life

*Systematic Review*

# Platelet APP Processing: Is It a Tool to Explore the Pathophysiology of Alzheimer's Disease? A Systematic Review

**Manuel Glauco Carbone [1,*], Giovanni Pagni [2], Claudia Tagliarini [2], Donatella Marazziti [3,4] and Nunzio Pomara [5]**

[1] Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, 21100 Varese, Italy
[2] PISA-School of Experimental and Clinical Psychiatry, 56100 Pisa, Italy; giovanni.a.pagni@gmail.com (G.P.); claudiatagliarini8@gmail.com (C.T.)
[3] Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, 56100 Pisa, Italy; dmarazzi@psico.med.unipi.it
[4] Department of Clinical Psychology, Saint Camillus International University of Health and Medical Sciences, 00131 Rome, Italy
[5] Geriatric Psychiatry Department, Nathan Kline Institute, 140 Old Orangeburg Road Orangeburg, New York, NY 10962, USA; Nunzio.Pomara@NKI.rfmh.org
* Correspondence: manuelglaucocarbone@gmail.com; Tel.: +39-0332-242324

**Abstract:** The processing of the amyloid precursor protein (APP) is a critical event in the formation of amyloid plaques. Platelets contain most of the enzymatic machinery required for APP processing and correlates of intracerebral abnormalities have been demonstrated in platelets of patients with AD. The goal of the present paper was to analyze studies exploring platelet APP metabolism in Alzheimer's disease patients trying to assess potential reliable peripheral biomarkers, to offer new therapeutic solutions and to understand the pathophysiology of the AD. According to the PRISMA guidelines, we performed a systematic review through the PubMed database up to June 2020 with the search terms: "(((((((APP) OR Amyloid Precursor Protein) OR AbetaPP) OR Beta Amyloid) OR Amyloid Beta) OR APP-processing) AND platelet". Thirty-two studies were included in this systematic review. The papers included are analytic observational studies, namely twenty-nine cross sectional studies and three longitudinal studies, specifically prospective cohort study. The studies converge in an almost unitary way in affirming that subjects with AD show changes in APP processing compared to healthy age-matched controls. However, the problem of the specificity and sensitivity of these biomarkers is still at issue and would deserve to be deepened in future studies.

**Keywords:** Alzheimer's disease; Aβ cascade; platelet activation; APP processing; Aβ amyloid

**Citation:** Carbone, M.G.; Pagni, G.; Tagliarini, C.; Marazziti, D.; Pomara, N. Platelet APP Processing: Is It a Tool to Explore the Pathophysiology of Alzheimer's Disease? A Systematic Review. *Life* **2021**, *11*, 750. https://doi.org/10.3390/life11080750

