n=11)
--- | --- | --- | --- | ---
Cortisol | 104.15 (42.48) | 106.25 (40.18) | 100.80 (50.65) | 144.00 (43.84) | **96.91 (39.98)**
Cortisone | 24.54 (4.89) | 25.12 (3.31) | 23.60 (7.13) | 28.00 (2.82) | **23.91 (5.01)**
Estrone | 0.05 (0.05) | 0.060 (0.05) | 0.019 (0.014) | 0.047 (0.032) | 0.047 (0.051)
Estradiol | 0.06 (0.07) | 0.079 (0.073) | 0.016 (0.017) | 0.062 (0.035) | 0.060 (0.073)
DHEA | 4.79 (2.76) | 5.54 (2.84) | 3.11 (1.89) | 5.72 (4.77) | 4.62 (2.58)
Androstenedione | 1.18 (0.72) | 1.43 (0.69) | 0.63 (0.45) | 1.58 (1.35) | 1.11 (0.63)
Differences between first and last sampling, patients only (n=10). Units are ng/ml.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Last follow-up</th>
<th>T-value</th>
<th>Correlation Δscore and Δchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy score</td>
<td>30 (range 35-22)</td>
<td>2.8 (range 0-27)</td>
<td>-10.786, df 9, p=0.000</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>96.50 (s.d. 42.11)</td>
<td>97.80 (s.d. 25.01)</td>
<td>-0.084, df 10, p=0.935</td>
<td>Rho=0.771*, p=0.009</td>
</tr>
<tr>
<td>Corrected cortisol</td>
<td>123 (23)</td>
<td>-1.862, df 10, p=0.092</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>23.6 (5.17)</td>
<td>26.8 (2.86)</td>
<td>-1.571, df 10, p=0.151</td>
<td>Rho=0.745*, p=0.013</td>
</tr>
<tr>
<td>Corrected cortisone</td>
<td>28.82 (2.7)</td>
<td>-2.631, df 10, p=0.025*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrone</td>
<td>0.034 (0.023)</td>
<td>0.042 (0.032)</td>
<td>-1.212, p=0.256</td>
<td>n.s.</td>
</tr>
<tr>
<td>Girls (n=5, mean age 14.33)</td>
<td>0.0495 (0.020)</td>
<td>0.0673 (0.027)</td>
<td>-1.284, p=0.268</td>
<td>Rho=1.0**, p=.00</td>
</tr>
<tr>
<td>Boys (n=4, mean age 15.65)</td>
<td>0.0242 (0.012)</td>
<td>0.0234 (0.001)</td>
<td>0.111, p=0.922</td>
<td></td>
</tr>
<tr>
<td>Prepubertal (n=2, mean age 11)</td>
<td>0.0072 (0.0062)</td>
<td>0.0088 (0.0046)</td>
<td>-1.455, p=0.383</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.0398 (0.035)</td>
<td>0.062 (0.060)</td>
<td>-1.516, p=0.160</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.065 (0.030)</td>
<td>0.109 (0.050)</td>
<td>-1.712, p=0.162</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>0.021 (0.017)</td>
<td>0.020 (0.004)</td>
<td>0.152, p=0.893</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>0.0057 (0.0065)</td>
<td>0.0069 (0.0014)</td>
<td>-3.31, p=0.795</td>
<td></td>
</tr>
<tr>
<td>DHEA</td>
<td>4.25 (2.39)</td>
<td>3.80 (1.56)</td>
<td>0.586, p=0.572</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td><strong>4.74 (2.73)</strong></td>
<td><strong>3.74 (0.93)</strong></td>
<td><strong>0.913, p=0.413</strong></td>
<td>Rho=0.9, p=0.037</td>
</tr>
<tr>
<td>Boys</td>
<td>3.61 (1.97)</td>
<td>4.26 (2.07)</td>
<td>-0.342, p=0.765</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>3.98 (3.34)</td>
<td>3.30 (2.94)</td>
<td>2.368, p=0.254</td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td>0.978 (0.476)</td>
<td>0.907 (0.434)</td>
<td>0.622, p=0.550</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>1.326 (0.240)</td>
<td>1.157 (0.314)</td>
<td>0.961, p=0.391</td>
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<tr>
<td>Boys</td>
<td>0.782 (0.407)</td>
<td>0.846 (0.399)</td>
<td>-0.237, p=0.835</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>0.405 (0.316)</td>
<td>0.376 (0.301)</td>
<td>2.636, p=0.231</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Differences between first and last sampling, patients only (n=10). Units are ng/ml.