Academic Editor: Marina Saresella

Received: 26 June 2021
Accepted: 20 July 2021
Published: 26 July 2021

**Supplementary Materials:**

**Table S1.** Studies detecting APP ratio.

| First author, year | Study design | Sample | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|
| | | AD or MCI | | | Control | | | | |
| | | N (M/F) | Age | APPr | N(M/F) | Age | APPr | | |
| Di Luca et al., 1996 | Cross sectional study | AD 10 (3/7) | 67.3±12.9 | 0.16±0.048 | 15 (7/8) | 61±14 | 0.76±0.280 | NINCDS-ARDA, DSM-IV, MMSE | Moderate (4) |
| Rosenberg et al., 1997 | Cross sectional study | AD 15 (4/11) | 72.5±1.9 | 5.61±0.41 | 19 (5/14) | 71.3±2.0 | 7.72±0.57 | NINCDS-ARDA | Moderate (3) |
| Di Luca et al., 1998 | Cross sectional study | mAD 11 (3/8) | 71.2±7.1 | 0.51±0.13 | 35 (18/17) | 67.6±13.5 | 0.84±0.24 | NINCDS-ARDA, MMSE | Strong (5) |
| | | MAD 11 (6/5) | 65.1±9.6 | 0.35±0.15 | | | | | |
| | | aAD 10 (4/6) | 78.4±9.0 | 0.25±0.08 | | | | | |
| Baskin et al., 2000 | Prospective Cohort Study | AD 10 1996 (N.S.) | N.S. | 5.83±0.27 | 11 1996 (N.S.) | N.S. | 8.09±0.61 | NINCDS-ARDA, MMSE | Moderate (4) |
| | | AD 10 1999 (N.S.) | | 3.57±0.47 | 11 1999 (N.S.) | | 8.31±0.27 | | |
| Padovani et al., 2001 | Cross sectional study | mAD 32 (14/18) | 69.2±7.6 | 0.45±0.12 | 95 (52/43) | 59.3±17.4 | 0.92±0.38 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| | | MAD 31 (10/21) | 67.0±8.4 | 0.31±0.17 | | | | | |
| | | aAD 22 (11/11) | 67.7±15 | 0.22±0.10 | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Padovani et al., 2002 | Cross sectional study | MCI 30 (13/17) | 69.6±6.9 | 0.62±0.33 | 25 (14/11) | 69.8 ± 9.0 | 0.93±0.30 | NINCDS-ARDA, MMSE, CDR, DSM-IV, MCC | Strong (5) |
| | | vmAD 21 (9/12) | 66.2±6.9 | 0.49±0.30 | | | | | |
| | | mAD 35 (12/23) | 69.2±8.5 | 0.44±0.24 | | | | | |
| Colciaghi et al., 2002 | Cross sectional study | AD 33 (13/20) | 68.15±6.2 | 0.31±0.19 | 26 (9/17) | 63.2±6.1 | 0.90±0.29 | NINCDS-ARDA, MMSE, CDR | Strong (5) |
| Borroni et al., 2002 | Cross sectional study | vmAD 16 (9/7) | 69.5±6.5 | 0.50±0.30 | 40 (18/22) | 68.3±9.0 | 0.91±0.30 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| | | mAD 24 (14/10) | 67.1±7.7 | 0.42±0.22 | | | | | |
| Borroni et al., 2003 | Cross sectional study | AD 60 (22/38) | 71.4±9.7 | 0.37±0.23 | 45 (16/29) | 71.2±8.7 | 0.96±0.35 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| Colciaghi et al., 2004 | Cross sectional study | vmAD 11 (4/7) | 67.8±6.3 | 0.447±0.160 | 15 (6/9) | 67.7±4.2 | 0.706±0.241 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| | | mAD 20 (8/12) | 68.0±7.5 | 0.419±0.168 | | | | | |
| Di Luca et al., 2005 | Cross sectional study | mAD 37 (17/20) | 67.3±6.8 | 0.44±0.18 | 25 (11/14) | 66.5±3.8 | 0.61±0.22 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| Sanchez-Gonzalez et al., 2006 | Cross sectional study | AD 26 (17/9) | 60.96±12.85 | 0.37± 0.19 | 46 (15/31) | 67.73± 9.46 | 0.68± 0.10 | NINCDS-ARDA, MMSE, DSM-IV | Moderate (4) |
| Tang et al., 2006 | Cross sectional | AD 31 | 76.0±8.7 | 5.97 | 10 (N.S.) | 76.3±4. | 7.32 | NINCDS-ARDA | Moderate (4) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | study | (N.S) | | | | 47 | | , MMSE, DSM-IV | |
| Liu, Wang et al., 2007 | Prospective cohort study | AD 66 T0 (41/25) | 76.5±9.9 | 1.35±0.81 | 46 T0 (27/19) | 72.5±10.9 | 1.44±0.79 | NINCDS-ARDA, MMSE, DSM-IV, CDR, CASI | Strong (5) |
| | | AD 29 T1 (19/10) | 77.1±9.4 | 1.03±0.74 | 30 T1 (19/11) | 72.4±10.3 | 1.34±0.73 | | |
| Zainaghi et al., 2007 | Cross sectional study | AD 23 (8/15) | 74.4±9.0 | 1.01±0.21 | 30 (7/23) | 70.0±5.8 | 1.24±0.21 | NINCDS-ARDA, MCC, DSM-IV, MMSE | Strong (5) |
| | | MCI 25 (8/17) | 70.9±5.7, | 1.18±0.21 | | | | | |
| Srisawat et al., 2013 | Cross sectional study | AD 13 (4/9) | 79.3 ± 8.1 | 7.32 ± 1.29 | 27 (6/21) | 68.3 ± 6.6 | 9.13 ± 3.00 | NINCDS-ARDA, MMSE | Strong (5) |
| Jelic et al., 2013 | Cross sectional study | AD 30 (12/18) | 67.0±9.9 | 5.9±1.37 | 23 (9/14) | 68.2±9.6 | 10.3 (2.82) | NINCDS-ARDA, MMSE | Strong (5) |
| Shi et al., 2019 | Cross sectional study | aMCI 43 (17/26) | 67.37±7.89 | 0.64±0.25 | 45 (19/26) | 64.60±8.03 | 0.75±0.24 | MCC, MMSE | Strong (6) |

Legend 1. N.S.= Not specified; AD= Alzheimer's Disease; vmAD= very mild Alzheimer's Disease; mAD= mild Alzheimer's Disease; MAD= moderate Alzheimer's Disease; aAD= advanced Alzheimer's Disease; MCI= Mild Cognitive Impairment; aMCI= amnestic Mild Cognitive Impairment; MCC= Mayo Clinic Criteria; NINCDS-ARDA= National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA); MMSE= Mini Mental State Examination; CDR= Clinical Dementia Rating Scale; DSM= Diagnostic and Statistical Manual of Mental Disorders.

**Table S2.** Studies detecting ADAM and BACE activities.

| First author, year | Study design | Sample | | | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AD or MCI | | | | Control | | | | | |
| | | N (M/F) | Age | α | β | N (M/F) | Age | α | β | | |
| Colciaghi et al., 2002* | Cross sectional study | AD 33 (13/20) | 68.15±6.2 | ↓ activity compared to controls | ↑ activity compared to controls | 26 (9/17) | 63.2±6.1 | | | NINCDS-ARDA, MMSE, CDR | Strong (5) |
| Colciaghi et al., 2004* | Cross sectional study | vmAD 11 (4/7) | 67.8±6.3 | 0.52±0.06 | 0.67±0.17 | 15 (6/9) | 67.7±4.2 | 0.81±0.07 | 1.47±0.20 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| | | mAD 20 (8/12) | 68.0±7.5 | 0.37±0.05 | 0.76±0.10 | | | | | | |
| Di Luca et al., 2005* | Cross sectional study | mAD 37 (17/20) | 67.3±6.8 | 0.43±0.23 | 0.84±0.73 | 25 (11/14) | 66.5±3.8 | 0.79±0.49 | 1.52±1.27 | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| Tang et al. 2006* | Cross sectional study | AD 31 (N.S) | 76.0±8.7 | 0.42 | 0.46 | 10 (N.S.) | 76.3±4.5 | 1.34 | 1.95 | NINCDS-ARDA, MMSE, DSM-IV | Moderate (4) |
| Liu, Todd et al., 2007 | Cross sectional study | MCI 52 (29/23) | 76.1 | | 0.19±0.06 | 75 (31/44) | 73.5 | | 0.51±0.04 | NINCDS-ARDA, MMSE | Strong (5) |
| Johnston et al., 2008 | Cross sectional study | AD 86 (25/61) | 80.0±6.6 | | 0.18 ± 0.05 | 115 (42/73) | 79.1±8.2 | | 0.15±0.04 | NINCDS-ARDA, MMSE | Strong (5) |
| Gorham et al., 2010 | Cross sectional study | AD 20 (10/10) | 71.6±9.8 | 36.2±5.8 | 285 ± 52** | 30 (7/23) | 61.7±7.5 | 37.6±6.9** | 279±57** | MMSE | Moderate (3) |
| | | MCI 6 (3/3) | 65.7±9. | 34.9±2.1 | 246 ± | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 8 | | 42** | | | | | |
| Decourt el al., 2013 | Cross sectional study | AD 15 (10/5) | 82.0±5.1 | | 65.10±7.07** | 12 (4/8) | 79.5±5.0 | | 73.97±12.95** | NINCDS-ARDA, MMSE | Strong (5) |
| Manzine et al., 2013 | Cross sectional study | mAD 10 (3/7) | 75.1±7.5 | 0.68 ± 0.15 | | 25 (9/16) | 75.8±6.9 | 0.78±0.4 | | NINCDS-ARDA, MMSE, CDR, DSM-IV | Strong (5) |
| | | MAD 11 (4/7) | 76.1±7.7 | 0.28±0.06 | | | | | | | |
| | | aAD 9 (3/6) | 74.6±7.8 | 0.148±0.05 | | | | | | | |
| Markesteiner et al., 2013 | Cross sectional study | AD 68 (N.S.) | 79±1 | | 6,054±1,307** | 33 (N.S.) | 71±1 | | 2,283±273 | NINCDS-ARDA, MMSE, MCC | Strong (5) |
| | | MCI 19 (N.S.) | 76±2 | | 5,682±1,738** | | | | | | |
| McGuiness et al., 2016 | Prospective cohort study | MCI 97 (36/61) | 72.4±9.3 | | 0.81 ± 0.55 | 85 (46/39) | 74.6±9.5 | | 0.74 ± 0.39 | NINCDS-ARDA, MMSE, MCC | Strong (6) |
| Bram et al., 2019 | Cross sectional study | AD 20 (6/14) | 76.2±7.2 | 0.78±0.43 | 1.74± 0.93 | 20 (5/15) | 74.9±4.5 | 1.66± 0.57 | 1.33± 0.82 | NINCDS-ARDA, MMSE, DSM-IV | Strong (6) |

Legend 2. α= ADAM-10 or alfa-secretase activity; β= BACE or Beta secretase activity. * indicates studies reported also in another table.