<table>
<thead>
<tr>
<th></th>
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<th>Last follow-up</th>
<th>T-value</th>
<th>Correlation Δscore and Δchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>1.66 (2.46)</td>
<td>1.50 (2.22)</td>
<td>1.587, p=0.144</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.309 (0.056)</td>
<td>0.262 (0.077)</td>
<td>1.263, p=0.275</td>
<td></td>
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<tr>
<td>Boys</td>
<td>5.31 (1.63)</td>
<td>4.83 (1.28)</td>
<td>1.406, p=0.295</td>
<td></td>
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<tr>
<td>Prepub</td>
<td>0.147 (0.071)</td>
<td>0.094 (0.074)</td>
<td>26.500, p=0.024</td>
<td></td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.09 (0.07)</td>
<td>0.10 (0.09)</td>
<td>-0.880, p=0.400</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.095 (0.076)</td>
<td>0.106 (0.098)</td>
<td>-0.879, p=0.987</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>0.064 (0.013)</td>
<td>0.054 (0.013)</td>
<td>1.487, p=0.211</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>0.018 (0.021)</td>
<td>0.030 (0.020)</td>
<td>0.408, p=0.754</td>
<td></td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>1.644 (0.695)</td>
<td>1.640 (0.735)</td>
<td>0.014, p=0.989</td>
<td></td>
</tr>
<tr>
<td>17-OH-Pregnenolone</td>
<td>3.162 (1.972)</td>
<td>2.316 (1.233)</td>
<td>1.336, p=0.214</td>
<td></td>
</tr>
<tr>
<td>Allopregnenolone</td>
<td>0.072 (0.048)</td>
<td>0.222 (0.408)</td>
<td>-1.159, p=0.27</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.546 (1.11)</td>
<td>1.231 (3.016)</td>
<td>-0.645, p=0.535</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.994 (1.513)</td>
<td>2.386 (4.138)</td>
<td>-0.634, p=0.560</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>0.0967 (0.040)</td>
<td>0.0967 (0.047)</td>
<td>0.000, p=1</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>0.100 (0.000)</td>
<td>0.045 (0.021)</td>
<td>3.667, p=0.170</td>
<td></td>
</tr>
<tr>
<td>OH-Progesterone</td>
<td>0.487 (0.288)</td>
<td>0.444 (0.231)</td>
<td>0.419, p=0.685</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.392 (0.157)</td>
<td>0.430 (0.255)</td>
<td>-0.251, p=0.814</td>
<td>0.9, p=0.037</td>
</tr>
<tr>
<td>Boys</td>
<td>0.767 (0.388)</td>
<td>0.603 (0.176)</td>
<td>0.628, p=0.594</td>
<td></td>
</tr>
<tr>
<td>Prepub</td>
<td>0.305 (0.050)</td>
<td>0.240 (0.028)</td>
<td>1.182, p=0.447</td>
<td></td>
</tr>
<tr>
<td>11-Deoxycortisol</td>
<td>0.717 (0.439)</td>
<td>0.550 (0.350)</td>
<td>1.052, p=0.320</td>
<td></td>
</tr>
<tr>
<td>Deoxycorticosterone</td>
<td>0.901 (0.544)</td>
<td>0.699 (0.411)</td>
<td>1.255, p=0.241</td>
<td></td>
</tr>
<tr>
<td>Corticosterone</td>
<td>6.432 (5.610)</td>
<td>5.100 (3.965)</td>
<td>0.643, p=0.537</td>
<td></td>
</tr>
</tbody>
</table>
Baseline cortisol/ symptom score (Spearman rho -.621, p=0.024)  
(Scores for two siblings zero, eleven patients to the right)
Fig. 1: Association between initial cortisol levels and days on gastric tube.

Fig. 2: Association between baseline cortisol levels and the parameter "days to turning point", which had already occurred in two cases at baseline.
Figure 2. Association between baseline cortisol levels and days on nasogastric tube (A), and number of days to first signs of recovery (B).
Figure 1. Box plots with distribution of concentrations of steroids in blood of apathetic refugee children at entry into the study (median symptom score 29.5) and at last follow-up after the recovery (median symptom score 0); A – cortisol, B – cortisone, C – total glucocorticoids (cortisol + cortisone), D – pregnenolone, E – 17OH pregnenolone, F – DHEA. Dotted line represents upper and lower limits of the reference intervals.
Fig. 3: Ratio cortisol/17-OH-progesterone and days to turning point.
Fig. 4: Pregnenolone (nanogr/ml) at first and last follow-up, when last symptom score was zero (F=17.451, p=0.055 (n.s.), df=9).

Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda.
Fig. 5: Concentration of pregnanes (pregnenolone, 17-OH-pregnenolone, and DHEA) (ng/ML) during illness and recovery.
What we learned in school

The Pituitary-Adrenal-Axis

hypothalamus

CRF (corticotrophin releasing factor)

anterior pituitary

ACTH (adrenocorticotrophic hormone)

adrenal cortex

cortisol

cortisol exerts a negative feedback effect on the hypothalamus that inhibits further release of CRF

cortisol increases:
- blood glucose
- blood pressure
- amino acids

Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda
The horrible truth

CHOLESTEROL

PREGNENOLONE 17OH-Pregnenolone DHEA

3α,5α-THP 3β 5α-THP 3α5β20αHHP 3αDHP 5αDHP 3βDHP 5βDHP

PROGESTERONE 17OH-Progesterone Androstenedione

3α,5β,20α-HHP 3β,5α-DHP 3α THDOC 5α DHDOC 3β DHDOC 5β DHDOC

DOC Cortisosterone Desoxycortisol CORTISOL TESTOSTERON

3α 5β THDOC 3β 5α THDOC 3α 5β THDOC 3β 5α THDOC 3α THDOC 5α DHDOC 3β DHDOC 5β DHDOC

ALDOSTERONE ESTRADIOL

3α,5β-THDOC 3α,5α-THDOC 5α-DHDOC 3β,5β-THDOC 3β,5α-THDOC

Cortisol Testosterone

3α,5α-THT 3β,5α-THT 5α-DHT

ANESTHETIC STEROIDS MINERALCORTICOIDs GLUCOCORTICOIDs GONADAL STEROIDS ANESTHETIC STEROIDS

Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda
Some steroids are neuroactive

CHOLESTEROL

PREGNENOLONE → 17OH-Pregnenolone → DHEA

PROGESTERONE → 17OH-Progesterone → Androstenedione

PROGESTERONE

DOC

Cortisosterone → Cortisone

ALDOSTERONE

ring-A-reduced metabolites

ANESTHETIC STEROIDS

MINERALCORTICOIDS

GLUCOCORTICOIDS

GONADAL STEROIDS

ANESTHETIC STEROIDS

Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda

GABA$_A$ receptor

Allo-, isopregna-nolone, testosterone, DOC

DHEAS, pregnenolone

+ GABA$_A$ receptor

-
Sigma1 receptor

- Pregnenolone negative
- DHEAS positive
- Sigma type 1 receptor


Theme: Health of Sans Papiers, refugees and asylum seekers: Towards a bioethics working agenda
Interpretation

• Low cortisol pattern typical of PTSD with dissociative features

Alternative interpretations

• Intoxication
  – Hardly possible in view of the many (unpublished) toxicological analyses carried out aided by police intervention

• Malingering
  – How would malingering co-vary with such a clear-cut steroid patterns?

• Neglect
  – Quite possible with regard to traumatized parents to traumatized children loosing their last hope

• Trauma
  – Most cases with reported high levels of trauma exposure

• Genetic aberrations
  – Possible but only associated with extreme stress, since the condition is extremely rare in normal populations (two-factor hypothesis)
‘Processes of exclusion should be addressed rather than focusing simply on addressing the characteristics of excluded groups. This approach has much potential when addressing the social and health problems of Roma and irregular migrants as well as those who suffer from less extreme forms of exclusion and dip in and out of vulnerable contexts’

(Marmot M et al. 2012)
Focus e.g. Person x event x surrounding environment that impact on illness/disorder development and recovery (Harvey 1996).

I will not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient. (WMA Geneva Declaration 2006)

Drawing from multidisciplinary work: medical doctors, nurses, psychologists, social workers, lawyers, alternative medicine, spiritual interventions/healing, support workers, ethicists/philosophers, economists, anthropologists etc.

Paradigm perceptions

Health field, e.g. trans/cultural psychiatry, refugee mental health, psychosocial interventions

Dignity Health

Bioethics

Public health ethics

Social Justice Human rights

Public health, public mental health, global or international health

Social determinants: legal system

References


The asylum process in Sweden

The Migration Court of Appeal

About 3% successful on appeal

The Migration Courts

The Swedish Migration Board (SMB)

SMB (2013) for year 2012:
Total no. asylum applications 2012: 43887 (100%)
Total no. persons rejected 2012: 38320 persons (ca. 71%)

Permission to stay 2012 (n=12576):
Convention refugee: ca. 30%
In need of protection: ca. 60%
Particularly distressing circumstances: ca. 8%
Other, for example temporary residence permit: ca. 2%

The Swedish Migration Board Impediments to enforcement

Police Enforcement

Deportation

Layout: D’Orazio, A. 2012/2013
Participants

• Chosen from a catchment area close to lab facilities
• Only clear-cut cases included
• N=11 and two siblings
• The final sample consisted of seven females and four males, along with two siblings, both female. Two patients did not need tube feeding at all. The mean age was 14 (s.d. 2.3) in girls and 14.75 (s.d. 2.2) years in boys. Two participants were pre-pubertal, two were in incipient puberty, and the rest were fully developed. The two sibling controls were both female, one prepubertal and one after menarche and development of secondary sexual maturation.