**Table S3.** Study calculating the platelet A-Beta40/42.

| First author, year | Study design | Sample | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|
| | | AD or MCI | | | Control | | | | |
| | | N (M/F) | Age | **A-Beta40/42** | N (M/F) | Age | **A-Beta40/42** | | |
| Tang et al. 2006* | Cross sectional study | 23 (N.S.) | N.S. | 2.21 | 10 (N.S.) | 76.3±4.5 | 0.97 | NINCDS-ARDA, MMSE, DSM-IV | Moderate (4) |

**Table S4.** Calculation of mRNA-APP isoform.

| **First author, year** | **Study design** | **Sample** | | | | | | | | | | | | | **Criteria of diagnosis** | **EPHPP** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **AD or MCI** | | | | | | | **Control** | | | | | | | |
| | | **N (M/F)** | **Age** | **Tot** | **KPI** | **770** | **751** | **695** | **N (M/F)** | **Age** | **Tot** | **KPI** | **770** | **751** | **695** | |
| Vignini et al., 2011 | Cross sectional study | AD 18 (7/11) | 79±4 | 6.26± 0.45 | 7.06± 0.56 | 6.70± 0.48 | 6.83± 0.45 | 13.6± 0.43 | 22 (10/12) | 76±6 | 6.86± 0.44 | 7.46± 0.38 | 7.11± 0.45 | 7.16± 0.45 | 13.4± 0.54 | NINCDS-ARDA, MMSE | Moderate (4) |
| Vignini et al., 2013 | Cross sectional Study | AD 20 (9/11) | 78±5 | 6.20± 0.42 | 6.97± 0.53 | | | | 18 (8/10) | 76±5 | 6.94± 0.37 | 7.53± 0.34 | | | | NINCDS-ARDA, MMSE | Moderate (4) |

**Table S5.** APP isoforms expressed as APP-N and APP-C.

| First author, year | Study design | Sample | | | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AD or MCI | | | | Control | | | | | |
| | | N (M/F) | Age | APP-N | APP-C | N (M/F) | Age | APP-N | APP-C | | |
| Mukaetova-Ladinska et al., 2012 | Cross sectional study | AD 25 (15/10) | 78.08±1.00 | 51.12±4.84 | 24.68±1.40 | 26 (8/18) | 70.81±1.98 | 45.42±3.25 | 24.02±1.38 | NINCDS-ARDA, MMSE, DSM-IV | Moderate (4) |

**Table S6.** Platelet Presenilin 1 activity.

| First author, year | Study design | Sample | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|
| | | AD or MCI | | | Control | | | | |
| | | N (M/F) | Age | PSEN1 | N (M/F) | Age | PSEN1 | | |
| Bram et al., 2019* | Cross sectional study | AD 20 (6/14) | 76.2±7.2 | 1.13±0.46 | 20 (5/15) | 74.9±4.5 | 1.66±0.69 | NINCDS-ARDA, MMSE, DSM-IV | Strong (6) |

**Table S7.** Differences in the expression of APP isoforms.

| **First author, year** | **Study design** | **Sample** | | | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AD versus Control values in % | | | | | | Control | | | |
| | | **N (M/F)** | Age | APP 130 | APP 110 | APP 65 | APP 42 | N(M/F) | Age | | |
| **Bush et al., 1990** | **Cross sectional study** | **AD 15 (n.s.)** | 76 | = | = | = | = | 11 (n.s.) | 76 | NINCDS-ARDA | Moderate (4) |
| Bush et al., | Cross | AD 34 | 67.9±8.9 | ↑ **50%** | = | ↓ **15-30%** | ↓ **20-35%** | 46 (n.s.) | 70.6± | NINCDS-AR | Moderate |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1992 | sectional study | (n.s.) | | | | 10.2 | DA, MMSE | (4) |

**Table S8.** Comparison of APP exposed on platelet surface and sAPP released by platelets between aAD patients and controls.

| First author, year | Study design | Sample | | | | | | Criteria of diagnosis | EPHPP |
|---|---|---|---|---|---|---|---|---|---|
| | | aADs versus Controls values | | | | Control | | | |
| | | N (M/F) | Age | APP on surface | sAPP | N(M/F) | Age | | |
| Davies et al., 1997 | Cross sectional study | AD 27 (23/4) | 70.5±5.4 | ↑ | ↓ | 17 (10/7) | 60.8±8.2 | DSM-IV, MMSE | Moderate (4) |